22 June 2017
EMA/CHMP/437168/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fotivda

International non-proprietary name: tivozanib

Procedure No. EMEA/H/C/004131/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-AMI	3-methylisoxazole-5-amine (preferred) or 5-amino-3-methylisoxazole (alternate)
8-MOP	8-Methoxypsoralen
AA	Aromatic amine/amine
A/G	Albumin/globulin
ACP	4-amino-3-chlorophenol hydrochloride
AD	*N*-{2-chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}acetamide
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
AUC	area under the concentration-time curve
$AUC_{0\text{-last}}$	area under the concentration-curve from time zero to time of last quantifiable concentration
$AUC_{0\text{-24hr}}$	area under the concentration-time curve from time zero to 24 hours
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
$AUC_{0\text{-t,ss}}$	area under the concentration-time curve during the dosing interval at steady state
AVEO	AVEO Pharmaceuticals, Inc.
BCRP	breast cancer resistance protein
bFGF	basic fibroblast growth factor
BNP	Brain natriuretic peptide
BP	Benzo(a)pyrene
BRK	breast tumour kinase
BSEP	bile salt export pump
cDNA	complementary deoxyribonucleic acid
CEP	Certificate of Suitability of the European Pharmacopoeia
c-Kit	mast/stem cell growth factor receptor
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady state
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
CNS	central nervous system
CPA	Cyclophosphamide
CYP	cytochrome P450
DDI	drug-drug interaction
DMA	Dimethylacetamine
DPQ	2-chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]aniline

DRF	Dose range-finding
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCTD	Electronic common technical document
EMA	European Medicines Agency
Eph	ephrin receptor
EU	European Union
Expt	Experiment
F	Female
FDA	Food and Drug Administration
FTIR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GD	Gestation day
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HDPE	High Density Polyethylene
hERG	human ether-à-go-go-related gene
HFSR	hand-foot skin reaction
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography – tandem mass spectrometry
HPLC-PDA	high performance liquid chromatography – Photodiode Array
HUVEC	human umbilical vein endothelial cell
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IFN-α	Interferon-alpha
IHC	Immunohistochemistry
IL-2	interleukin-2
IP	Intraperitoneal
IV	Intravenous
LDH	Lactate dehydrogenase
LDPE	Low density polyethylene
M	Male
MC	1-{2-chloro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-3-(5methylisoxazol-3-yl)urea
MC	Methylcellulose
MCH	Mean corpuscular haemoglobin
MD	4-(4-amino-3-chlorophenyl)-6-methoxyquinolin-7-ol
MDR1	multidrug resistance protein 1
MED	Minimal erythema dose
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose

M/E	Myeloid/erythroid
MMC	Mitomycin C
MN	Micronucleated
MRP2	multidrug resistance-associated protein 2
MS	Mass Spectrometry
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NA	Not applicable
NAG	N-acetyl beta-D glucosaminidase
NCE	Normochromatic erythrocyte
NEFA	Non-esterified fatty acid
NMR	Nuclear magnetic resonance
NMT	Not more than
NO	nitric oxide
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OATP1B1	Organic anion-transporting polypeptide 1B1
OATP1B3	Organic anion-transporting polypeptide 1B3
OCT 1	Organic cation transporter 1
OD	Optical density
PCE	Polychromatic erythrocyte
PDGFR	platelet-derived growth factor receptor
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	package leaflet
PlGF	placental growth factor
PPE	Palmar-plantar erythrodysaesthesia syndrome
PRES	Posterior reversible encephalopathy syndrome
PSUR	periodic safety update report
PT	preferred term
QC	4-chloro-6,7-dimethoxyquinoline
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia method
RBC	Red blood cell
RCC	renal cell carcinoma
RMP	Risk management plan
RPLS	Reversible posterior leukoencephalopathy syndrome
RTK	receptor tyrosine kinase
S-9	Liver microsomal fraction
SAE	serious adverse event
SmPC	Summary of Product Characteristics

SMQ	standardised MedDRA query
SOC	system organ class
STD	standard deviation
TEAE	treatment emergent adverse event
TGA	Thermo-Gravimetric Analysis
TGI	tumour growth inhibition
$t_{1/2}$	half-life
Tie-2	TEK, TEK tyrosine kinase, endothelial
TIBC	Total iron-binding capacity
TK	Toxicokinetic
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
UGT	uridine diphosphate glucuronosyltransferase
UIBC	unsaturated iron-binding capacity
US	United States
USP	United States Pharmacopoeia
UVR	Ultraviolet radiation
UV-Vis	Ultraviolet-visible
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VTE	venous thromboembolic event
WBC	White blood cell
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant EUSA PHARMA submitted on 29 February 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Fotivda, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 December 2014.

Fotivda was designated as an orphan medicinal product EU/3/10/747 on 9 June 2010 in the following condition: Treatment of renal cell carcinoma. The orphan designation was withdrawn by the applicant on 24 April 2017 with official request presented to the European Commission.

The applicant applied for the following indication:

Treatment of adult patients with advanced renal cell carcinoma (RCC) who are VEGFR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with interferon-alpha (IFN-α) or interleukin-2 (IL-2).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance tivozanib hydrochloride monohydrate contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25 June 2009, 17 February 2011 and 19 May 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 29 February 2016.
- The procedure started on 24 March 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 June 2016.
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 November 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 January 2017.
- During the PRAC meeting on 12 January 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 26 January 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 13 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 May 2017.
- During the CHMP meeting on 17 May 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22 June 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fotivda on 22 June 2017.
- The CHMP adopted a report on similarity of Fotivda with Torisel on 26 January 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Renal cell carcinoma (RCC) is the most common type of kidney cancer and originates in the lining of the proximal convoluted tubule, a part of the very small tubes in the kidney that transport primary urine.

2.1.2. Epidemiology and risk factors, screening tools / prevention

Renal cell carcinoma (RCC) accounts for 90-95% of neoplasms arising from the kidney and for 2% to 3% of all adult malignancies. There is a 1.5:1 male preponderance, with peak incidence between 60 and 70 years (Siegel et al, Cancer Statistics 2016 CA Cancer J Clin 2016; 66: 7-30).

Globally, the incidence of renal cell carcinoma (RCC) varies widely from region to region, with the highest rates observed in the Czech Republic and North America. In the EU, there were approximately 84,000 cases of RCC and 35,000 deaths due to kidney cancer in 2012.

2.1.3. Biologic features, Aetiology and pathogenesis

The main histological subtypes of RCC (Vancouver classification) are clear cell, multi-lobular cystic, papillary and chromophobe. Clear cell RCC (ccRCC) is the most common type of RCC and accounts for 70-85% of sporadic cases of RCC.

A complex biological classification of RCC (and especially of its clear cell histotype) is currently emerging and RCC is proving to be an extremely heterogeneous disease (Gerlinger M et al; *N Eng J Med* 2012 366; 883-892) beyond the seminal genetic alteration (mutation, deletion or hypermethylation) of the *VHL* tumour suppressor gene, which is present in the vast majority of sporadic RCCs. Other genetic alterations may also occur, especially over time, such as mutations in the mTOR pathway and especially in the highly conserved FAT (FRAP–ATM–TTRAP) and kinase domains of the *MTOR* gene (Voss MH et al Clin Cancer Res 2014; 20: 1954-1966).

In RCC, overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) promotes neoangiogenesis, which contributes to the development and progression of RCC.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

About 25-30% of patients have metastatic disease at diagnosis, and fewer than 5% have a solitary metastasis. Metastatic deposits are generally found in the bone and lung. RCC is also associated with hypercalcaemia, fever, erythrocytosis or wasting syndromes. Patients with localised disease at diagnosis have a 5-year survival rate of approximately 85% compared with 10% in those with metastatic disease at diagnosis. According to SEER Cancer Statistics for years 2002 to 2008, individuals with localised disease at diagnosis had a 5-year relative survival rate of 91.1% compared with 11.6% in individuals with metastatic disease at diagnosis (approximately 1/4 of patients) (NCI, cited 19 May 2012, SEER Stat Fact Sheets: Kidney and Renal Pelvis).

Whether the tumour subtype (i.e., clear cell versus papillary or chromophobe carcinoma) affects prognosis is controversial. In addition to the histologic grade and anatomic extent of disease, clinical factors (e.g. performance status, interval from diagnosis to metastasis, number of metastatic sites, organ involvement, weight loss) can influence survival. (Delahunt B, Cheville JC, Martignoni G et al Am J Surg Pathol 2013 37: 1490 –1504).

Advanced RCC in adults is most often diagnosed as early as 55 years of age and at an average age of 64 years (ACS, 2012, Kidney Cancer (Adult): RCC).

2.1.5. Management

Surgical resection remains the only known curative treatment for localised renal cell carcinoma, and it is also used to improve outcome or for palliation in metastatic disease. Targeted therapy and immunomodulatory agents are considered standard of care in patients with metastatic disease. Chemotherapy is used only occasionally, in certain tumour types.

Advanced RCC is highly resistant to conventional chemotherapy, radiotherapy, and hormonal therapy (Hartmann, 1999, Anticancer Research; Hudes et al, 2011, J Natl Compr Canc Netw).

Renal cell carcinoma is an immunogenic tumour, and spontaneous regressions have been documented. Many immune modulators have been used successfully, including the following: Interferon (IFN) and interleukin-2 (IL-2); the programmed cell death–1 protein (PD-1) receptor blocker nivolumab and similar agents; Bacillus Calmette-Guérin (BCG) vaccination; Lymphokine-activated killer (LAK) cells plus IL-2; Tumour-infiltrating lymphocytes; Nonmyeloablative allogeneic peripheral blood stem-cell transplantation.

In metastatic RCC, targeted therapy is now the first-line standard of care. VEGF inhibitors (e.g. axitinib, bevacizumab), multi-target tyrosine kinase inhibitors (e.g. sorafenib, sunitinib, pazopanib) and mTOR inhibitors (e.g. temsirolimus) are already approved in the EU for the first-line treatment of advanced RCC.

About the product

Tivozanib hydrochloride is a tyrosine kinase inhibitor (TKI), with a long half-life that preferentially binds to the three vascular endothelial growth factor receptors (VEGFR-1, 2, and 3) but needs to be present at higher concentrations to inhibit other tyrosine kinase receptors. The specificity to the VEGFR targets differentiates tivozanib hydrochloride from other available TKIs used in RCC.

Proposed indication

Treatment of adult patients with advanced renal cell carcinoma (RCC) who are VEGFR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with interferon-alpha (IFN-α) or interleukin-2 (IL-2).

Proposed posology

The recommended dose of tivozanib is 1340 microgram once daily for 21 days, followed by a 7-day rest period to comprise one complete treatment cycle of 4 weeks.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 890 micrograms or 1340 micrograms of tivozanib (as hydrochloride monohydrate) as active substance, equivalent to 1 mg tivozanib hydrochloride monohydrate and 1.5 mg tivozanib hydrochloride monohydrate, respectively.

Other ingredients are: mannitol, magnesium stearate, gelatin, titanium dioxide (E171) and yellow iron oxide (E172). The 890 microgram product also contains indigo carmine (E132).

Imprint ink contains: shellac, propylene glycol, strong ammonia solution, indigo carmine aluminium lake (E132). The 890 microgram product also contains titanium dioxide and tartrazine aluminium lake (E102).

The product is available in a white HDPE bottle with a child resistant closure containing 21 hard capsules as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of tivozanib hydrochloride monohydrate is 1-{2-Chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-3-(5-methylisoxazol-3-yl)urea hydrochloride hydrate corresponding to the molecular formula $C_{22}H_{19}ClN_4O_5$-Hydrochloride-H_2O and has a relative molecular mass 509.34 g/mol and has the following structure:

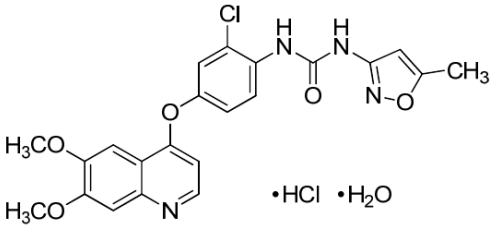


Figure 1: Structure of tivozanib hydrochloride monohydrate

The chemical structure was confirmed via Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy, Carbon Nuclear Magnetic Resonance (^{13}C NMR) Spectroscopy, Elemental Analysis, Mass Spectrometry (MS), Ultraviolet-visible (UV-Vis) Spectroscopy and Fourier Transform Infrared (FTIR) Spectroscopy. The results of additional characterisation tests including Hot Stage Polarized Light Microscopy, Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), Dynamic Vapor Sorption, Polymorphism study, and Crystalline Form were also presented.

Tivozanib hydrochloride monohydrate is a white to light brown powder. It is not hygroscopic. It has low solubility across the physiological pH range (pH 1-7), is practically insoluble in water and slightly soluble in ethanol and methanol. Tivozanib hydrochloride monohydrate does not contain any chiral centres.

Polymorphism has been observed for tivozanib. It has been demonstrated that the current manufacturing process consistently produces Form I (tivozanib hydrochloride monohydrate salt). Stability studies have shown that the Form I drug substance does not undergo a change in crystalline form after storage at both the long-term condition of 25°C/60% RH and the accelerated condition of 40°C/75% RH.

The CHMP considers that tivozanib is to be qualified as a new active substance in itself.

Manufacture, characterisation and process controls

Tivozanib is synthesized in three main steps using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The critical process parameters are duly justified, methodology is presented and control is adequate.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in a low-density polyethylene (LDPE) bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description, identity (FTIR, HPLC, chloride), assay (HPLC), impurities (HPLC), residual solvents (GC), heavy metals (USP), residue on ignition (Ph. Eur.), water content (Ph. Eur.), crystalline form (XRPD) and particle size distribution (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (including pre-clinical, development and commercial scales) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on eight commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36-48 months under long term conditions at 25ºC / 60% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided. Results from 60ºC/75% RH stress storage conditions for 6 weeks were provided on two batches. Results from a forced degradation study at high temperature (150°C), acid, oxidative and basic conditions were also provided on one batch.

The parameters tested are the same as for release with additional tests for thermal profile by DSC and microbiological quality included. The analytical methods used were the same as for release and were stability indicating (aside from DSC and microbiological methods which were as per the method used for characterisation and the Ph. Eur respectively).

All tested parameters were within the specifications and no trends were observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Tivozanib hydrochloride 890 microgram capsules are described as a dark blue opaque cap and bright yellow opaque body, imprinted in yellow ink with “TIVZ” on the cap and in dark blue ink with “LD” on the body.

Tivozanib hydrochloride 1340 microgram capsules are described as a bright yellow opaque cap and a bright yellow opaque body, imprinted in dark blue ink with “TIVZ” on the cap and in dark blue ink with “SD” on the body.

The excipients in the capsule fill are mannitol and magnesium stearate. The composition of empty hard gelatin capsules and imprint inks are provided. The qualitative and quantitative composition is well defined and the final product is packaged into a high-density polyethylene (HDPE) bottle with a polypropylene cap with an induction seal.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The finished product is manufactured by dry blending the active substance tivozanib hydrochloride with excipients magnesium stearate and mannitol and filling the blend in hard gelatin capsules. Tivozanib hydrochloride has limited solubility at physiologic pH range. A milling step of tivozanib hydrochloride during the active substance manufacturing process ensures consistency of the particle size of the active substance used batches in the manufacture of finished product.

The dissolution method was developed and optimized via changes to the paddle speed and dissolution medium composition. The discriminatory power of the dissolution method has been demonstrated. The primary packaging is a white HDPE bottle with a child resistant closure. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by dry blending the active substance tivozanib hydrochloride with excipients magnesium stearate and mannitol and filling the blend into hard gelatin capsules.

The in-process controls performed during the manufacturing process are appropriate and have been well described and justified.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description, identification (HPLC, HPLC-PDA), assay (HLPC), impurities (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.) and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial scale batches of each strength of finished product stored under long term conditions for 48 months at 25ºC / 60% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided. The batches of Fotivda are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, impurities, water content, dissolution and microbial limit test. The analytical procedures used are stability indicating. No significant changes have been observed.

One batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on the results for description, assay, impurities, water content and dissolution, it is concluded that the finished product is photostable.

Forced degradation studies conducted on the capsule contents (thermal, light, base, acid and oxidative stress conditions) showed similar results to the drug substance studies and confirmed the suitability of the HPLC degradation product method for use in the analysis of stability samples.

In addition, a study of one batch of each strength of the bulk product stored for 24 months under long term conditions at 25ºC/60%RH and intermediate conditions at 30ºC/75%RH and for 9 months under accelerated conditions at 40ºC/75%RH were provided. Based on available stability data, the proposed hold time of 24 months for bulk product is acceptable.

Based on available stability data, the proposed shelf-life of 5 years with the bottle tightly closed in order to protect from moisture as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Gelatin obtained from animal sources is used in the product. Valid TSE CEP from the suppliers of the gelatin used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development programme employed a series of *in vitro* studies to assess the biochemical and cellular properties of tivozanib hydrochloride as an inhibitor of the VEGF receptors (VEGFRs) VEGFR-1, VEGFR-2 and VEGFR-3 and a series of *in vivo* studies to evaluate the potency and breadth of the anti-tumour activity of tivozanib hydrochloride through an anti-angiogenic mechanism. All studies were conducted using tivozanib hydrochloride drug substance manufactured at Hamari (Osaka, Japan).

Safety pharmacology studies were performed in rats and monkeys. In vitro and in vivo pharmacokinetic (PK) studies investigated the ADME properties and potential for drug-drug interactions (DDIs). Toxicology studies in multiple species (mice, rats, rabbits, and monkeys), evaluating single-dose and repeat-dose toxicity (up to 26 weeks in rats and 39 weeks in cynomolgus monkeys), as well as genotoxicity, reproductive and developmental toxicity, mechanistic toxicology, and phototoxicity studies and assessment of the impurities profile for tivozanib hydrochloride were submitted.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

In Vitro Activity of Tivozanib Hydrochloride Against Recombinant Receptor Tyrosine Kinases (Studies 1172, KBC008, KBC009, and KBC010)

Table 1: IC50 Values for Tivozanib Hydrochloride: 26 Recombinant Kinases (Study 1172)

Kinase	IC_{50} (nM)	Kinase	IC_{50} (nM)
VEGFR-2	6	MuSK	785
VEGFR-3	15	SRC	960
Eph-B2	24	FGFR-3	1250
VEGFR-1	30	FGFR-4	1400
PDGFR-α	40	Flt-3	2550
PDGFR-β	49	EGFR	4175
BRK	48	INS-R	5675
Tie-2	78	ErbB-2	5575
c-Kit	78	FAK	7125
Eph-B4	475	ErbB-4	9225
FGFR-1	525	IGF1-R	> 10000
c-Met	550	JAK-2	> 10000
Abl-1	618	WEE1	> 10000

Three additional in vitro studies were performed to assess the overall selectivity of tivozanib hydrochloride for kinases (Studies KBC008, KBC009, and KBC010). Minimal inhibition was observed for any kinase at concentrations of 0.1 and 10 nM. At a concentration of 10 nM tivozanib hydrochloride, 12 kinases showed inhibition of ≥ 50%. These potently inhibited kinases included various members of the ephrin receptor family, Janus kinase-3 (JAK-3), c-Kit, rearranged during transfection oncogene (Ret), CSF1R macrophage colony-stimulating factor 1 receptor (Fms), BRK, and Ableson leukemia oncogene cellular homolog 1. At concentrations of 100 nM tivozanib hydrochloride, most of the kinases showed little or no inhibition, while 39 kinases were inhibited by ≥ 50%. Among the set of 39 kinases against which tivozanib hydrochloride showed activity at 100 nM, VEGFR-1, VEGFR-2, and VEGFR-3 ranked among the most strongly inhibited, with 18%, 0, and 3% activity remaining relative to control, respectively. Of the other kinases inhibited, Eph-B2, PDGFR–α, PDGFR–β, BRK, Tie-2 and c-Kit were strongly inhibited by 100 nM of tivozanib hydrochloride, which is consistent with the findings in Study 1172. Also inhibited at this concentration were the mitogen-activated protein kinase (kinase 4), Eph-A, Eph-B, Fms, lymphocyte-specific protein tyrosine kinase, Ret, neurotrophic tyrosine kinase receptor type B, and v-yes-1 Yamaguchi sarcoma viral related oncogene homolog kinases.

Cell-based assays were used to evaluate tivozanib hydrochloride inhibition of the phosphorylation of RTKs and demonstrated higher selectivity of tivozanib hydrochloride for the 3 VEGFR kinases.

Three studies evaluated the inhibition of tivozanib hydrochloride on the cellular activity of VEGFR-1, VEGFR-2, or VEGFR-3 (Studies 951-03, 951-09, and 951-41, respectively). Tivozanib hydrochloride potently and selectively inhibited the VEGF-induced phosphorylation of intracellular VEGFR-1, VEGFR-2, and VEGFR-3 with IC50 values of 0.21, 0.16, 0.24 nM, respectively.

Analogous studies were performed with various other receptor-expressing cells to assess the tivozanib hydrochloride-mediated inhibition of ligand-stimulated intracellular phosphorylation of other RTKs. Although tivozanib hydrochloride effectively inhibited phosphorylation of c-Kit and PDGFR-β, the cellular IC_{50} values were approximately 10-fold higher than for VEGFR-2. The concentrations of tivozanib hydrochloride required to inhibit the phosphorylation of all other tested kinases were considerably higher (≥ 1870-fold) than the concentration required for inhibition of VEGFR-2.

Two mechanism of action studies were conducted with tivozanib hydrochloride to evaluate the direct inhibition of endothelial cell proliferation as opposed to tumour cell inhibition.

The functional selectivity of tivozanib hydrochloride on cells was evaluated (Study 951-04) by determining its effect on both VEGF- and basic fibroblast growth factor (bFGF)-stimulated endothelial cell proliferation. As with VEGFR-2 phosphorylation in cells (IC_{50} = 0.16 nM), tivozanib hydrochloride at very low concentrations strongly inhibited the VEGF-induced proliferation of HUVEC (IC_{50} = 0.67 nM). In contrast, the inhibitory activity of tivozanib hydrochloride against bFGF-induced proliferation of HUVECs was weak (IC_{50} ≥ 300 nM). Similarly, the IC_{50} value for tivozanib hydrochloride inhibition of phosphorylation of FGFR-1 (normal human dermal fibroblast [NHDF] cells), one of the primary receptors for bFGF, was 299 nM in Study 951-33. This concentration translates to > 400-fold selectivity for inhibiting VEGF-induced versus bFGF-induced HUVEC proliferation.

Study 951-28 evaluated the inhibitory activity of tivozanib hydrochloride on 8 human tumour cell lines in culture. Tivozanib hydrochloride at a concentration of ≥1 µM demonstrated limited inhibition of in vitro growth of all the cancer cell lines studied. In 4 of the cell lines administered a concentration of 10 µM of tivozanib hydrochloride, cell proliferation was reduced to about 50%.

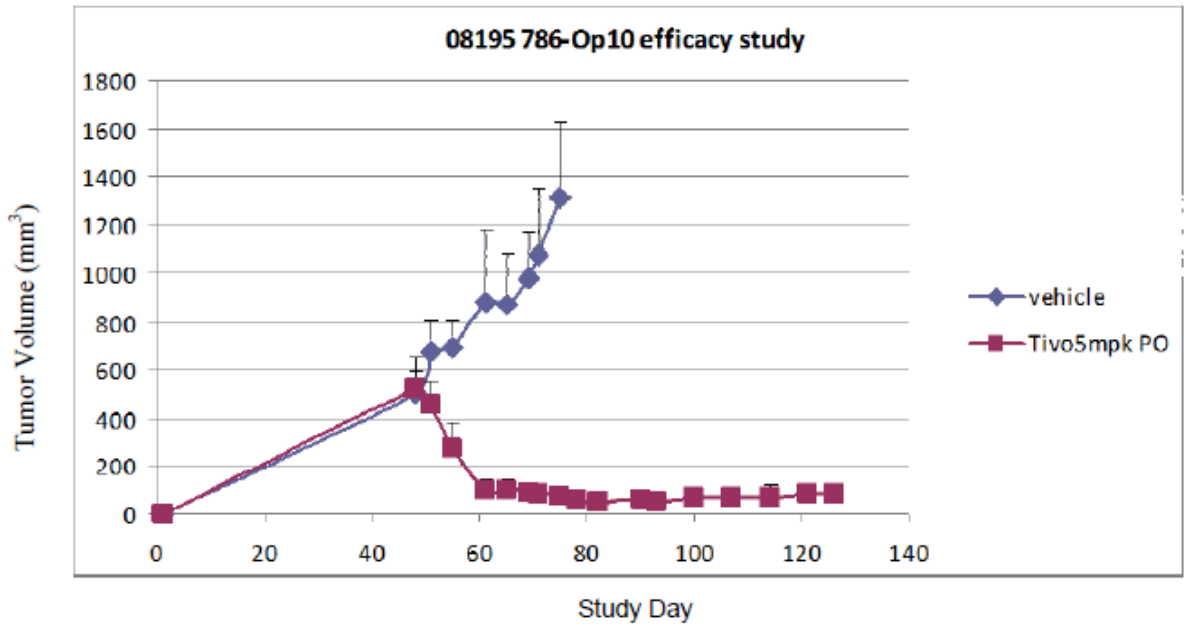
In vivo

Tivozanib hydrochloride's anti-tumour efficacy was evaluated in a broad range of human tumour xenograft mouse models. Overall, tivozanib hydrochloride demonstrated substantial and dose dependent anti-tumour activity ranging from significant tumour growth inhibition (TGI) to near complete tumour regression.

Study AV951-08195 examined the effects of daily oral administration of tivozanib hydrochloride alone and in combination with rapamycin, an mTOR inhibitor, on tumour growth, angiogenesis, and cell proliferation of human RCC 786-O xenografts implanted in nude mice.

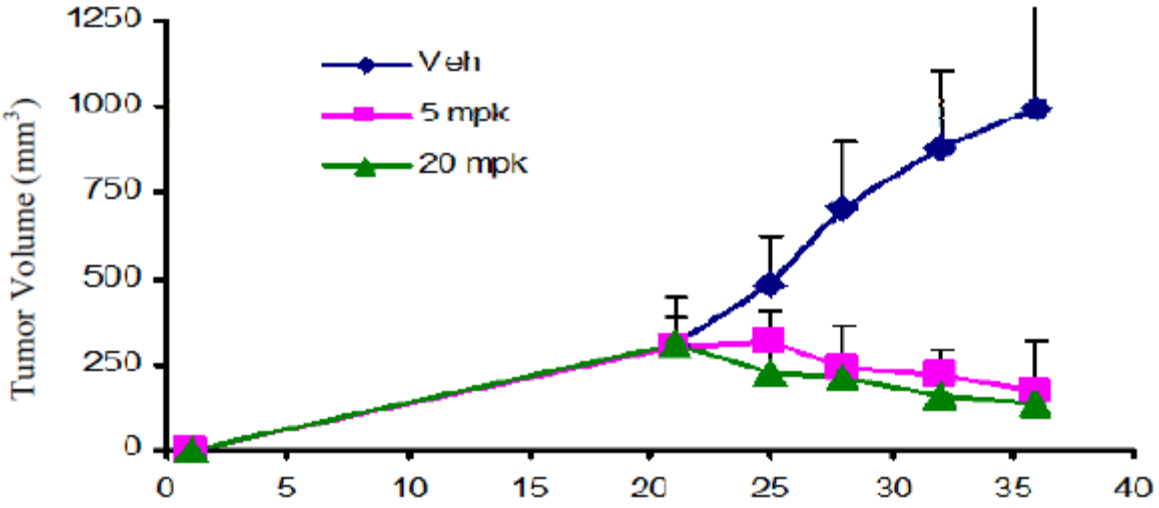
Oral administration of tivozanib hydrochloride at a dose of 5 mg/kg once daily led to a dramatic tumour regression of 86% in this model, relative to the pre-dose tumour volume (Figure 2). The effect was sustained through the extended dosing period. A comparison of tivozanib hydrochloride monotherapy and vehicle control is provided in Figure 2.

Figure 2: Efficacy of Single Agent Tivozanib Hydrochloride in 786-O Renal Cell Carcinoma Xenografts (Study AV951-08195)



Study AV951-08048 was designed to determine the effect of tivozanib hydrochloride in a murine lung tumour allograft model bearing a KRAS mutation (LK216) in SCID mice.
Treatment with tivozanib hydrochloride resulted in significant regression of LK216 tumours at both dose levels (44.1% for the 5 mg/kg dose group and 56.4% for the 20 mg/kg group). Mean tumour volumes at Day 36 were 996, 189, and 135 mm^3, for the vehicle control, 5 mg/kg, and 20 mg/kg dose groups, respectively (Figure 3). The difference in relative tumour volumes in both tivozanib hydrochloride groups was considered statistically significant (p value < 0.01) compared with that of vehicle control.

Figure 3: Effect of Tivozanib Hydrochloride Treatment on LK216 Lung Tumour Allografts (Study AV951-08048)



A series of similar studies evaluated the anti-tumour efficacy of tivozanib hydrochloride against a broad spectrum of human tumour xenografts. In each of these studies, animals administered either dose of tivozanib hydrochloride had statistically significantly smaller relative tumour volumes than animals

administered vehicle control (p value < 0.05). This difference correlated to > 50% TGI in all studies at all doses tested.

Two studies were conducted to evaluate the efficacy of tivozanib hydrochloride on tumour growth in rat models (Studies PRT/02149.1 and 951-31). Study PRT/02149.1 investigated the anti-tumour activity of 0.2 and 1.0 mg/kg tivozanib hydrochloride administered by oral gavage in a panel of 14 human tumours subcutaneously xenografted into nude rats. Doses of 0.2 mg/kg and 1.0 mg/kg were selected to enable correlation between efficacy and pharmacokinetic data (Study PKP0227).
At daily oral doses of 0.2 mg/kg tivozanib hydrochloride for 14 days, TGI was > 50% in 10 of the 14 models studied. At daily oral doses of 1 mg/kg, TGI was > 85% in all models studied (Table 2). The most potent activity (> 100% inhibition, i.e., tumour regression) was observed with MDA-MB-231 breast carcinoma, LoVo colon carcinoma, DU145 prostate carcinoma, and Caki-1 RCC.

Table 2: Effects of Tivozanib Hydrochloride on Tumour Growth in Vivo in Nude Rats (Study PRT/02149.1)

Cancer Cell	Tissue	Tumor Growth Inhibition (%)	
		0.2 mg/kg/day Tivozanib Hydrochloride	1 mg/kg/day Tivozanib Hydrochloride
Caki-1	Renal carcinoma	27	> 100*
MDA-MB-231	Breast carcinoma	77*	> 100*
ZR-75-1	Breast adenocarcinoma (ductal)	77*	94*
LoVo	Colon adenocarcinoma	60*	> 100*
LS174T	Colon carcinoma	86*	100*
CGL-9	Glioma	46*	96*
SK-HEP-1	Liver adenocarcinoma	60	90*
Calu-6	Lung carcinoma	44*	99*
NCI-H460	Lung carcinoma	69*	86*
OVCAR-3	Ovarian adenocarcinoma	25	99
SK-OV-3	Ovarian carcinoma	93	99*
BxPC-3	Pancreas carcinoma	61[a]	94[a]*
DU145	Prostate carcinoma	90	> 100
PC-3	Prostate carcinoma	74*	96*

Study 951-31 evaluated the anti-tumour efficacy of tivozanib hydrochloride in rats with A549 lung carcinoma xenografts, as well as the ability of tivozanib hydrochloride to inhibit angiogenesis. Tumour growth inhibition was stated to be 42.91% in the 0.04 mg/kg/day dose group and > 100% in the 0.2 and 1.0 mg/kg/day dose groups, indicating that administration of tivozanib hydrochloride results in dose-dependent anti-tumour efficacy in rats. A dose-dependent effect was also noted on vascular permeability.

Four studies evaluated the effect of tivozanib hydrochloride on angiogenesis and vascular permeability suppression in nude mice and rats. In addition to an analysis of anti-tumour efficacy Study AV951-08195 also evaluated the impact of tivozanib hydrochloride on viable tumour area and microvasculature in an RCC xenograft model in nude mice. The effects of treatment with oral tivozanib hydrochloride as monotherapy and tivozanib hydrochloride in combination with IP rapamycin on tumour killing, angiogenesis, and tumour cell proliferation were analysed at the end of the study. The combination of 5 mg/kg oral tivozanib hydrochloride and 1 mg/kg rapamycin IP resulted in similar tumour shrinkage (86%) as tivozanib hydrochloride monotherapy whereas most of the remaining tumours in the tivozanib hydrochloride treatment group were necrotic and angiogenesis had been effectively blocked at the end of

the treatment. The combination therapy significantly (p value < 0.05) reduced the remaining lesion to residual disease with a very low number of viable tumour cells compared with tivozanib hydrochloride monotherapy, as measured by Ki67. In tumours treated with the combination therapy, the percent viable tumour area was 15.4% compared with 57.2% in the tivozanib hydrochloride monotherapy group. Similarly, the average number of microvessels per viable tumour area was 10/mm^2 in the combination therapy group compared with 62/mm^2 in the tivozanib hydrochloride monotherapy group, as measured by CD31.

Study AV951-08008 evaluated the effect of tivozanib hydrochloride on tumour growth and proliferation after 2 to 5 days of continuous daily oral dosing of tivozanib hydrochloride at 5 or 20 mg/kg (12 per group) or vehicle control (3 per group) in mice subcutaneously implanted with BH505 mouse breast HER2 tumour cells.

After 2 days of oral dosing at 5 and 20 mg/kg, a dose responsive significant decrease (p value < 0.05) in viable tumour areas was observed in the tivozanib hydrochloride treated groups. Viable tumour areas were also significantly smaller in tumours treated with 20 mg/kg tivozanib hydrochloride than those treated with 5 mg/kg at all time points. A statistically significant but modest decrease in tumour cell proliferation rate (as measured by Ki67 staining) was observed in the 20 mg/kg dose group only at the 72-hour and 96-hour time points compared with the vehicle group (p value < 0.05). No significant difference in CD31 microvasculature between the treatment groups in the number of tumour vessels per mm^2 was observed; however, vessel cross-section area and therefore MVD were significantly decreased in both tivozanib hydrochloride-treated groups compared with vehicle control.

Tumour hypoxia increased at both doses of tivozanib hydrochloride. At the 5 mg/kg dose level, tumour hypoxia increased gradually, reaching its highest level at 120 hours. At the 20 mg/kg dose level, tumour hypoxia increased steeply at 72 hours and remained fairly constant until the 120-hour time point.

Mechanism of Action Studies in Rats To Evaluate the Antiangiogenic Properties of Tivozanib Hydrochloride (Studies 951-38 and 951-31)

Two studies were conducted in nude rats subcutaneously implanted with A549 human lung cancer xenografts. The first (Study 951-38) investigated the ability of tivozanib hydrochloride to suppress vascular permeability and angiogenesis at oral dose levels of 0, 0.04, 0.2 or 1.0 mg/kg. The second (Study 951-31) directly tested the ability of tivozanib hydrochloride to block angiogenesis in lung carcinoma and its effect on anti-tumour efficacy. A dose-dependent decrease was noted in the quantity of Evans blue dye present in tumours, indicating decreased vascular permeability. Similarly, a dose-dependent decrease was also observed in MVD, indicating reduced angiogenesis. At doses of 1.0 mg/kg daily, statistically significant effects were observed in both MVD and permeability, which correlated with > 100% TGI.

Table 3: Effect of Tivozanib Hydrochloride on Vascular Permeability and Microvessel Density and Correlation with Tumour Growth Inhibition (Studies 951-38 and 951-31)

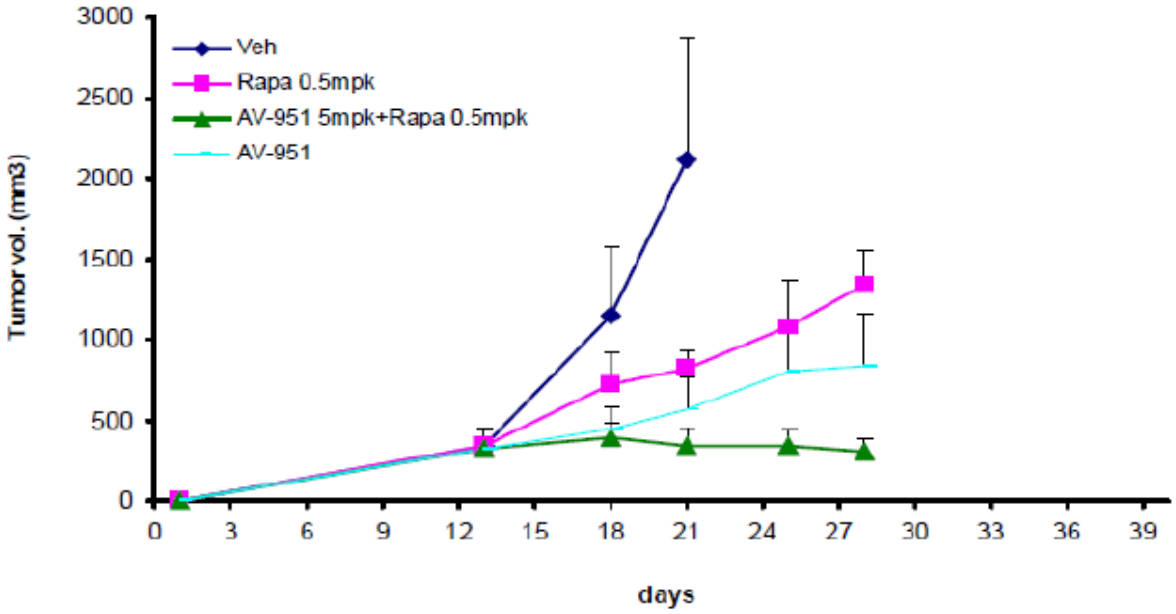
Dose (mg/kg)	Quantity of Evans Blue Dye per 1 g of Tumor (µg/g) (SE)	MVD Mean % (SE)	TGI (%)
0	36.6 (1.34)	9.22 (0.69)	-
0.04	33.2 (2.53)	7.77 (1.24)	42.91
0.2	23.9 (4.44)*	7.31 (2.28)	> 100
1	15.1 (2.01)***	2.01** (0.29)	> 100

Combination Therapy with Tivozanib Hydrochloride and Other Cancer Therapeutics (Studies AV951-08046, AV951-08195, and AV951-08011r)

Three studies were conducted to evaluate the anti-tumour effect of tivozanib hydrochloride alone or in combination with rapamycin, an mTOR inhibitor, as compared with vehicle control (0.5% MC).

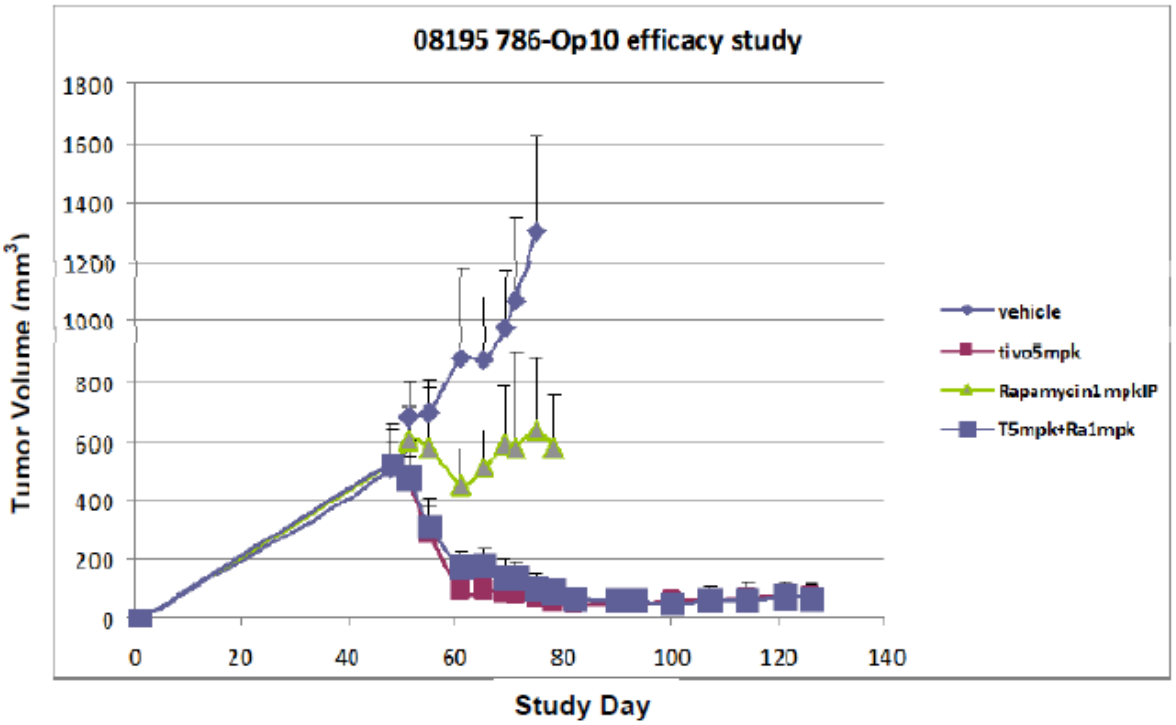
In studies AV951-08046 and AV951-08195 combination therapy of tivozanib hydrochloride and rapamycin was more effective than monotherapy with either agent. Figure 4 and Figure 5 present the change of tumour volumes after treatment in Study AV951-08046 and Study AV951-08195, respectively.

Figure 4: Tumour Growth Inhibition in BH504R3 Murine Breast HER2 Xenografts with Tivozanib, Rapamycin, and Combination Treatment (Study AV951-08046)



Abbreviations: AV-951 = tivozanib hydrochloride at 5 mg/kg; Rapa = rapamycin; Veh = vehicle control (0.5% MC).
Note: Study drug treatment initiated Day 13.

Figure 5: Tumour Growth Inhibition in 786-O Renal Cell Carcinoma Xenografts with Tivozanib Hydrochloride and Rapamycin Administered as Single Agents and in Combination (Study AV951-08195)



Abbreviations: IP = intraperitoneal; tivo = tivozanib hydrochloride; Rapamycin1mpkIP = 1 mg/kg IP rapamycin; T5mpk = 5 mg/kg tivozanib hydrochloride; vehicle = 0.5% methylcellulose.
Note: Study drug treatment initiated on Day 48.

Study AV951-08011r evaluated 5 mg/kg tivozanib hydrochloride, 1 mg/kg rapamycin, and the combination of both treatments, as compared with vehicle control (0.5% MC) for 43 days in the genetically engineered mouse breast HER2 tumour model BH469. On Day 42, tumour volumes were 1186.4, 956.9, and 1343.6 mm^3 smaller than the Day 24 vehicle control tumour volume (1522.5 mm^3) in the tivozanib hydrochloride, rapamycin, and combination treatment arms, respectively. Statistical significance was not calculated for this study.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted.

Safety pharmacology programme

Table 4 Tabular summary of the safety pharmacology studies

					Test Article: Tivozanib hydrochloride			
Organ Systems Evaluated	**Study Title**	**Species/ Strain**	**Method of Admin.**	**Dose**	**Gender and No. per Group**	**Noteworthy Findings**	**GLP**	**Study Number**
Cardiovascular (In vitro hERG assay)	Effect of KRN951 on HERG tail current recorded from stably transfected HEK293 cells	HEK293 cells stably transfected with hERG cDNA	in vitro (0.1% DMSO)	0, 0.82 µg/mLa)	NA	Tivozanib hydrochloride, at a test concentration of 0.82 µg/mL, produced no inhibition of hERG tail current in HEK293 cells stably transfected with hERG cDNA.	Yes	DRZZ1020
Cardiovascular (Telemetry study)	Cardiovascular effects of KRN951 in conscious, telemetered cynomolgus monkeys	Cynomolgus monkey	oral gavage (0.5% MC)	0, 0.015, 0.3, 3b),c) mg/kg	4M 1/group	Doses of 0.015 and 0.3 mg/kg tivozanib hydrochloride had no significant impact on blood pressure or ECG parameters. Doses of 3.0 mg/kg had no impact on ECG parameters, but resulted in small but statistically significant increases in blood pressure. However, these changes were not correlated with changes in gross morphology or rhythm.	Yes	DRZZ1019
Cardiovascular	KRN951: multiple oral dosing in crab eating monkeys (cynomolgus monkey) toxicity study	Cynomolgus monkey	oral gavage (0.5% MC)	0, 1 mg/kg (28 days), or 3 mg/kg (14 days)	9M 3/group	A slight increase in blood pressure was recognized for both the 1 and 3 mg/kg tivozanib hydrochloride-treated animals during the 3-day period near the end of dosing. A reduction in heart rate, carotid artery blood flow, and reduction in renal artery flow were also noted at both doses. No effects were noted in plasma renin activation or plasma CPK at any dose of tivozanib hydrochloride. The purported mechanism of blood pressure changes was suggested to be due to an inhibitory effect on vascular endothelial-derived nitric oxide production, causing a rise in peripheral vascular resistance and blood pressure.	Yes	4655
Central nervous system (Irwin test)	Effects of KRN951 in the Irwin test in rats	Sprague Dawley rat	oral gavage (0.5% MC) chlorpromazine (RO water)	tivozanib hydrochlorided) (0, 0.3, 3, 30, 400 mg/kg) chlorpromazine (20 mg/kg)	36M 6/group	Administration of tivozanib hydrochloride did not result in any behavioral or physiological changes as compared to vehicle control. The observations noted in the reference substance group were consistent with the known pharmacological effects of chlorpromazine.	Yes	DRZZ1017
Respiratory	Effects of KRN951 on respiration rate and tidal volume in rats	Sprague Dawley rat	tivozanib hydrochloride oral gavage (0.5% MC) IV (morphine)	tivozanib hydrochloride (0, 0.3, 3, 30 400 mg/kg) morphine (20 mg/kg)	48M 8/group	Oral administration of tivozanib hydrochloride (0.3, 3, 30 and 400 mg/kg) had no significant effect on the respiration rate or tidal volume of conscious rats at any of the time points tested (4 or 24 hours postdose). As expected, the reference substance, morphine, caused a significant depression of respiration rate and tidal volume, an effect consistent with its pharmacological classification as a respiratory depressant.	Yes	DRZZ1018

Additional Information:

a) Due to solution and apparatus adsorption problems, the actual achieved concentration of tivozanib hydrochloride was 0.82 µg/mL. The intended concentration was 3 µg/mL.

b) Lot CDM-001 of tivozanib hydrochloride was used in this study. Dose levels are expressed in terms of the hydrated salt. No adjustment to free base was made. Doses were corrected for purity.

,c) Doses reported in the table are the target doses. Based on formulation analysis, the actual doses were 0.011 to 0.029 mg/kg (0.015 mg/kg); 0.244 to 0.274 mg/kg (0.3 mg/kg); 2.584 to 3.019 mg/kg (3.0 mg/kg).

d) In this study, Lot CDM-001 of tivozanib hydrochloride was used. Tivozanib hydrochloride levels were expressed in terms of the hydrated salt and no adjustment to free-base was made, although a correction factor of 1.012 was applied to correct for purity.

cDNA = complimentary deoxyribonucleic acid; CPK = creatine phosphokinase; DMSO = dimethyl sulfoxide; ECG = electrocardiogram; GLP = Good Laboratory Practice; hERG = human ether-à go-go-related gene; IV = intravenous; M = male; RO = reverse osmosis.

Pharmacodynamic drug interactions

Non-clinical pharmacodynamics drug interaction studies were not submitted.

2.3.3. Pharmacokinetics

Absorption

Following a single oral dose of tivozanib hydrochloride in mice, rapid absorption took place with T_{max} ranging from 0.5 to 2 hours. Systemic exposure (C_{max} and AUC) increased proportionally with dose and a relatively short elimination $t_{1/2}$ of approximately 2.2 to 6.11 hours was observed.

Following a single oral and IV doses of tivozanib hydrochloride in rats there was no sex related difference in exposure, a low CL of 23.9 mL/hr/kg, moderate Vd of 263 mL/kg, moderate rate of absorption with T_{max} ranging from 2.63 to 4.25 hours, good oral bioavailability of 71.8 to 82.4%. Elimination $t_{1/2}$ was long and similar after both IV (9.0 hours) and oral administration (9.8 to 10.7 hours) in Sprague-Dawley rats. A long $t_{1/2}$ of 7.8 to 9.3 hours was also observed in nude rats. Systemic exposure (C_{max} and AUC) increased proportionally with dose.

After repeat oral doses of tivozanib hydrochloride in rats there was no sex related difference in exposure, a moderate rate of absorption with T_{max} ranging from 2.0 to 4.0 hours not affected by dose level or duration of dosing. The systemic exposure (C_{max} and AUC) increased proportionally with dose.

Single and repeat oral doses of tivozanib hydrochloride in pregnant rabbits resulted in minimal accumulation with repeated dosing between GDs 6 and 18 and mean $t_{1/2}$ estimates within approximately 2 to 4 hours.

After repeat oral dose of tivozanib hydrochloride in monkeys there was no sex related difference in exposure, a moderate rate of absorption with T_{max} ranging from 1.8 to 8.0 hours not affected by dose level or duration of dosing. The systemic exposure (C_{max} and AUC) increased with repeat dosing.

Overall, the oral PK and TK parameters of tivozanib hydrochloride appeared to be dose-linear in all species (mice, rats, and monkeys), and with no marked sex differences. The absorption was rapid in mice and more moderate in rats and monkeys. In all nonclinical species, concentration-time profiles for tivozanib hydrochloride showed secondary peaks, indicating that enterohepatic recirculation may occur. This observation was stated to be consistent with clinical data from healthy human subjects and cancer patients. The $t_{1/2}$ was species dependent, being longer (generally ≥ 6.7 hours) in rats and monkeys and shorter (approximately 2.5 hours at dose levels used in pharmacodynamics studies) in nude mice.

Distribution

The tissue distribution of radioactivity was measured by quantitative whole body autoradiography in fasted male and female Sprague-Dawley albino rats as well as in male Lister Hooded pigmented rats after a single oral administration of 1.0 mg [^{14}C]-tivozanib hydrochloride/kg.

Tissue distribution in rats revealed that the highest concentrations of radioactivity post-dose were in the liver, white fat and Harderian gland, with the lowest found in the brain and spinal cord. Elimination was rapid in albino rats with all tissues BLQ at 72 hours post-dose. No sex differences were apparent in most tissues and there was limited distribution to sex-specific tissues. In pigmented rats, melanin binding to the choroid layer of eye displayed longer apparent elimination $t_{1/2}$ compared with other tissues.

The association of tivozanib hydrochloride within the red blood cells of rat after an oral dose of 1 mg/kg [^{14}C]-tivozanib hydrochloride was limited. In vitro assessment of human blood-to-plasma partitioning showed that [^{14}C]-tivozanib hydrochloride primarily partitions into the plasma/serum component of blood and is independent of concentration in the target range of 0.1 to 5 µM.

The protein binding properties of tivozanib hydrochloride were investigated in 2 separate studies. One evaluated these properties in rat, monkey, and human plasma (Study DRZZ1039); the other addressed human plasma and serum protein binding and assessed tivozanib hydrochloride binding to human serum albumin (HSA) and AAG (Study 8236152). Tivozanib hydrochloride is highly protein bound in the monkey (97.6%), and in the rat and human (> 99%). Binding is independent of gender. Human protein binding is the same (> 99%) in plasma and serum. HSA is the major plasma/serum protein component that binds tivozanib hydrochloride.

Metabolism

Study DRZZ1027 evaluated the comparative metabolic profile of [^{14}C]-tivozanib hydrochloride in human, cynomolgus monkey, dog, and rat microsomes. In addition, metabolite formation was assessed in the presence of heterologously expressed human cDNA derived CYP450 enzymes to evaluate the involvement of CYP450 isoforms in the metabolism of [^{14}C]-tivozanib hydrochloride. The results demonstrate the involvement of CYP450 in the metabolism of tivozanib hydrochloride. The disappearance of the drug was NADPH-dependent, and the percent tivozanib hydrochloride remaining decreased with increasing incubation times.

At a concentration of 0.50 µM, the most extensive metabolism occurred in monkey liver microsomes, with 79.0% of [^{14}C]-tivozanib hydrochloride remaining at 60 minutes. This result was followed by human (88.7%), rat (89.8%), and dog (97.1%). The metabolite profile in rat and monkey was similar to that in human, while that in the dog was dissimilar to the human profile. Of the various heterologously expressed human CYP enzymes incubated with [^{14}C]-tivozanib hydrochloride, only CYP1A1 (at 0.50 and 5.0 µM) and CYP3A4 (at 5.0 µM) metabolised tivozanib hydrochloride. As CYP1A1 is mainly expressed in extrahepatic tissues such as the lung and intestine, it is unlikely that this isoform would be extensively involved in generating the metabolites observed after incubation with human liver microsomes.

The in vitro study 8133-100 was conducted to further investigate the findings from Study DRZZ1027 in terms of structurally identifying the metabolites produced in human hepatic microsomal incubations.

In Study 8201725 identification of the specific UGT isoenzymes involved in the metabolism of [^{14}C]-tivozanib hydrochloride was evaluated using cDNA expressed human UGTs. This study also evaluated the inhibitory potential of tivozanib hydrochloride towards microsomal UGT activity. Substantial levels of [^{14}C]-tivozanib hydrochloride desmethyl glucuronide metabolites were formed by UGT isoenzymes UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9 and UGT1A10, but not by UGT isoenzymes UGT1A4, UGT1A6, UGT2B4, UGT2B7, UGT2B15, and UGT2B17. The predominant metabolite formed (M14) was a desmethyl glucuronide metabolite. The M14 metabolite was formed by several UGT enzymes (UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9 and UGT1A10). Consistent with these results, M14 was also the predominant metabolite formed in vitro by human primary hepatocyte incubations.

Other observed glucuronide metabolites were M10, another desmethyl glucuronide metabolite previously identified as a minor metabolite in human primary hepatocyte incubations (Study 8201725) and M25, a previously unidentified metabolite. Metabolite M10 was formed mainly by UGT1A1, UGT1A3 and UGT1A7 isoenzymes, and metabolite M25 was formed mainly by UGT1A1 and UGT1A9 isoenzymes.

Study 8201725 evaluated the in vitro metabolism of tivozanib hydrochloride in rat, monkey and human hepatocytes, including structural evaluation of metabolites. Tivozanib hydrochloride appeared to be metabolised mainly by the addition of oxygen, demethylation, glucuronidation, sulfation, or a combination of these pathways. Twenty two different metabolites, M1 to M24, were detected by using LC-MS/MS methods. Metabolites M10 (desmethyl glucuronide), M11 (glucuronide), M14 (desmethyl glucuronide), M4/M5 (oxide or N-oxide), M23 (desmethyl sulfate) and M24 (desmethyl sulfate) were also observed in incubations of human hepatocyte with [^{14}C]-tivozanib hydrochloride by using HPLC-RAD methods. Thus, these metabolites are considered to be the more prominent human metabolites and of

these only M14 (desmethyl glucuronide) was present at > 10% of total radioactivity and was designated as a predominant in vitro metabolite. All prominent human metabolites were present in both rat and monkey with the exception of M11 (glucuronide), which was unique to human hepatocytes, and M10, which was not observed with rat hepatocytes.

In Study 8255110, a single oral dose of [^{14}C]-tivozanib hydrochloride (5 mg/kg; approximately 200 µCi/kg) was administered to 2 male bile duct-intact and 2 bile duct-cannulated rats to identify the metabolites of tivozanib hydrochloride. On the basis of the HPLC-RAD analysis, unchanged parent was the predominant circulating component representing approximately 91% of the total radioactivity exposure in serum. Metabolites M4 (mono-oxidation)/M5 (N-oxide of tivozanib hydrochloride)/M63 (reduction of the isoxazole ring of tivozanib hydrochloride) co-eluting, represented approximately 9% of the total radioactivity exposure in serum. HPLC-RAD profiles obtained from bile duct-intact and bile duct-cannulated rat urine were generally qualitatively similar with up to 15 radioactive peaks detected. Unchanged parent was not detected in the urine. None of the metabolites detected in urine represented greater than 0.5% of the administered radioactive dose. Metabolites identified in urine were products of both Phase 1 and Phase 2 biotransformation pathways (demethylation, mono-oxidation, hydrolysis and various conjugations along with the cleavage products of the conjugates).

HPLC-RAD profiles obtained from bile duct-intact and bile duct-cannulated rat fecal extracts were generally qualitatively similar with up to 5 radioactive peaks detected. Unchanged parent was the predominant radioactive component representing 32.2 and 33.3% of the administered radioactive dose in intact and bile duct-cannulated rats, respectively. Predominant metabolites detected were M7 (*O*-demethylation; intact rats only), M42 (structure not proposed), and M37 (structure not proposed)/M57 (structure not proposed) co-eluting. In intact rats M7 represented 4.99% of the administered radioactive dose. M42 and M37/M57 represented 2.86 and 2.62% of the administered radioactive dose in intact rats, and 4.11 and 1.01% of the administered radioactive dose in bile duct cannulated rats, respectively. Metabolite M59 (structure not proposed) was present in trace amounts (less than 1% of the administered radioactive dose) in intact rats only.

The HPLC-RAD profile obtained from bile showed 9 radioactive peaks, including unchanged tivozanib hydrochloride. Unchanged parent was a minor component in the bile representing 0.388% of the administered radioactive dose. Predominant metabolites detected in bile were metabolites M55 (glutathione conjugation)/M56 (*N*-oxidation couple with glutathione conjugation followed by cleavage of the conjugate) co-eluting, and M15 (mono-oxidation coupled with glucuronidation)/M60 (*O*-demethylation coupled with sulfation) co-eluting, and representing 6.42 and 8.22% of the administered radioactive dose, respectively. Each of the other unknown metabolites detected in bile represented less than 1.5% of the administered radioactive dose.

Following oral administration, unchanged parent was the predominant circulating component, representing approximately 91% of the total radioactivity exposure in serum, with metabolites M4 (mono-oxidation)/M5 (*N*-oxide of tivozanib hydrochloride)/M63 (reduction of the isoxazole ring of tivozanib hydrochloride) co-eluting, which represented approximately 9% of the total radioactivity exposure in serum. Unchanged parent was not detected in the urine, and none of the metabolites detected in urine represented >0.5% of the administered radioactive dose. In bile, unchanged parent was a minor component in the bile, and predominant metabolites detected were products of both Phase 1 and Phase 2 biotransformation pathways. In faeces, up to 5 radioactive peaks were detected, with unchanged parent as the predominant radioactive component.

The in vivo metabolism of tivozanib hydrochloride was evaluated in rat, monkey, and human serum, urine, and faeces. In rats, metabolites were also evaluated in the bile.

Unchanged parent molecule is the predominant component in the serum and faeces in rats, monkeys and humans. The percentage of the total reactivity of unchanged parent in serum ranged from 77.6 to 95.1%

in humans, which is comparable to the 91% found in rats, and the 78% found in monkeys. Predominant serum metabolites in monkeys and rats were M4/M5 and M63 (rat only) representing a total of 9-17% of the total reactivity in rats and monkeys, respectively. In humans, no major metabolites were detected in serum. Each minor unknown metabolite detected represented ≤ 4% of the total radioactivity.

No urinary excretion of the parent molecule was noted in any species. No major metabolites at amounts greater than 0.5% of the total administered radioactive dose were detected in rats and monkeys. In humans, urinary predominant metabolites (M40, M35 and M29) represented 0.764-10.3% the total radioactive dose. Minor metabolites (M26, M27, M28 and M31) represented less than 3% the total radioactive dose. Of these, the only human metabolite excreted in urine that was not seen in either serum, urine, bile, and/or faeces in rats or monkeys was M40, a glutathione conjugate.

Unchanged tivozanib hydrochloride was a minor component in the bile of the rat representing 0.388% of the administered radioactive dose. Predominant metabolites detected in bile were metabolites M55/M56 and M15/M60, representing 6.42 and 8.22% of the administered radioactive dose, respectively.

In faeces, unchanged parent is the primary radioactive component for all species, with the percentage of total reactivity ranging from 7.82-46.1% in humans and 32.2 and 20.6% in intact rats and monkeys, respectively. In monkeys, 4 metabolites were observed, representing an average of less than 1% of the administered radioactive dose. In intact rats, the M7 metabolite represented 5% of the administered radioactive dose. Other metabolites, M42 and M37/M57 represented 2.86 and 2.62% of the administered radioactive dose respectively, in intact rats. In humans, the predominant radiolabelled components detected in faecal extracts were unchanged parent and metabolites M37, M42 and M7/M48. The predominant metabolites, together, represented a total of 6.35 to 34.3% of the radioactive dose.

Potential of Tivozanib Hydrochloride to Inhibit Cytochrome P450 Isoforms In Vitro

Two separate sets of experiments were conducted to evaluate the potential of tivozanib hydrochloride to inhibit various CYP450 pathways in vitro. One investigated the effect of tivozanib hydrochloride on various drug metabolising CYP450 isoforms (Study PK0501); the other (Study AV951-08274) focused specifically on the effect on the CYP 3A4 pathway.

Effect of Tivozanib Hydrochloride on CYP450 Isoforms (Study PK0501)

The effect of tivozanib hydrochloride on multiple CYP isoforms was investigated using human liver microsomes.

Table 5: Enzyme Inhibition of CYP450 Isoforms by Tivozanib Hydrochloride in Human Liver Microsomes (Study PK0501)

CYP Isoform	Specific Reaction	IC_{50} (μM)
CYP1A2	Ethoxyresorufin-O-deethylation	74.0
CYP2A6	Coumarin 7-hydroxylation	> 100
CYP2C9	Tolbutamide hydroxylation	29.8
CYP2C19	(S)-Mephenytoin 4'-hydroxylation	> 100
CYP2D6	Bufuralol 1'-hydroxylation	> 100
CYP3A4	Midazolam 1'-hydroxylation	15.6

Abbreviations: CYP = cytochrome P450; IC50 = half-maximal inhibitory concentration

Effect of Tivozanib Hydrochloride on CYP3A4 (Study AV951-08274)

The mean IC50 for tivozanib hydrochloride for α-OH-triazolam formation (without preincubation) was 43 µM. When tivozanib hydrochloride was preincubated with microsomal protein before addition of substrate, the IC_{50} increased to 103 µM, indicating no evidence of mechanism based or irreversible inhibition. Corresponding IC_{50} values for tivozanib hydrochloride for 4-OH-triazolam formation were: 65 µM without preincubation and 93 µM with preincubation. Therefore, tivozanib hydrochloride is a weak inhibitor of human CYP3A4 activity.

Evaluation of the Influence of CYP3A4 Inhibitors and CYP3A4 Substrates on the Human In Vitro Metabolism of Tivozanib Hydrochloride (Study AV951-08274)

In this system, tivozanib hydrochloride consistently yielded 4 chromatographic peaks, labelled as A, B, C, and D. A fifth peak (E) was produced in low abundance by some but not all liver samples. The metabolite peaks were preliminarily identified as having molecular weights of 441 (deletion of methyl), 471 (addition of oxygen), and 457 (addition of 2H), as well as the parent compound (molecular weight of 455). Another peak had a molecular weight of 373.

The estimated IC_{50} values for ketoconazole versus formation of metabolites A, B, C, and D were 1.12, 1.97, 1.31, and 1.39 µM, respectively. These IC_{50} values are at least an order of magnitude higher than IC_{50} values for ketoconazole versus pure CYP3A4 substrates such as triazolam.

These data indicate that tivozanib hydrochloride biotransformation is only partially dependent on CYP3A4, and inhibitors of CYP3A4 co-administered with tivozanib hydrochloride are not likely to have a major effect on tivozanib hydrochloride CL in vivo.

Further experiments were conducted to evaluate the impact of potential co-administered agents, temsirolimus and everolimus (both CYP3A4 substrates), on the metabolism of tivozanib hydrochloride. Both agents were found to be weak inhibitors of tivozanib hydrochloride biotransformation. The extent of inhibition did not exceed 50% even at concentrations substantially greater than usual levels of clinical exposure. IC_{50} values could not be calculated. These data indicate that these agents would not be expected to have a clinically meaningful impact on the CL of tivozanib hydrochloride in vivo.

Potential of Tivozanib Hydrochloride to Inhibit Human UDP-glucuronosyltransferase Pathways In Vitro (Study 8242516)

The inhibitory potential of tivozanib hydrochloride towards microsomal UGT activity was evaluated. This study also investigated the specific UGT isoenzymes involved in the metabolism of [^{14}C]-tivozanib hydrochloride,

Dose-dependent inhibition of UGT activities by tivozanib hydrochloride was observed using either 4-MU or p-NP as substrates. At the highest concentrations evaluated (50 µM), UGT activities were 65.0% and 71.6% using 4-MU and p-NP as substrates, respectively. Since tivozanib hydrochloride did not inhibit UGT activity by > 50% compared with solvent control, the results were not analysed by curve fitting, and IC_{50} values were not determined.

These data indicate that tivozanib hydrochloride is not likely to be a potent inhibitor of UGT activities and clinically relevant DDIs because of inhibition of UGT enzymes by tivozanib hydrochloride are not likely.

Enzyme Induction (Study 8231061)

A study was conducted to measure the extent of induction of specific CYP450 enzymes (CYP1A, CYP2B6, CYP2C9, CYP2C19, and CYP3A) after exposure of human hepatocytes to tivozanib hydrochloride and to compare the effects with those of prototypical inducers rifampicin, omeprazole, and phenobarbital.

Human hepatocyte cultures responded as expected to the prototypical inducers under the experimental conditions. Exposure of the cultures to 0.1, 0.5, and 5 µM tivozanib hydrochloride did not elicit substantial increases in CYP1A, CYP2B6, CYP2C9, CYP2C19 (except for 1 donor, considered as an experimental artefact) or CYP3A enzyme activities. The increases in all enzyme activities were < 40% compared with the induction by prototypical inducers. While induction of CYP3A mRNA was observed in all 3 donor hepatocyte cultures treated with tivozanib hydrochloride, the induction was considerably lower than that observed with the positive control, rifampicin. Additionally, as mentioned above, no induction of CYP3A activity was found for any donor. Thus, in vivo DDIs resulting from the induction of CYP1A, CYP2B6, CYP2C9, CYP2C19, and CYP3A enzyme activities by tivozanib hydrochloride are unlikely.

Substantial decreases in enzyme activities were observed with CYP1A and CYP3A at supra-therapeutic concentrations of 5 µM (equivalent to approximately 2274 ng/mL tivozanib hydrochloride which is ~20 times higher than levels found in human serum at steady state) tivozanib hydrochloride for all 3 donors. However, these decreases were not observed consistently at 0.1 or 0.5 µM and thus were not considered clinically relevant. Overall, the results indicate that clinical in vivo DDIs resulting from the induction of CYP1A, CYP2B6, CYP2C9, CYP2C19, and CYP3A enzyme activities are unlikely to occur at tivozanib hydrochloride concentrations achievable in human subjects.

Excretion

The in vivo excretion of tivozanib hydrochloride was investigated as follows: the excretion of [^{14}C]-tivozanib hydrochloride into the urine, faeces, and expired air of rats; the biliary excretion of [^{14}C]-tivozanib hydrochloride in rats; the excretion of [^{14}C]-tivozanib hydrochloride into the urine and faeces of monkeys.

After oral administration, a mean of 87.8 and 1.70% of the total radioactivity dosed was recovered in faeces and urine, respectively, by 72 hours post-dose, suggesting that most of the test article was excreted during this period. Similar results were observed after IV administration, suggesting the principal route of tivozanib hydrochloride excretion is faecal excretion through bile. At the end of the collection period (168 hours post-dose), a mean total of 95.7 and 93.9% of the dose was recovered in urine, faeces, cage wash, expired air and carcass after oral and IV administration, respectively. Total recoveries after both routes of administration were generally good, indicating that no [^{14}C]-tivozanib hydrochloride was being retained in rats.

Additional evaluations of the 24-hour urine and faecal excretion of [^{14}C]-tivozanib hydrochloride were conducted in rats as part of Study 8255110. Two male bile duct-intact Sprague-Dawley rats were orally dosed with 5 mg/kg (~200 µCi/kg) [^{14}C]-tivozanib hydrochloride (suspended in 0.5% MC). Within 24 hours post-dose an average of 1.26 and 53.7% of the administered dose was eliminated in the urine and faeces, respectively. Therefore, the bile represents a significant route of excretion of drug-derived material in the rat and another non-biliary route of excretion of tivozanib hydrochloride and/or its metabolites from the systemic circulation into the gastrointestinal tract exists.

Excretion of [^{14}C]-Tivozanib Hydrochloride into Urine and Feces of Monkeys (Study 8255111)

A single oral dose of 3 mg/kg (~60 µCi/kg) [^{14}C]-tivozanib hydrochloride (suspended in 0.5% MC) was administered to 2 male cynomolgus monkeys. The amount of radioactivity that was excreted in the urine and faeces within 24 hours was then determined by liquid scintillation. Within 24 hours post-dose, an average of 3.40 and 27.4% was eliminated in the urine and faeces, respectively

Potential for Serum-Protein-Binding Interactions between [^{14}C]-Tivozanib Hydrochloride and Warfarin (Study 8236152)

Because of the high serum protein binding properties of tivozanib hydrochloride, an in vitro study was conducted to evaluate the potential interactions between [^{14}C]-tivozanib hydrochloride and warfarin in human serum. This study also addressed overall protein binding and the specific proteins tivozanib hydrochloride binds in serum.

The in vitro binding of 3H-warfarin to human serum in the absence or presence of 6 concentrations (0, 0.1, 0.3, 1, 3, and 5 µM) of tivozanib hydrochloride was 98.0, 98.0, 98.1, 98.1, 98.1, and 98.1%, respectively.

The mean protein binding of [^{14}C]-tivozanib hydrochloride to human serum was 100, 99.9, 100, and 100% at 0, 1, 3, and 6 µM warfarin, respectively. These data show that the binding of tivozanib hydrochloride was independent of the concentration of warfarin over the evaluated range.

These data show that the binding of warfarin was independent of the concentration of tivozanib hydrochloride over the concentration range evaluated. Overall, these data indicate that protein binding interactions between tivozanib hydrochloride and warfarin are unlikely.

2.3.4. Toxicology

Single dose toxicity

Key Findings After a Single Oral or IV Administration of Tivozanib Hydrochloride (Studies RZZ1011, RZZ1010, RZZ1009, and RZZ1008)

	Dosing Regimen and Route	Approximate Lethal Dose (mg/kg)	MTD or MFD (mg/kg)	Notable Findings in the Main Study Animals
Mice	Single Oral Gavage	750	524	At 524 mg/kg, a slight reduction in body weight gain, transient decreases in WBC and lymphocyte counts and increases in ALT, AST, and ALP were noted; therefore, the MTD is considered to be between 524 and 750 mg/kg.
	Single IV Bolus	> 30	30	On Day 4, reticulocyte counts were decreased in tivozanib hydrochloride males and to a lesser extent in females (resolved by Day 15). No toxicologically significant clinical chemistry, clinical observations, or necropsy findings were noted. Under the conditions of this study, 30 mg/kg was well tolerated.
Rats	Single Oral Gavage	369	276	Clinical signs, body weight loss or reduced body weight gains were noted in tivozanib hydrochloride treated animals. Transient increased reticulocyte and neutrophil counts and reduced WBC and lymphocyte counts were noted after tivozanib hydrochloride. PT was extended in all animals. ALT and AST were increased after treatment. Urinalysis showed increased urine urobilinogen. All hematology, clinical chemistry, and urinalysis changes resolved. No significant necropsy findings were noted. Under the conditions of this study, the MTD was considered to be 276 mg/kg.
	Single IV Bolus	> 30	30	Limited observations of subdued behavior, agitation, and abnormal gait that resolved within 15 minutes were noted. No change in body weights. Transient increases were noted in RBC parameters; transient reduction in neutrophils, reticulocyte and platelet counts; transient increases in ALT, AST, cholesterol, phospholipids, and serum iron; and reduced unsaturated iron binding capacity. Urinalysis showed decreased osmolality. These changes resolved by the end of the observation period. Under the conditions of this study, 30 mg/kg was well tolerated.

There were 4 single-dose toxicity studies, 2 in mice and 2 in rats. The oral MTD in mice was considered to be 524 mg/kg, with doses ≥ 750 mg/kg producing severe adverse clinical effects resulting in early sacrifice. The oral MTD in rats was considered to be 276 mg/kg; lethality and/or severe adverse clinical signs were noted at doses of ≥ 369 mg/kg.

The tolerability of a single IV administration of 30 mg/kg tivozanib hydrochloride (the maximal feasible dose [MFD] for this formulation) was also assessed in mice and rats. Only mild adverse clinical observations were noted, and it was concluded that a single IV dose of 30 mg/kg tivozanib hydrochloride was well tolerated in both mice and rats.

Repeat dose toxicity

Table 6 Summary table of Non-Pivotal Studies

Repeat-Dose Toxicity			Non-Pivotal Studies			Test Article: Tivozanib hydrochloride		
Species/ Strain	Method of Administration (Vehicle/ Formulation)	Lot No.	Duration of Dosing	Doses (mg/kg/day)	Total No. of Animals Gender and No. Per Group	NOAEL (mg/kg/ day)	Noteworthy Findings	Study Number
Sprague-Dawley rat	Tivozanib hydrochloridea oral gavage (0.5% MC)	CDM-001	1 week	Phase 1: 0, 0.1, 0.7, 5.0 Phase 2: 0.1, 5.0	80 animals Main study 4M/ 4F TK studyb 12M/ 12F	NA	Dosing at 0.7 and 5.0 mg/kg associated with abnormal clinical signs, reduced weight gain or weight loss, and reduction in food consumption. Dosing at 0.1 mg/kg resulted in modest effect on weight gain in both sexes and slight effect on food consumption in males. Doses of 0.01, 0.03, 0.1, and 0.3 mg/kg chosen for the 4-week study (RZZ1013).	RZZ1012
Sprague-Dawley rat	Tivozanib hydrochloridea oral gavage (0.5% MC)	CDM-001	4 weeks	0, 0.01, 0.03, 0.1, 0.3	460 animals Main study 0, 0.01, 0.03, 0.1, 0.3: 10M/10F Recovery 0, 0.1, 0.3 5M/5F TK studyb 40 M/40 F	0.1	Administration of 0.3 mg/kg resulted in abnormal clinical signs, reduction in food consumption, body weights, and organ weights, and increases in ALT, AST, and NEFA. Abnormalities in incisor teeth, growth plate hypertrophy, acinar cell hypertrophy (exocrine pancreas), and hyperkeratosis (non-glandular stomach). All findings resolved or showed signs of ongoing reversal by end of recovery. Administration of 0.1 mg/kg resulted in no histopathological changes. Changes in hematology and/or clinical chemistry were considered too small to be toxicologically significant.	RZZ1013
Cynomolgus monkey	Tivozanib hydrochloridea oral gavage (0.5% MC)	CDM-001	Phase 1: 6 weeks Phase 2: 2 weeks	Phase 1: 0.025 to 3.0 Phase 2: 1.5	4 animals Phase 1: 1M/ 1F Phase 2: 1M/ 1F	NA	Some effects observed in body weight, hematology parameters, blood chemistry, and urinalysis; however none of these changes were consistent or dose-related. 1.5 mg/kg considered to be the MTD due to weight loss. Dose level of 1.0 mg/kg selected for 4 week study.	RZZ1014

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Lot No.	Duration of Dosing	Doses (mg/kg/day)	Total No. of Animals Gender and No. Per Group	NOAEL (mg/kg/ day)	Noteworthy Findings	Study Number
Cynomolgus monkey	Tivozanib hydrochloridea oral gavage (0.5% MC)	CDM-001	4 weeks	0, 0.1, 0.23-0.3c, 1.0/0.358c	32 animals Main study 0, 0.1, 0.23-0.3, 1.0/0.358 3M/3F Recovery 0: 2M/1F 1.0/0.36: 2M/2F	0.23-0.3	1.0 mg/kg dose was reduced to 0.36 mg/kg based on deterioration of overall clinical condition. 1.0/0.36 mg/kg was associated with abnormal clinical signs, loss of bodyweight, lower organ weights, and hematological changes. One male showed several focal, pale lesions medial to optic disc however the relation to treatment is unclear. At 1.0/0.36 mg/kg and 0.23 to 0.3 mg/kg, growth-plate hypertrophy observed.	RZZ1015

Under the conditions of a 13-Week Oral Toxicity Study in Rats with a 5-Week Recovery (Study 6691-158), the NOAEL in rats, based upon body weight effects in females, was 0.01 mg/kg. Based upon gross pathology findings, the NOAEL in rats was 0.03 mg/kg. In doses above the NOAEL (0.1, 0.3, and 1.0 mg/kg) the clinical conditions of rats generally improved during the recovery period. Some tivozanib hydrochloride-related effects persisted through the end of the recovery period; however, they appeared to be resolving. Conversely, in the 1.0 mg/kg dose group the microscopic findings in the kidney were more severe in the recovery-1 group (2 weeks after treatment) than at terminal sacrifice.

In a 26-Week Oral Toxicity Study in Rats With a 6-Week Recovery (Study 1458-005) at the top dose (0.08 mg/kg), the haematological effects noted in both males and females were slight and resolved during the recovery phase. The body weight effect in females at 0.08 mg/kg that was observed during the last 9 weeks of treatment was considered to be treatment-related but not an adverse effect because the magnitude was small. Thus, the NOAEL was the top dose of 0.08 mg/kg, which corresponded to Week 26 mean $AUC_{0\text{-}24hr}$ of 3935 ng·hr/mL.

Under the conditions of a 13-Week Oral Toxicity Study in Cynomolgus Monkeys With a 5-Week Recovery (Study 6691-159), the NOAEL after 13 weeks of treatment in cynomolgus monkeys was determined to be 0.1 mg/kg. This dose was correlated with $AUC_{0\text{-}24hr}$ values on Day 91 (Week 13) of 619 and 703 ng·hr/mL in males and females, respectively. Findings at 1.0 mg/kg group after at least 2 weeks of recovery and at 0.1 and 0.3 mg/kg after at least 5 weeks of recovery indicate reversal or abatement of tivozanib hydrochloride-related changes.

In a 39-Week Oral Toxicity Study (1458-006) in Cynomolgus Monkeys With a 6-Week Recovery tivozanib hydrochloride was well tolerated when administered daily to both male and female cynomolgus monkeys at all dose levels evaluated. The NOAEL was 0.1 mg/kg, the highest dose level administered. This dose correlated with AUC0-24hr values on Day 273 (Week 39) of 905 and 651 ng·hr/mL in males and females, respectively. In this study there were no treatment related adverse effects reported, not even on body weights. At the NOAEL the systemic exposure of the test animals was only 0.5 times that of clinical exposure at steady state.

Genotoxicity

In an Ames Mutation Assay, tivozanib hydrochloride (with and without S-9 mix) was tested against the required bacterial strains at 5 dose levels over a concentration range of 0.32 to 5000 µg/plate. Tivozanib hydrochloride showed no mutagenic potential in the bacterial reverse mutation assay under the conditions of this test.

An in Vitro Chromosomal Aberration Assay in CHO Cells (Study RCK0002) was considered unreliable as the test material was very toxic to the cells in this treatment, and it appears that it may have caused cells to undergo abnormal cell division leading to diploid cells and hyperdiploid cells (cells with greater than the normal diploid count but not polyploidy). No induction of endoreduplication occurred.

An in Vivo Mouse Micronucleus Cytogenetic Assay in CHO Cells (Study RCK0003) showed no evidence of clastogenicity or aneugenicity after oral (gavage) administration of tivozanib hydrochloride up to the MTDs of 320 and 200 mg/kg for males and females, respectively.

Carcinogenicity

No carcinogenicity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

The maternal and paternal NOAEL of tivozanib hydrochloride in rats for fertility and general reproduction was determined to be 0.1 mg/kg (Study 311-007). Based upon a calculated human equivalent dose, 0.1 mg/kg is 0.7-fold the recommended clinical dose. In the pilot study, doses ≥ 0.3 mg/kg in male and female rats produced mortality, adverse clinical and necropsy observations, and reduced body weights and feed consumption. In male rats these doses caused increased epididymis and testis weights and infertility. In the embryo foetal study in rats, the maternal NOAEL was determined to be 0.01 mg/kg. Based upon a calculated human equivalent dose, 0.01 mg/kg is 0.07-fold the recommended clinical dose. Doses ≥ 0.03 mg/kg resulted in increased incidences of early and late foetal resorptions, reduced foetal body weight, and gross external and skeletal malformations (0.03 mg/kg is approximately 5-fold lower than the recommended clinical dose); therefore, the developmental NOAEL was determined to be 0.01 mg/kg (Studies 311-005P and 311-005). In the pilot study, presumed pregnant dams dosed with ≥ 0.3 mg/kg tivozanib hydrochloride produced no live foetuses.

In an embryo foetal developmental study in rabbits, the maternal and developmental no observed effect level (NOEL) of tivozanib hydrochloride was > 1.0 mg/kg because no maternally toxic effects were noted at that dose (Study 311-006). This dose was associated with an AUC_{0-24hr} on Day 18 of 1050 ng·hr/mL. This exposure level is approximately 0.6-fold the exposure levels observed in subjects with RCC ($AUC_{0-t,ss}$ 1641 ng·hr/mL; Study AV-951-07-201).

Toxicokinetic data

Table 7: Overview of GLP Toxicokinetic Data - AUC_{0-24hr} (ng·hr/mL)

Daily Dose	Male	Female	Study Duration
26-Week Oral Toxicity Study Conducted in Rat			
0.005 mg/kg	Day 1: 103 Week 13:266 Week 26: 247	Day 1: 105 Week 13: 262 Week 26: 259	26 weeks (oral)
0.02 mg/kg	Day 1: 371 Week 13:787 Week 26: 852	Day 1: 422 Week 13: 957 Week 26: 895	
0.08 mg/kg	Day 1: 1830 Week 13: 3340 Week 26: 3700	Day 1: 1720 Week 13: 3880 Week 26: 4170	
Embryofetal Development Toxicity Study Conducted in Rabbitb			
0.01 mg/kg	-	GD 6: 139 GD 18: 6.39	13 days (oral) (GD 6 to 18)
0.1 mg/kg	-	GD 6: 135 GD 18: 170	
1.0 mg/kg	-	GD 6: 1150 GD 18: 1050	
13-Week Oral Toxicity Study Conducted in Cynomolgus Monkey			
0.01 mg/kg	Day 1: 30.0 Week 4: 60.1 Week 13: 86.9	Day 1: 25.2 Week 4: 70.0 Week 13: 85.6	13 weeks (oral)
0.03 mg/kg	Day 1: 77.0 Week 4: 102 Week 13: 146	Day 1: 83.7 Week 4: 106 Week 13: 155	
0.1 mg/kg	Day 1: 274 Week 4: 678 Week 13: 619	Day 1: 436 Week 4: 908 Week 13: 703	
0.3 mg/kg	Day 1: 833 Week 4: 1632 Week 13: 2105	Day 1: 929 Week 4: 1430 Week 13: 1563	
1.0 mg/kg	Day 1: 3500 Week 4: 4320	Day 1: 3525 Week 4: 3933	4 weeks (oral)
39-Week Oral Toxicity Study Conducted in Cynomolgus Monkey			
0.01 mg/kg	Day 1: 59.2 Week 13: 60.2 Week 39: 69.4	Day 1: 59.0 Week 13: 64.6 Week 39: 66.3	39 weeks (oral)

Exposures ($AUC_{0\text{-}24hr}$) obtained at the NOAEL in the 26-week rat study (3935 ng·hr/mL for a dose of 0.08 mg/kg at Day 182) were approximately 2-fold over the steady state exposure measured in RCC patients administered 1.5 mg/day tivozanib hydrochloride (equivalent to 1340 micrograms/day tivozanib free base) in the Phase 2 study ($AUC_{0\text{-}24hrs}$ at steady state 164 ng·hr/m). In monkeys, a dose of 0.1 mg/kg, the

NOAEL from the 39-week study resulted in an exposure of 764 ng·hr/mL at Day 273, which is 0.5-fold the exposures observed in humans at steady state.

Local Tolerance

A standard local irritation study in rabbits via IV, subcutaneous, and/or intramuscular injection was not performed. The intended route of administration of tivozanib hydrochloride is oral.

Other toxicity studies

Potential impurities in tivozanib hydrochloride drug substance were evaluated for genotoxic potential in a structural-activity risk assessment, and those with a positive structural alert were then assessed in Ames assays. Of those compounds with a structural alert that were relevant for the drug substance synthesis, Ames assays suggested genotoxic potential for DPQ, QC, ACP, MD, and 5-AMI. The level of QC, ACP, MD, and 5-AMI in the drug substance are lower than 1.5 µg/day, which is the level considered acceptable in ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. The proposed specification for DPQ is ≤ 0.25% in the drug substance and ≤ 0.35% in the drug product, which translates to ≤ 5.3 µg/day. (See Quality aspects).

2.3.5. Ecotoxicity / environmental risk assessment

Table 8: Summary of main study results

Substance (INN / Invented Name): Tivozanib			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …		Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.09 at 40° C <4.5 by HPLC	Inconclusive : log Kow to be performed using an acceptable method
	BCF		log Kow calculated by HPLC method, however in this case (log Kow ≥4) the slow stirring method (OECD 123) is preferred. The MAH is asked to perform a new log Kow calculation based on
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		

			the slow stirring method and covering the environmentally relevant pH-range.
PBT-statement :	Available data do not allow a definite conclusion on the potential risk of this substance to the environment.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.000281 based on a DOSEAI of 1.34 mg/inhabitant/day and a fraction market penetration of 0.00042	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate: not performed			

2.3.6. Discussion on non-clinical aspects

Primary pharmacology studies conducted at both molecular and cellular levels and in tumour models have demonstrated that tivozanib hydrochloride is a potent and highly selective inhibitor of the VEGF pathway that exerts strong anti-tumour activities in a broad spectrum of tumour types by blocking tumour angiogenesis.

No secondary pharmacodynamic and pharmacodynamic drug interaction studies were performed by the applicant, which is considered acceptable, considering the high level of selectivity of tivozanib hydrochloride for the VEGF pathway.

Safety pharmacology findings demonstrated an increase in blood pressure (see discussion on Clinical Safety).

The pharmacokinetics, toxicokinetics, distribution, metabolism, excretion of tivozanib hydrochloride and the potential for drug-drug interactions (DDIs) with tivozanib hydrochloride were characterized after oral administration in several animal models including nude mice, nude rats, Sprague-Dawley rats and cynomolgus monkeys. Intravenous (IV) administration was also evaluated in Sprague-Dawley rats.

Oral PK and toxicokinetic parameters were approximately dose-linear in all species (mice, rats, rabbits, and cynomolgus monkeys) with the systemic exposure in terms of C_{max} and AUC increasing in an approximately dose-proportional manner. However, the rate of absorption was species dependent, ranging from 2.0 to 4.0 hours in rats, 1.8 to 8.0 hours in monkeys and from 0.5 to 1 hour in mice. These differences in exposure are probably driven by the differences in clearance among the species and correlate with the observed differences in $t_{1/2}$ across species.

Tivozanib hydrochloride was highly bound to proteins in the plasma of all species tested (97.6% in monkeys and > 99% in rats and humans), and bindings were independent of concentration and sex. In

humans, protein binding was high (> 99%) in both plasma and serum. Binding was predominantly to albumin, with low binding to α1-acid glycoprotein (AAG). Tivozanib hydrochloride had an extensive distribution throughout the tissues investigated; however, organ levels were low, with tissue/blood ratios of less than unity in most tissues. The lowest concentrations were detected in the brain and spinal cord. In the pigmented rats, melanin binding to the choroid layer of the eye was apparent with a longer elimination $t_{1/2}$ of radioactivity than all other tissues; however, the amount of radioactivity bound to melanin steadily decreased after 120 hours post-dose.

Tivozanib hydrochloride was metabolised by only 2 complementary deoxyribonucleic acid (cDNA)-derived cytochrome P450 (CYP) isoforms, CYP1A1 and CYP3A4, and the formation of the predominant metabolite, a desmethyl glucuronide metabolite (M14) was mediated by multiple cDNA-expressed human uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9 and UGT1A10. *In vivo*, the metabolic profiles in serum, urine, and faeces were similar in rats and monkeys. After a single oral dose of [^{14}C]-tivozanib hydrochloride in rats and monkeys, unchanged tivozanib hydrochloride was the major circulating component, representing approximately 91 and 78% of the total radioactivity exposure in serum, respectively, along with metabolites M4 (mono-oxidation) and M5 (N-oxide of tivozanib hydrochloride) co-eluting in both species.

In vitro studies with tivozanib indicate that it is not a CYP enzyme inducer. *In vitro* studies conducted in human liver microsomes and hepatocytes evaluating the activity of CYP1A2, CYP2B6, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 suggested that tivozanib is a weak inhibitor of CYP2B6 and CYP2C8. Based on the *in vitro* IC_{50} and *in vivo* unbound C_{max}, tivozanib was unlikely to interact in a clinically relevant manner with active substances that are metabolised by these enzyme pathways (see SmPC section 4.5). Studies conducted *in vitro* have shown that tivozanib is not a potent inhibitor of UGT metabolic activities and clinically relevant drug-drug interactions are unlikely with medicinal products metabolised by these pathways. *In vitro* studies have shown that tivozanib is neither a substrate nor inhibitor of the multidrug efflux pump, P-glycoprotein.

Tivozanib hydrochloride was not a clinically relevant inhibitor of CYPs 1A2, 2A6, 2C9, 2C19, 2D6, and 3A4 (including mechanism-based inhibition) and not an inhibitor of human liver UGTs. These data suggest that tivozanib hydrochloride has minimal potential to cause a DDI by inhibiting the metabolism of a co-administered agent that is a CYP or UGT substrate. *In vitro*, the inhibition of tivozanib hydrochloride metabolism by the potent CYP3A4 inhibitor ketoconazole and the CYP3A4 substrates temsirolimus and everolimus was limited, indicating a low likelihood of a DDI with these agents. Tivozanib hydrochloride did not elicit substantial increases in CYP1A, CYP2B6, CYP2C9, CYP2C19, or CYP3A enzyme activities with the increases in all enzyme activities below 40% compared with the induction by prototypical inducers. These results indicate that clinical DDIs resulting from the induction of CYP enzyme activities by tivozanib hydrochloride are unlikely to occur at concentrations of tivozanib achievable in human subjects.

Tivozanib hydrochloride inhibits the transporter protein BCRP *in vitro*, at concentrations that are likely to restrict the effect to intestinal BCRP activity *in vivo*. Tivozanib hydrochloride was not an inhibitor of transport proteins OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K and BSEP. Tivozanib hydrochloride was not a substrate or inhibitor of P-glycoprotein (P-gp) at clinically relevant concentrations of 0.1 to 0.5 µM. Thus, tivozanib hydrochloride is not expected to be at great risk of clinical DDIs when coadministered with substrates or inhibitors of P-gp. The potential for tivozanib to be a substrate of transporters other than P-glycoprotein has not been studied. The applicant should perform the evaluation of tivozanib as a substrate of OCT1, OATP1B1, OATP1B3, P-gp, BCRP, BSEP and MRP2 as a post-authorisation measure (see RMP).

Excretion studies indicate that the principal route of elimination is faecal excretion. Biliary excretion is a significant route of excretion but another non-biliary route of excretion of tivozanib hydrochloride and its metabolites from the systemic circulation into the gastrointestinal tract also exists.

When considering the toxicological profile of tivozanib hydrochloride identified over repeat-toxicity studies, sustained treatment with tivozanib hydrochloride resulted in treatment-related effects on the teeth, and bones and cardiovascular, adrenal, renal, gastrointestinal, and reproductive systems. Haematological and clinical chemistry alterations were also noted after exposure to tivozanib hydrochloride and appear to be reversible. No clinically meaningful changes were observed in electrocardiogram (ECG) parameters in the cynomolgus monkey repeat-dose studies. The lack of QT and QTc changes are consistent with findings in the *in vitro* study indicating that tivozanib hydrochloride does not inhibit the hERG channel.

In rodents, mortality or moribundity were attributed to decreases in body weight and food consumption that were possibly related to the toxicities noted in teeth which included thinner, brittle, discoloured or maloccluded teeth, and tooth loss. Similar reductions in body weight and food consumption were observed in the 13-week study and the 26-week study; however, the findings in the 26-week study were less severe because of the lower dose levels used. Corresponding to the clinical observations of tooth toxicities observed in rats, histopathological evidence of dentin degeneration and dysplasia were also observed and may have been a result of disruption of dentin formation, which also relies on angiogenesis. The observed effects on teeth are believed to only affect growing teeth, a process which is continuous throughout the entire lifespan of the rat. The effect on incisors in rats is unlikely to be relevant to human adults. In contrast, in cynomolgus monkeys, which do not have continuous tooth growth, no tooth effects were noted; however, oral lesions were observed; these lesions may have contributed to the body weight loss observed at high dose levels.

The NOAEL exposures ($AUC_{0\text{-}24hr}$) obtained in the pivotal toxicology studies were 3935 ng·hr/mL (0.08 mg/kg dose at Day 182) and 764 ng·hr/mL (0.1 mg/kg dose at Day 273). The mean exposure obtained in subjects with RCC administered 1.5 mg/day tivozanib hydrochloride (equivalent to 1340 microgram/day tivozanib) in a Phase 2 study was 1641 ng·hr/mL ($AUC_{0\text{-}t,ss}$; Study AV-951-07-201). This exposure corresponds approximately to an exposure in humans that is 2-fold below the exposure obtain at the NOAEL in the 6-month rat study and is greater than the exposure observed at the NOAEL in the 9-month monkey study (the exposure in monkeys was approximately 0.5-fold that of RCC patients).

In the 4-week and 13-week repeat-dose studies in rats and cynomolgus monkeys, growth plate hypertrophy of the femur and tibia were observed in males and females at dose levels ranging from 0.1 to 1.0 mg/kg. This finding was not observed after the recovery period. Growth plate hypertrophy was not observed in the 26-week rat study, likely because of the lower dose levels used in this study. In monkeys, the growth plate effects were noted at doses ≥ 0.3 mg/kg, which corresponded to an $AUC_{0\text{-}24hr}$ of 1531 ng·hr/mL (Study 6691-159), systemic exposure approximately equivalent to the exposures observed at steady state in the Phase 2 study in subjects with RCC (AUC during the dosing interval at steady state [$AUC_{0\text{-}t,ss}$] 1641 ng·hr/mL). The mechanism of this change is likely a result of disruption of the normal ossification of the growth plate. This process relies on VEGF-dependent capillaries, which invade the growth plate, initiating calcification, bone production and bone resorption. The principal reason for the thickening of the growth plate is the accumulation of hypertrophic chondrocytes. This finding is likely to be of reduced relevance in post-pubescent humans, for whom fusion of the epiphysis and diaphysis has already occurred.

Adrenal cortical changes were noted in both rats and cynomolgus monkeys after 13 weeks of dosing over a dose range of 0.1 to 1.0 mg/kg. These changes included degeneration, necrosis and congestion/haemorrhage. In cynomolgus monkeys the adrenal findings were observed at doses ≥ 0.5-fold the human exposure levels observed in subjects with RCC (mean $AUC_{0\text{-}t,ss}$ 1641 ng·hr/mL; Study AV-951-07-201). The safety margin is considered low and special attention should be given to these alterations.

Kidney changes, including glomerulopathy and chronic nephropathy, were observed in rats after 13 weeks of dosing at doses ≥ 0.3 mg/kg (Study 6691-158). Based upon a calculated human equivalent dose, 0.3 mg/kg is 2-fold the recommended clinical dose. Increases in urinary albumin, urobilinogen and other proteins were also noted. The kidney lesions in the 1.0 mg/kg were more severe at the recovery than at terminal sacrifice and were observed at 2- to 7-fold the approximate human equivalent dose. Similar kidney lesions were not observed in cynomolgus monkeys. In the SmPC sections 4.2 and 5.2 caution is advised with tivozanib use in patients with severe renal impairment as clinical experience is limited.

In the gastrointestinal system, occasional macroscopic or microscopic findings were observed, including congestion and hyperplasia/metaplasia of the fundic epithelium in rats dosed with ≥ 0.3 mg/kg for 13 weeks (Study 6691-158). This was observed in rats and cynomolgus monkeys with severity and frequency increasing in a dose- and duration-responsive manner. The adverse clinical observations and histopathological findings reversed after cessation of treatment.

Although they were considered not primary toxicities associated with tivozanib hydrochloride, liver and bile duct inflammation and biliary hypertrophy/hyperplasia were noted after sustained tivozanib hydrochloride administration in rats administered ≥ 0.3 mg/kg for 13 weeks. Elevations in ALT and AST were observed in rats. Pronounced changes considered secondary to bile duct inflammation occurred in the pancreas (atrophy) and duodenum (transmural and mucosal hypertrophy).

The mechanism of the adrenal, renal and gastrointestinal toxicities is unknown; however, similar changes have been observed with other VEGF inhibitors such as sunitinib and pazopanib (CDER, 2009; Hamberg et al, 2010; Patyna et al, 2008). It is likely that the adrenal, renal and gastrointestinal toxicities noted in nonclinical models after tivozanib hydrochloride administration are a result of the VEGF dependence of the normal microvasculature in these organ systems; however, the impact of these changes at clinically relevant dose levels has minimal impact on the overall health of the animal.

Tivozanib hydrochloride did not produce genotoxic, mutagenic or clastogenic effects in any of the systems tested. As it is intended for advanced Renal Cell Carcinoma, in accordance with ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, carcinogenicity studies are not required.

In repeat-dose toxicity studies in rats, abnormalities were noted in growing incisors (thin brittle teeth, tooth loss, malocclusions) at doses approximately 2-fold greater than the calculated human equivalent dose and growth plate hypertrophy was observed at doses approximately 0.7- to 7-fold greater than the calculated human equivalent dose. Tivozanib was shown to cause growth plate hypertrophy, absence of active corpora lutea and no maturing follicles in cynomolgus monkeys at dose levels that produced exposures equivalent to those seen at the recommended clinical dose.

In studies assessing mating and fertility parameters in male rats, doses > 2-fold higher than the recommended clinical dose, produced increased epididymis and testis weights associated with infertility. Increased testis weights were observed at a dose 7-fold higher than the recommended clinical dose.

In female rats, an increase in non-viable foetuses was noted at a dose 0.7-fold the recommended clinical dose, while dose levels ≥ 2 fold the recommended clinical dose resulted in infertility (see SmPC section 5.3).

Tivozanib was shown to be teratogenic, embryotoxic and foetotoxic in pregnant rats at dose levels 5 times lower than the recommended clinical dose (based on a 60 kg human). Studies in pregnant rabbits showed no effect on maternal health or embryo foetal development at doses approximately 0.6 times the human exposure at the recommended dose (see SmPC section 5.3).

The fertility and embryo foetal findings observed in rats are consistent with the intended pharmacology of VEGF inhibition (Hoeben et al, 2004; Josko et al, 2000). Vascular endothelial growth factor is a key

regulator of angiogenesis during embryogenesis and skeletal growth. A number of studies have indicated that angiogenesis is critical to placental and foetal development; therefore, the inhibition of angiogenesis after administration of VEGF inhibitors such as sunitinib and tivozanib hydrochloride would be expected to have adverse effects on pregnancy.

In conclusion, reproductive toxicity studies in rats showed that tivozanib hydrochloride affected fertility and foetal development in rats. Reproductive studies in rabbits showed no tivozanib hydrochloride-mediated effects at the highest dose tested. Because of these reproductive toxicity findings, tivozanib hydrochloride is not recommended in pregnant women (See SmPC section 4.6.).

The applicant performed an ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00). A PEC surface water (0.000281 mg/L) based on a DOSEAI of 1.34 mg /inhabitant day and a fraction market penetration of 0.00042 (orphan drug designation for renal carcinoma effects), resulted very low and did not trigger the action limit calculation. A log Kow value of 4.09 at 40ºC has also been calculated by HPLC and demonstrated to be below 4.5 (action limit for PBT screening); however these ERA data do not allow definite conclusions on the potential hazard of tivozanib to the environment. Thus, regarding the possible hazard impact of tivozanib (Log Kow 5.2 at pH 7.4) in the environment, the applicant is recommended to perform a stepwise assessment, taking into account results of the amount produced per year and /or the ready biodegradability test. In the event that the substance is not degraded, persistence in the water / sediment system study and bioaccumulation in fish should be performed. Depending on the results of both studies, a further toxicity study may be requested.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical aspects of tivozanib are sufficiently characterised and relevant information is included in the SmPC.

The CHMP considers the following measures necessary to address the non-clinical issues:

The Applicant should perform the evaluation of tivozanib as a substrate of OCT1, OATP1B1, OATP1B3, P-gp, BCRP, BSEP and MRP2. Based on the findings collected, a discussion on the need for further interaction studies should be provided along with the study reports.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular Overview of Clinical Pharmacology,

Study No	methods	Objective	treatment	population
Study AV-951-10-111	Phase 1 study	to investigate the absorption,	[14C]-tivozanib hydrochloride	healthy male volunteers.

Study No	methods	Objective	treatment	population
		metabolism, and excretion of tivozanib	single oral dose administration	
Study AV-951-10-112	An open-label cardiac safety study	to evaluate the electrocardiograms (ECG) and PK-ECG dynamics	of tivozanib hydrochloride	subjects with advanced solid tumors
Study AV-951-10-115	A Phase 1, single center, open-label, randomized, two-period crossover	food effect study	single doses of tivozanib hydrochloride	healthy volunteers
Study AV-951-11-116	Phase 1, open-label study	to evaluate the effect of ketoconazole on the PK, safety, and tolerability	a single dose of tivozanib hydrochloride	healthy volunteers
Study AV-951-11-117	Phase 1, open-label, two-period, single-sequence study	to evaluate the effect of rifampin on the PK, safety, and tolerability	single dose of tivozanib hydrochloride	healthy volunteers
Study AV-951-12-118	Phase 1, open-label, single dose study	to evaluate the pharmacokinetics, safety and tolerability	tivozanib	subjects with hepatic impairment and normal hepatic function
Study AV-951-09-109	Phase 1, open-label, single center, randomized, two-period crossover	bioequivalence study	single doses of tivozanib hydrochloride	healthy volunteers.
Study AV-951-03-B01	Phase 1 open-label, non-randomised	dose escalation	dose escalation tivozanib hydrochloride administered orally	subjects with solid tumours
Study AV-951-08-105	A Phase 1b/2a open-label study	PK, safety and activity	once daily oral administration of tivozanib hydrochloride	subjects with non-small cell lung cancer
Study AV-951-07-201	A Phase 2, placebo-controlled, randomized	discontinuation trial	tivozanib hydrochloride	in subjects with RCC

Study No	methods	Objective	treatment	population
Study AV-951-07-102	A Phase 1b, open-label, dose-finding study	Pk, safety of Combination Therapy	tivozanib hydrochloride in combination with temsirolimus	in subjects with metastatic RCC.
Study AV-951-07-103	Phase 1b, open-label,	dose-escalation	tivozanib hydrochloride plus mFOLFOX6	subjects with advanced colorectal cancer and other gastrointestinal cancers
Study AV-951-08-104	Phase 1b/2a, open-label multicenter study	PK	tivozanib hydrochloride in combination with paclitaxel	in subjects with advanced or metastatic breast cancer

- Tabular overview of clinical efficacy studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
AV-951-09-301	76 sites: N. America, Europe, India, Chile	Pivotal study: Phase 3, randomized, controlled, open-label study	Tivozanib[1] 1.5 mg QD Sorafenib 400 mg bid	To compare the PFS and OS of patients with advanced RCC randomized to treatment with tivozanib or sorafenib	Tivozanib: 260/151 (PD) Sorafenib: 257/171 (PD)	2 years	M=374 F=143 Median age = 59.0	Recurrent or metastatic RCC with clear cell component, and prior nephrectomy	PFS by IRR
AV-951-09-902	55 sites: N. America, Europe, India, Chile	Open-label extension study for patients completing the pivotal study	Tivozanib[1] 1.5 mg QD Sorafenib 400 mg bid	To allow continued access to randomized treatment (or tivozanib if progressed on sorafenib)	Previous tivozanib: 88 Previous sorafenib: 189	3 years	M=189 F=88 Median age 60	Recurrent or metastatic RCC	Safety and tolerability endpoints
AV-951-07-201	28 sites in Russia, Ukraine, India	Phase 2 randomized. Placebo-controlled, discontinuation study	Tivozanib[1] 1.5 mg QD	Determine safety of tivozanib with this dose schedule	274 enrolled; 272 dosed; 196 exposed for ≥ 16 weeks	28 weeks	M=191, F=81 Median age 56.0 years	Recurrent or metastatic RCC	Safety and tolerability endpoints
AV-951-10-202	21 sites in US and Canada	Phase 2, open-label, single arm study	Tivozanib[1] 1.5 mg QD	To evaluate biomarkers and their correlation with	105 enrolled and dosed	6 months	M=81 F=24 Median age 61 years	Locally recurrent or metastatic RCC.	% progression-free at 6 months

				clinical activity (not done)					
AV-951-09-901	31 sites in Russia, Ukraine, India and US	Open-label extension study (ongoing)	Tivozanib – same dose and regimen as parent protocol	To allow continued access to tivozanib for studies who have participated in other Phase 1 or 2 tivozanib protocols	87 (enrollment ongoing)	Long-term	M=43, F=44 Median age 60	RCC	Long-term safety and tolerability

2.4.2. Pharmacokinetics

Absorption

In study AV-951-10-115 all 30 enrolled healthy volunteers received at least one dose, and 29 completed the study. In this 2x2 crossover study, subjects received a single oral dose of 1.5 mg tivozanib hydrochloride (equivalent to 1340 microgram tivozanib) after a 10-hour fast or within 30 minutes after a high-fat meal. PK samples were collected predose and at 1, 3, 5, 7, 10, 12, 18, 24, 36, 48, 96, 168, 336, and 504 hours post-dose. The washout period was 6 weeks.

In 30 healthy volunteers after a single oral dose of tivozanib hydrochloride in the fasted state the following PK parameters were derived:

Table 9: Summary of PK parameters for tivozanib in the fasted state (study AV-951-10-115)

Parameter (Units)	Tivozanib (Free Base) Fasted Arithmetic Mean (STD)	N
AUC_{0-t} (ng·hr/mL)	2188 (647)	29
$AUC_{0-\infty}$ (ng·hr/mL)	2309 (745)	28[a]
C_{max} (ng/mL)	18.8 (5.50)	29
T_{max} (hr)[b]	3.00 (3.00, 96.0)	29
$t_{1/2}$ (hr)	121 (29.9)	28[a]
CL/F (L/hr)	0.640 (0.206)	28[a]
Vz/F (L)	107 (28.4)	28[a]

Source: Study AV-951-10-115, Table 14.2.1-2a and Table 14.2.1-2b.

[a] $t_{1/2}$ of subject 20 could not be estimated due to no distinct terminal elimination phase, so other related PK parameters such as $AUC_{0-\infty}$, CL/F, and Vz/F could not be calculated.

[b] Median (min, max) presented for T_{max}.

AUC_{0-t} = area under the concentration-time curve from zero to last measurable time point t; $AUC_{0-\infty}$ = area under the concentration-time curve from zero to infinity; CL/F = apparent oral clearance; C_{max} = maximum concentration; STD = standard deviation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to reach maximum concentration; Vz/F = apparent oral volume of distribution.

Following oral administration of tivozanib, peak serum levels are achieved after approximately 2 to 24 hours. After a single 1340 microgram dose, mean C_{max} was 10.2 to 25.2 ng/mL across healthy subject and patient studies. Single dose AUC_{0-inf} for healthy volunteers dosed with 1340 microgram tivozanib was 1,950 to 2,491 ng.hr/mL. After once daily dosing of 1340 microgram tivozanib for 21 or 28 days in RCC patients, C_{max} was 67.5 to 94.3 ng/mL and AUC_{0-24} was 1,180 to 1,641 ng.hr/mL. Exposure is dose proportional between 890 and 1340 microgram and dose-related over the wider range of 450 mg and 1790 microgram. Accumulation at steady-state is approximately 6- to 7-fold the exposure observed at

single-dose levels. Clearance is similar between acute and chronic dosing indicating no time-dependent changes in PK. (See SmPC section 5.2.)

Food effect study (AV-951-10-115)

The effect of food on the PK of tivozanib hydrochloride was investigated in study AV-951-10-115. Food delayed absorption, with median T_{max} of 3.0 hours and 24.0 hours in the fasted and fed state respectively. Multiple peaks were observed during the first 48 hours after dosing. In the fed state, there was a mean decrease of 23.4% for C_{max}, but AUC_{0-t} and $AUC_{0-\infty}$ were comparable for fasted and fed states, as were CL/F and V_Z/F.

Table 10: Statistical Analysis for Pharmacokinetic Parameter Data (Study AV-951-10-115)

Parameter (units)	LS Mean[a] N[d]	Test (Fed)	LS Mean[a] N[d]	Reference (Fasted)	Test/ Reference[b] (%)	(90% CI)[c]
C_{max} (ng/mL)	30	14.1	29	18.2	77.5	(72.9, 82.4)
AUC_{0-t} (ng·hr/mL)	30	2218	29	2111	105.1	(99.8, 110.6)
$AUC_{0-\infty}$ (ng·hr/mL)	29	2372	28	2209	107.4	(102.8, 112.3)

Source: Study AV-951-10-115, Table 14.2.2.

[a] Least squares means from ANOVA, calculated by transforming the natural log means back to the linear scale (ie, geometric means).

[b] Ratio of parameter means (expressed as a percent), transformed back to the linear scale.

[c] 90% CI for ratio of parameter means (expressed as a percent), transformed back to the linear scale.

[d] N is the number of observations in each treatment used in the model.

ANOVA = analysis of variance; AUC_{0-t} = area under the concentration-time curve from zero to last measurable time point t; $AUC_{0-\infty}$ = area under the concentration-time curve from zero to infinity; CI = confidence interval; C_{max} = maximum concentration; LS = least squares.

Distribution

In an *in vitro* human protein binding study (8236-152), [^{14}C]-tivozanib hydrochloride primarily partitioned into the plasma/serum component of blood. Protein binding was high (>99%), with no concentration dependence over the range 0.1 to 5 µM tivozanib hydrochloride. Albumin, rather than α-1-glycoprotein, is the major tivozanib hydrochloride binding component in human plasma.

In an *in vitro* P-glycoprotein substrate inhibition study (8231062), the permeability of [^{14}C]-tivozanib hydrochloride (0.1, 0.5 and 5 µM) was shown to be low in a Caco-2 permeability assay.

The volume of distribution (Vz/F) after administration of the final formulation is about 100 L which has been confirmed by the PopPK outcomes (125 L with a 95%CI of 120-131 L). According to the PopPK analysis, volume of distribution (Vd) was found to increase nearly proportionally with body weight.

Elimination

In fasted healthy volunteers the mean half-life was 4.5 to 5.0 days (108 to 121 hours).

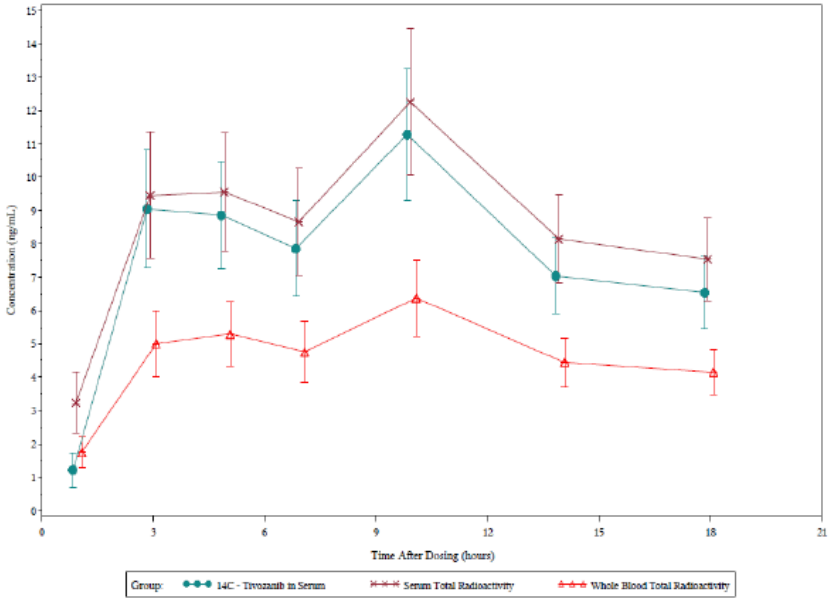
Absorption, metabolism and excretion study (AV-951-10-111)

The objective of this study was to determine the absorption and excretion kinetics (mass balance) of oral tivozanib hydrochloride and to characterise the metabolites present in serum, urine, and faeces in healthy male volunteers. After a 10 hour fast, 8 subjects were administered a single oral dose of 1.5 mg (160 µCi) of [^{14}C]-tivozanib hydrochloride. Blood samples for PK and radio-analysis were collected pre-dose and at

1, 3, 5, 7, 10, 14, 18, 24, 36, 48 and 72 hours postdose; and at 24 hours thereafter until study completion. For metabolite profiling and identification, samples were taken at predose, and at 7, 14, 24, 36, 48, 72, 96, 120, 192, 264, 360, 456, 552, and 648 hours postdose.

Seven subjects completed the study; one subject withdrew consent for personal reasons. Median T_{max} was 10.0 hours. Multiple peaks were observed within the first 48 hours after dosing. The mean half-life was 89.3 hours and 99.1 hours for [^{14}C]-tivozanib and total radioactivity in the serum, respectively. C_{max} and AUC values for [^{14}C]-tivozanib were approximately 93% and 80%, respectively, of those values for total radioactivity in serum. Across all subjects, the mean recovery of total radioactivity was 91.1%, with 11.8% recovered in urine (as metabolites only) and 79.3% recovered in faeces.

Figure 6: Mean (± STD) Concentration-Time Profiles for [14C]-Tivozanib (Free Base) in Serum and Total Radioactivity in Serum and Whole Blood (Study AV-951-10-111)



Source: Study AV-951-10-111, data on file. Available upon request.
Study Population: Full Analysis
Note: Concentration unit for total radioactivity in serum and whole blood is ng equiv/g
STD = standard deviation.

Unchanged tivozanib was the predominant circulating component, with a median of 90.1% of the total radioactivity. There were no major metabolites detected at exposure levels ≥10% of the total radioactivity exposure.

Unchanged tivozanib was not detected in urine. The predominant metabolites detected in urine were M29, M35 and M40, together representing 0.764% to 10.3% (median 4.5%) of the radioactive dose. Minor metabolites (M26, M27, M28 and M31) together represented 0.136% to 2.85% (median 1.48%) of the radioactive dose.

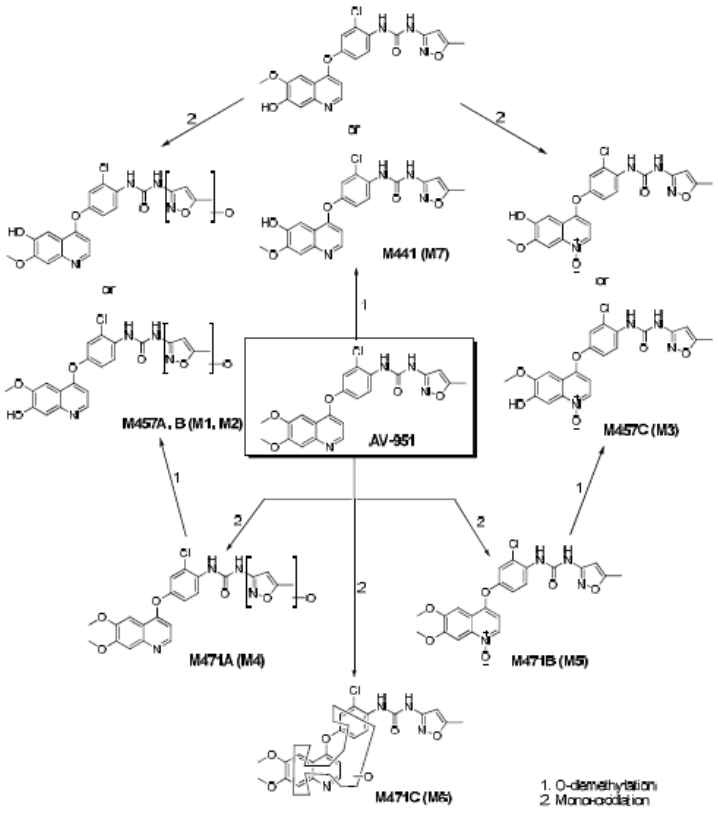
In faeces, the predominant radiolabelled components were unchanged tivozanib, and the metabolites M37, M42 and M7/M48 co-eluting. Unchanged drug represented 7.82% to 46.1% (median 26.2%) of the radioactive dose. The metabolites represented 6.35% to 34.3% (median 20.5%) of the radioactive dose.

Metabolism

An *in vitro* human metabolism study (DRZZ1027) investigated the metabolic profile of [^{14}C]-tivozanib hydrochloride in human liver microsomes. There was NADPH-dependent disappearance of the drug, with a total of 4 metabolites detected (peaks 1-4). Metabolite formation was also assessed in the presence of human cDNA-derived CYP450 enzymes (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C19, CYP2D6*1, CYP2E1, CYP3A4, CYP3A5 and CYP4A11). The only CYP450 isoforms capable of metabolising tivozanib hydrochloride were CYP1A1 (at 0.5 and 5.0 µM) and CYP3A4 (at 5.0 µM). Three metabolites generated in the presence of CYP3A4 were tentatively identified as peaks 1, 3 and 4. Peak 2 was not generated following incubation with any of the human CYP isoforms.

In vitro study 8133-100 was conducted to structurally identify the metabolites produced in human hepatic microsomal incubations. Hepatic clearance was estimated to be <25% of blood flow. A total of seven metabolites (M1 to M7) were observed using HPLC-MS/MS methods. All metabolites were generated by demethylation and/or oxidation. A schematic of the proposed metabolic pathway based on these results is presented below:

Figure 7: Proposed Metabolic Pathway of Tivozanib Hydrochloride from Human Hepatic Microsomal Incubations (Study 8133-100)



Source: Study 8133-100, abstract.
AV-951 refers to tivozanib hydrochloride.

In vitro study 8242-516 using cDNA-expressed human UGTs showed that substantial levels of [^{14}C]-tivozanib hydrochloride desmethyl-glucuronide metabolites were formed by several UGT enzymes (UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9 and UGT1A10). For this step to occur, CYP3A4 needed to be present. The predominant desmethyl-glucuronide metabolite, formed by UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9 and UGT1A10, was M14. Other observed glucuronide metabolites were M10 and M25.

[^{14}C]-tivozanib hydrochloride was incubated with human hepatocytes to evaluate the *in vitro* metabolism and structurally evaluate the metabolites (study 8201725). The estimated hepatic clearance of tivozanib hydrochloride was estimated to be < 1% of hepatic blood flow for human hepatocytes based on > 99% protein binding. The observed prominent human metabolites were M10, M11, M14, M4/M5, M23 and M24. Of these, only M14 was present at >10% of total radioactivity.

Dose proportionality and time dependencies

A dose escalation study in patients with solid tumours (AV-951-03-B01) investigated the 1.0 mg, 1.5 mg and 2.0 mg doses (of tivozanib hydrochloride) once daily for 28 days, followed by a 14 day rest period. Treatment cycles were repeated in the absence of progressive disease or unacceptable AEs. Forty-two subjects were screened and treated, and all 42 completed the study.

Blood samples for PK assessments were collected on the first and last day of treatment for each cycle (Day 1 and Day 28) before dosing and 0.5, 1, 2, 4, 6, 8 and 10 hours after dosing. On Day 2 of treatment for each cycle, samples were taken 24 hours after dosing on the previous day. Samples were also taken 24 hours and 48 hours after the last drug administration on Day 28, and each day of the rest period for each cycle.

Table 11: Selected Pharmacokinetic Parameters of Tivozanib (Free Base) on Cycle 1 Days 1 and 28 after Once Daily Oral Administration of Tivozanib Hydrochloride for 28 Days and on Cycle 2, Day 1 after a 14-Day Rest Period

Cycle and Day	PK parameter	Dose					
		1.0 mg		1.5 mg		2.0 mg	
		Arithmetic Mean (STD)	n	Arithmetic Mean (STD)	n	Arithmetic Mean (STD)	n
Cycle 1 Day 1	C_{max} (ng/mL)	9.293 (6.386)	18	10.19 (4.934)	16	17.65 (6.861)	7
	AUC_{0-t} (ng·hr/mL)	131.2 (52.6)	18	159.2 (69.4)	16	274.3 (83.6)	7
Cycle 1 Day 28	$C_{max,ss}$ (ng/mL)	50.03 (21.17)	16	67.46 (45.55)	13	110.0 (61.43)	5
	$AUC_{\tau,ss}$ (ng·hr/mL)	856.0 (396.6)	15	1180.2 (813.4)	13	1997.2 (1054.6)	5
Cycle 2 Day 1	C_{max} (ng/mL)	14.40 (8.090)	19	13.35 (5.355)	9	24.97 (15.03)	3
	AUC_{0-t} (ng·hr/mL)	245.4 (116.4)	19	236.6 (100.5)	9	400.2 (244.4)	3

Source: Study AV-951-03-B01, PK Report Q-24073 (free base), 07 Feb 2011, Tables 3, 4, and 5.
AUC_{0-t} = area under the concentration-time curve from zero to the last measurable time point t; $AUC_{\tau,ss}$ = area under the serum concentration-time curve during a dosing interval at steady-state; C_{max} = maximum observed concentration; $C_{max,ss}$ = maximum concentration during a dosing interval at steady state; STD = standard deviation.

A Phase 1b dose finding study of tivozanib in combination with mFOLFOX6 (study AV-951-07-103) provided PK data after single tivozanib hydrochloride doses of 0.5 mg (n=9), 1.0 mg (n=3) and 1.5 mg (n=18), 5 days prior to commencement of temsirolimus:

Table 12: Summary of Baseline (Day -5) Tivozanib PK Parameters (Study AV-951-07-103)

Dose	Statistic	C_{max} (ng/mL)	T_{max} (hr)	AUC_{all} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	CL/F (L/hr)	$t_{1/2}$ (hr)
0.5 mg	N	9	9	9	8	8	8
	Arithmetic Mean	5.033	10.01	404.8	765.1	0.8157	129.7
	STD	0.9349	10.71	215.1	464.6	0.4756	58.30
	Min	3.22	1.00	85.9	288	0.287	63.3
	Median	5.240	4.000	348.6	613.5	0.7740	129.2
	Max	6.10	24.0	709	1560	1.55	209
	95% CI	(4.31, 5.75)	(1.78, 18.2)	(239.0, 570.0)	(377.0, 1150)	(0.418, 1.21)	(80.9, 178.0)
1.0 mg	N	3	3	3	3	3	3
	Arithmetic Mean	8.067	9.333	680.4	845.2	1.057	76.67
	STD	2.476	12.70	53.56	29.31	0.03786	6.199
	Min	6.32	2.00	620	812	1.03	72.0
	Median	6.980	2.000	699.8	859.0	1.040	74.30
	Max	10.9	24.0	722	865	1.10	83.7
	95% CI	(1.92, 14.2)	(-22.2, 40.9)	(547.0, 813.0)	(772.0, 918.0)	(0.963, 1.15)	(61.3, 92.1)
1.5 mg	N	18	18	18	15	15	15
	Arithmetic Mean	13.10	14.15	1071	1448	1.218	82.83
	STD	8.144	10.46	520.4	623.0	0.8491	37.95
	Min	3.70	1.00	308	415	0.505	27.8
	Median	11.50	15.97	1111	1463	0.9160	74.70
	Max	38.0	25.3	2290	2650	3.23	178
	95% CI	(9.05, 17.2)	(8.95, 19.4)	(812.0, 1330)	(1100, 1790)	(0.748, 1.69)	(61.8, 104.0)

Source: Study AV-951-07-103 PK Report, Table 8.

AUC_{all}= area under the concentration versus time curve for all observations, calculated by the linear trapezoidal rule; $AUC_{0-\infty}$ = area under the concentration-time curve from zero to infinity; CI = confidence interval; CL/F = apparent total clearance; C_{max} = maximum concentration; Max = maximum; Min = minimum; STD = standard deviation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum concentration.

Population Pharmacokinetics

A population pharmacokinetic (PopPK) analysis was completed to characterize the PK of tivozanib in healthy volunteers and in subjects with solid tumours utilising data from various studies (AV-951-03-B01, AV-951-09-109 [capsule data only], AV-951-07-201, and AV-951-09-301; total N = 350 subjects), and updated in order to include one further study (AV951-10-202). This analysis evaluated the effects of individual-specific covariate factors (i.e., gender, race, age, weight, serum creatinine, BMI, serum albumin, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and their potential contribution to PK variability between subjects. Volume of distribution was found to increase nearly proportionally with body weight. Estimates of clearance were different between males and females, with females having a 25.4% lower value. Gender differences in clearance were most likely responsible for the longer $t_{1/2}$ determined for females (128 hours) compared to males (110 hours). The clearance differences between males and females were independent of weight. Other parameter-covariate relations that were evaluated and not found to affect the PK of tivozanib included age, ALT, AST, creatinine and race on CL/F, and albumin and gender on volume of distribution.

In the population model an analysis by creatinine clearance suggests no effect of renal impairment on exposure however there was no data in subjects with severe impairment. In patients with hepatic impairment, an increase in exposure is seen.

Special populations

	Age 65-74 years (Older subjects number /total number)	Age 75-84 years (Older subjects number /total number)	Age 85+years (Older subjects number /total number)
PK Trials	147/744	25/744	0/744

Pharmacokinetic interaction studies

Three combination studies in which tivozanib hydrochloride was coadministered with temsirolimus (Study AV-951-07-102), mFOLFOX6 (Study AV-951-07-103), or paclitaxel (Study AV-951-08-104) assessed the PK of each coadministered agent as a secondary endpoint, using a limited PK sampling regimen.

Two DDI studies were conducted in healthy volunteers with either a potent inhibitor (ketoconazole) (Study AV-951-11-116) or a potent inducer (rifampin) (Study AV-951-11-117) of CYP3A4 to evaluate their influence on the PK of tivozanib.

Ketoconazole did not cause a clinically significant change in the PK of tivozanib, indicating that tivozanib hydrochloride can be dosed concomitantly with CYP3A4 inhibitors. Conversely, coadministration of tivozanib hydrochloride with rifampin resulted in an increased apparent oral clearance (CL/F) of tivozanib (mean of 0.583 to 1.21 L/hr), leading to a decreased tivozanib terminal elimination half-life ($t_{1/2}$) by approximately 55% (mean of 121 to 54.0 hours).

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Tivozanib potently and selectively blocks all 3 Vascular Endothelial Growth Factor receptors (VEGFR) and has been shown to block various VEGF induced biochemical and biologic responses *in vitro*, including VEGF ligand induced phosphorylation of all three VEGFR 1, 2 and 3, and proliferation of human endothelial cells. The next most potently inhibited kinase is c-kit which is 8-fold less sensitive to inhibition by tivozanib compared to VEGFR 1, 2 and 3. VEGF is a potent mitogenic factor that plays a central role in angiogenesis and vascular permeability of tumour tissues. By blocking VEGF induced VEGFR activation, tivozanib inhibits angiogenesis and vascular permeability in tumour tissues, leading to inhibition of tumour growth *in vivo*.

Primary and Secondary pharmacology

Primary pharmacology

Primary pharmacodynamic parameters were measured in two clinical studies, a dose escalation study (AV-951-03-B01) and a Phase 2 RCC study (AV-951-07-201). In response to treatment with tivozanib, VEGF-A levels increased in a dose-dependent manner. Concomitantly there was a decrease in sVEGF2 levels (a truncated soluble form of membrane-bound VEGFR2). Dynamic contrast-enhanced (DCE)-MRI

scans were used to measure tumour perfusion. There was a trend to diminishing internal vascularization of tumours over time, which is consistent with the proposed mechanism of action.

Secondary pharmacology

Study AV-951-10-112 was an open-label, non-randomised, single-arm cardiac safety study of tivozanib to evaluate the ECG and PK-ECG dynamics in patients with solid tumours. Fifty subjects received 1.5 mg (tivozanib hydrochloride) daily for 21 days. The maximum mean QTcF change from baseline was 9.3 ms (90% CI 5.0 ms, 13.6 ms) at Day 21, when steady state is expected. For 2 subjects (4%), there was a new (not present at baseline) QTcF >480 ms $\leqslant$ 500 ms. For 6 subjects (12%) there was a change of 30-60 ms in QTcF, and in one subject (2%) a change of > 60 ms in QTcF. An exposure effect relationship was observed for QTcF with a slope of 0.08464.

Relationship between plasma concentration and effect

The applicant has submitted a PK/PD report, an exposure-response analysis of tivozanib for changes in sVEGFR2, blood pressure, hand and foot syndrome, tumour growth, and progression-free survival in patients with advanced RCC. All patients in this analysis received tivozanib 1.5 mg (tivozanib hydrochloride) for 21 days, followed by a 7 day rest, in a 4-week cycle for multiple cycles. For every 10 ng/mL increase in Cavg, sVEGFR-2 decreased by approximately 6%. No exposure-response relationship could be identified for blood pressure measurement. The observed Cavg was significantly higher among patients experiencing at least one hand and foot syndrome event. Exploratory plots of the change in tumour size in study 301 as a function of time suggested that tumours shrank more rapidly with increasing tivozanib exposure (Cavg). The shrinkage rate increased a maximal 0.23% per week for each 10% increase in Cavg relative to the average value of 59 ng/mL. Kaplan-Meier plots of PFS vs. time by Cavg quartile suggested that increased tivozanib exposure was associated with an increase in PFS, from 26.4 weeks in the lowest exposure quartile to 72.1 weeks in the highest exposure quartile.

Concentration / effect analyses for dysphonia and fatigue AEs, which were reported by 27% and 26% of patients in study 301 respectively were provided.

Table 13: Dysphonia by plasma concentration quintiles and gender

Quintile Cmin.C2 (ng/mL)	Median in quintile	Female no dysphonia	Female dysphonia (Proportion of female with dysphonia)	Males no dysphonia	Males dysphonia (Proportion dysphonia in males)	Total number
1.58 – <14.22	10.9	12	0 (0)	49	12 (0.20)	73
14.22-<21.36	18.2	9	2 (0.18)	45	17 (0.27)	73
21.36-<29.12	25.2	10	2 (0.17)	39	22 (0.36)	73
29.12-<41.02	35.8	15	5 (0.25)	30	23 (0.43)	73
41.02-107.7	51.0	35	9 (0.20)	14	14 (0.50)	72
Total Number		**81**	**18**	**177**	**88**	**364**

Patients experiencing Dysphonia N=106 (Study 202 N=51 and Study 301 N=55)

Table 14: Fatigue Grade ≥3 by exposure quintile and prior history of fatigue

Quintile Cavg (ng/mL)	Median in quintile	No prior history of fatigue No grade ≥3 event	No prior history of fatigue Patients experiencing Fatigue grade ≥3 (Proportion)	Prior history of fatigue No grade ≥3 event	Prior history of fatigue Patients experiencing Fatigue grade ≥3 (Proportion)	Total number
17.5-<42.31	34.5	55	4 (0.07)	14	0 (0)	73
42.31-<52.48	46.5	59	2 (0.03)	10	2 (0.17)	73
52.48-<63.01	57.2	62	2 (0.03)	7	2 (0.22)	73
63.01-<77.93	69.6	59	3 (0.05)	9	2 (0.18)	73
77.93-180	88.0	57	5 (0.08)	7	3 (0.30)	72
Total Number		**292**	**16**	**47**	**9**	**364**

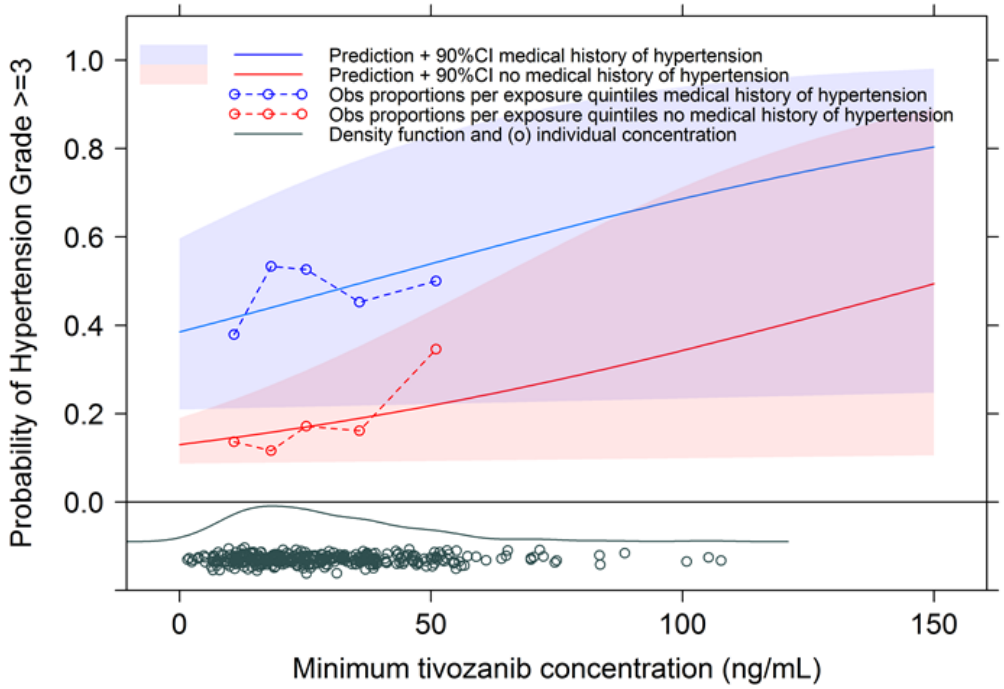
Exposure-response analyses were provided for hypertension AEs, which were reported by 48% of patients in study 301.

Table 15: Hypertension adverse events by exposure quintiles

Quintile (Cmin.C2)	Median in quintile	Patients with No hypertension event	Patients experiencing hypertension any Grade (Proportion)	Total number
1.58 – <14.22	10.9	44	29 (0.40)	73
14.22-<21.36	18.2	35	38 (0.52)	73
21.36-<29.12	25.2	37	36 (0.49)	73
29.12-<41.02	35.8	38	35 (0.48)	73
41.02-107.7	51.0	27	45 (0.63)	72
Total Number		**181**	**183**	**364**

Note: Patients experiencing hypertension in study 301 N=116 and in study 202 N=67 total 183.

Figure 8: Predicted probability of hypertension grade ≥3 vs predicted plasma concentrations of tivozanib by medical history of hypertension



2.4.4. Discussion on clinical pharmacology

The applicant has conducted a comprehensive clinical pharmacology program. This included 7 clinical pharmacology Phase I studies, 6 in healthy volunteers, and one in subjects with advanced solid tumours. An additional 7 clinical studies also include PK endpoints. Supportive PK data from Phase 2 and Phase 3 studies in subjects with advanced RCC are also included. A pop PK analysis was also conducted using

tivozanib plasma concentrations from 4 clinical studies (2 phase 1 studies, 1 phase 2 study and 1 phase 3 study). In addition, several *in vitro* studies with human biomaterials were performed to determine protein binding, metabolism, and the potential for tivozanib to cause DDIs.

The key PK parameters of tivozanib have been derived. Although no information is provided and considering that the drug substance is practically insoluble in aqueous solutions across the pH range tivozanib can be classified as a BCS class II or class IV compound.

Following a single dose administration of tivozanib, absorption is rapid with peak plasma concentrations occurring at approximately 3 hours after administration. However the absorption process is highly variable, probably due to enterohepatic recirculation. Tivozanib is highly bound to albumin (>99%) with no concentration dependence over the range 0.1 to 5 µM and widely distributed throughout the body with a volume of distribution (Vz/F) about 100 L. Its half-life determined in healthy volunteers is 4.5 to 5.1 days.

In vivo studies demonstrated that no unchanged tivozanib is excreted in the urine, and it is suggested that tivozanib is primarily hepatically eliminated. CYP3A4 has been identified as one of the metabolic pathway. This has been confirmed with the results of the in vivo studies. Drugs known to be CYP3A4 inhibitors are not likely to affect the PK of tivozanib to a clinically meaningful extent. However induction of CYP3A4 results in a significant reduction of the elimination half-life of tivozanib.

After chronic dosing of tivozanib in RCC patients for 21 days followed by 7 days without administration of tivozanib, tivozanib C_{min} is approximately 16.0 to 30.9 ng/mL. The elimination phase was best described by a 1-compartment elimination model. No evidence of a second compartment was found. Upon inspection of concentration time profiles densely sampled subjects in study AV-951-09-109, multiple concentrations peaks could be observed on a single day with an overall pattern in the occurrence. This was indicative of enterohepatic recirculation (EHRC) of tivozanib.

The effects of subject-specific characteristics on tivozanib PK were evaluated in study 109 and two important relationships were identified: gender on CL/F, and body weight on V1/F, respectively. Volume of distribution increased nearly proportionally with body weight as suggested by the point estimate of the power relationship being close to unity (0.826). This is in line with expectations, as volume of distribution generally scales linearly with body weight. Women showed a 25.6% lower value for CL/F than men in this dataset. Body weight was evaluated as an explanatory covariate on CL/F instead of and in addition to gender, and gave almost no improvement to the model fit. In contrast, the inclusion of gender resulted in a substantial (ΔOFV-44.8) improvement in the fit. It is worth noting that two other tyrosine kinase inhibitors, sunitinib and sorafenib, have been found to have gender-related differences in clearance. Other parameter-covariate relations that were evaluated and not found to affect the PK of tivozanib included age, ALT, AST, creatinine and race on CL/F and albumin and gender on V1/F.

In the target population the C_{max} and T_{max} after a single 1.5 mg tivozanib hydrochloride (equivalent to 1340 microgram tivozanib) dose are comparable to that observed in healthy volunteers.

The clinical pharmacology program for tivozanib hydrochloride for the treatment of patients with advanced renal cell carcinoma (RCC) has involved both human *in vitro* and *in vivo* studies. Overall, tivozanib hydrochloride is characterised by having a long elimination half-life (~4.5 to 5.1 days), possibly due to enterohepatic recirculation process, and being highly bound to plasma proteins (> 99%). It does not however interact with warfarin at the protein binding level.

Tivozanib hydrochloride has low potential to perpetrate drug-drug interactions (DDIs) at the cytochrome P450 (CYP) and P-glycoprotein (P-gp) level. The applicant has performed studies to investigate inhibition of CYP 2B6, 2C9 and several drug transporters. Results indicated that tivozanib is a weak inhibitor of CYP 2B6, CYP 2C8 and the drug transporter BCRP. No studies were yet presented for establishing tivozanib as

a drug transporter substrate, but these studies were agreed to be presented as a post-authorisation procedure (see discussion on non-clinical aspects and RMP).

In vitro and in vivo studies showed that ketoconazole does not impair the metabolism or overall clearance of tivozanib. Conversely, a clinical study did show that rifampin increased the clearance of tivozanib in a clinically meaningful manner. It is recommended that concomitant administration of tivozanib with strong CYP3A4 inducers, if used, should be undertaken with caution. Moderate CYP3A4 inducers are not expected to have a clinically relevant effect on tivozanib exposure. Herbal preparations containing St. John's wort (*Hypericum perforatum*) are contraindicated. If a patient is already taking St John's wort, this should be stopped before starting tivozanib treatment. The inducing effect of St John's wort may persist for at least 2 weeks after cessation of treatment with St John's wort (see SmPC sections 4.3 and 4.5). A total of 14 clinical studies have been completed, including 5 studies in healthy volunteers and 1 study in subjects with or without hepatic impairment, as well as 5 monotherapy and 3 combination therapy studies in subjects with solid tumours.

Studies involving healthy volunteers assessed mass balance and in vivo metabolism, DDIs (ketoconazole and rifampin), bioequivalence and food effect. The potential for DDIs with combination therapies was also assessed in subjects with solid tumours.

The pharmacokinetics (PK) of tivozanib in humans are characterized by a variable absorption period with a median time to peak serum concentration (T_{max}) ranging from approximately 2 to 24 hours in most studies. This is most likely due to enterohepatic recirculation of tivozanib, which was also seen in non-clinical mouse, rat and monkey studies.

Exposure (C_{max} and AUC) of tivozanib generally increased in a dose-proportional manner across the dose range evaluated (0.5 mg to 2.0 mg). Accumulation at steady-state is approximately 6- to 7- fold the exposure observed at single-dose levels, which is consistent with the long terminal elimination half-life (t½) of tivozanib (~4.5 to 5.1 days). Clearance is similar between acute and chronic dosing indicating no time-dependent changes in PK.

The PK of tivozanib in general is similar in subjects with solid tumours compared to healthy volunteers, with slightly higher variability of parameters found in subjects with solid tumours. Dosing with food (Study AV-951-10-115) was shown not to have a significant impact on the exposure (AUC) of tivozanib compared to the fasted state (although a reduction in C_{max} is observed).

In the mass balance study (Study AV-951-10-111), the majority of circulating radioactivity was associated with unchanged tivozanib. No major metabolites were detected in the serum at exposure levels ≥ 10% of the total radioactivity exposure, indicating there were no disproportionate metabolites present in humans. The mean total radioactivity recovered was 91.1%, with a mean of 79.3% recovered from faeces. Urine accounted for a mean 11.8% of recovered radioactivity. There was no detectable parent compound in urine but various metabolites were detected. Unchanged tivozanib was the major component in faeces suggesting incomplete absorption and/or biliary excretion.

When tivozanib was evaluated in a food effect study in healthy subjects, a high fat meal decreased the peak serum concentrations (C_{max}) by 23% compared to the fasted state. There was no effect of food on the overall exposure (AUC). Based on these data, tivozanib can be taken with or without food (see SmPC section 4.2).

Based on the population pharmacokinetic analysis, it is suggested that there is a relationship between gender and tivozanib clearance. Females were found to have a 25.6% lower clearance compared to males. Also based on the Population PK analysis body weight did show a significant correlation with tivozanib volume of distribution.

Results from a single dose study to evaluate the pharmacokinetics, safety and tolerability of tivozanib in subjects with hepatic impairment show that across the entire measurement period, tivozanib was eliminated more slowly in subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Tivozanib exposure was increased in patients with severe hepatic impairment (mean $AUC_{0-\infty}$ by 4.0-fold) and in patients with moderate hepatic impairment (mean $AUC_{0-\infty}$ by 2.6-fold). No significant increase in exposure was observed in patients with mild (Child-Pugh Class A) hepatic impairment (mean $AUC_{0-\infty}$ by 1.2-fold). Therefore, no dose adjustment is required when administering tivozanib to patients with mild hepatic impairment (see SmPC section 4.2). Tivozanib should be used with caution in patients with moderate hepatic impairment and the dose reduced to one 1340 microgram capsule every other day.

Tivozanib should not be used in patients with severe hepatic impairment (see SmPC sections 4.2, 4.4 and 5.2). All patients should have liver function tests evaluated, including aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (AP), to determine hepatic function before starting and during treatment with tivozanib.

Clinical studies with tivozanib were conducted in RCC patients with serum creatinine concentration ≤ 2 times the upper limit of normal, including those who may have had a prior nephrectomy. Although the impact of further impairment of renal function on the overall disposition of tivozanib is unknown, a clinical study has shown that no unchanged tivozanib is excreted in the urine indicating that tivozanib does not undergo renal excretion. According to the population pharmacokinetic analysis of tivozanib exposure, no dose adjustment is required in patients with mild or moderate renal impairment. Experience of tivozanib use in patients with severe renal impairment is limited and caution is advised (See SmPC sections 4.2 and 5.2).

Tivozanib hydrochloride inhibits VEGFR-1, -2, and -3 and has been shown to block various VEGF-induced biochemical and biologic responses *in vitro*. In response to treatment with tivozanib hydrochloride, VEGF-A levels increase in a dose-dependent manner. Concomitantly there is a decrease in sVEGF2 levels. (See section 5.1 of the SmPC).

The applicant conducted a cardiac safety study. At steady state, the mean QTcF change was 9.3 ms (90% CI 5.0 ms, 13.6 ms). An exposure effect relationship was observed for QTcF with a slope of 0.08464. According to ICH E14, tivozanib exceeds the threshold level of regulatory concern, since the upper bound of the 90% confidence interval for the largest time-matched mean effect of the drug on the QTc interval is greater than 10 ms. However, only one event of QTc prolongation was identified in the core RCC monotherapy studies (see discussion on clinical safety). QT/QTc interval prolongation may lead to an increased risk for ventricular arrhythmias. It is recommended that tivozanib be used with caution in patients with a history of QT interval prolongation or other relevant pre-existing cardiac disease and those receiving other medications known to increase the QT interval. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range is recommended (see SmPC sections 4.4 and 5.1).

The exposure response analyses for dysphonia suggested that there is a clear relation to plasma concentrations in males and that the probability of a dysphonia event is smaller in women. The reason for the observed difference between the genders is unknown. Even if a larger proportion of women would have been dose reduced (not explored) it is difficult to see that dose reductions from 1.5 mg to 1 mg (tivozanib hydrochloride) which would result in 33% reduction of exposure could explain the difference observed, but rather suggests that plasma concentration alone is not a good predictor of dysphonia events.

There was no significant relation between tivozanib concentration during Cycle 2 of treatment and fatigue of any grade when explored separately. For events of fatigue grade ≥3, the medical history of fatigue was

a strong predictor although the number of grade ≥3 events were relatively few hence the prediction is uncertain. Gender was not a significant explanatory factor. A significant relation to Cavg could only be identified after medical history of fatigue was included in the model. The observed proportion of patients having a severe fatigue event was low for patients without prior history of fatigue (5 out of 57 in the highest exposure quintile) while the observed proportion of patients having a severe fatigue event in patients with a prior history of fatigue was substantially higher although the overall number of patients was low (3 out of 7) in the highest exposure quintile. Given the low number of patients with a severe fatigue event these results should be interpreted with some caution but suggests that medical history of fatigue is more important than plasma exposure in predicting risk of grade ≥3 adverse events.

There appears to be an exposure-response relationship for grade ≥3 hypertension in patients without a history of hypertension. As might be expected, patients with a history of hypertension have a higher probability of grade ≥3 hypertension irrespective of exposure. The finding of an exposure-response relationship for grade ≥3 hypertension is consistent with the known mechanism of action. Section 4.4 of the proposed SmPC includes a warning to reduce the dose or interrupt treatment and to consider discontinuation of treatment in cases of persistent severe hypertension, posterior reversible encephalopathy syndrome, or other complications of hypertension. In addition, section 4.2 includes general advice to temporarily interrupt treatment and/or to lower the dose to 890 micrograms in the event of undesirable effects. The SmPC recommendations are supported by the outcome of the exposure-response analysis for hypertension AEs, and are acceptable.

There appears to be an exposure-response relationship for sVEGFR-2, HFS, tumour growth and PFS. There also appears to be an exposure-response relationship for grade ≥3 hypertension in patients without a history of hypertension. As might be expected, patients with a history of hypertension have a higher probability of grade ≥3 hypertension irrespective of exposure. (See discussion on clinical Safety, SmPC section 4.4 and RMP).

2.4.5. Conclusions on clinical pharmacology

The clinical Pharmacology aspects of tivozanib are well characterised and all relevant information is included in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose-response studies

The first-in-human phase 1 Study AV-951-03-b01 was a dose escalation study designed to determine the maximum tolerated dose of tivozanib hydrochloride. The initial dose selected for the study was 2.0 mg tivozanib hydrochloride once daily, with a dosing regimen of 4 weeks of treatment followed by a 2-week rest period. The starting dose was based on the highest non-severely toxic dose observed in monkeys and the minimally effective dose in pharmacology studies.

The study evaluated further doses of 1.0 mg and 1.5 mg (tivozanib hydrochloride) and reported a dose-dependent effect of tivozanib hydrochloride on both dose limiting toxicity and hypertension (see also section Dose proportionality and time dependencies). Exploratory efficacy results from this study showed that 4/12 (33%) patients in the Efficacy Population at the 1.5 mg dose level had documented SD. Pharmacodynamic analysis demonstrated dose-dependent increases in serum VEGF-A levels, dose-dependent decreases in serum soluble VEGFR-2 levels and a dose-dependent reduction in tumour perfusion.

The maximum tolerated dose was 2 mg in study AV-951-03-B01 (protocol KRN951/03-B01), whereas the 1.5 mg dose was identified as the highest dose level with an acceptable safety/tolerability profile and was the dose selected for evaluation in other monotherapy clinical trials of tivozanib in patients with solid tumours.

2.5.2. Main study(ies)

Study AV-951-09-301

Methods

This was a 2-year pivotal Phase 3, Randomised, Controlled, Multicentre, Open-label Study to Compare Tivozanib Hydrochloride (AV-951) to Sorafenib in Patients with recurrent or metastatic RCC with a clear cell component who had undergone prior nephrectomy (complete or partial) for excision of the primary tumour. Patients had no prior therapy or no more than 1 prior systemic therapy for metastatic RCC (prior systemic therapy could include immunotherapy, chemotherapy, hormonal therapy or an investigational agent, but prior VEGF-directed therapy and prior therapy with an agent targeting the mammalian target of rapamycin [mTOR] pathway were prohibited).

Study Participants

Planned enrolment was approximately 500 patients.

The key eligibility criteria are presented below:

Inclusion criteria

- At least 18 years of age
- Recurrent or metastatic RCC
- Prior nephrectomy (complete or partial) for excision of primary tumour
- Histologically or cytologically confirmed RCC with a clear cell component
- Measurable disease per the RECIST criteria, version 1.0
- Treatment naïve patients or patients who had received no more than 1 prior systemic treatment (immunotherapy including interferon-alfa or interleukin-2 based-therapy, chemotherapy, hormonal therapy or an investigational agent) for metastatic RCC
- ECOG performance status of 0 or 1, and life expectancy of at least 3 months

Exclusion criteria

- Any prior therapy with agents targeting the VEGF or mTOR pathway
- Primary CNS malignancies or CNS metastases
- Significant haematological or serum chemistry abnormalities
- Significant cardiovascular disease (including uncontrolled hypertension), gastrointestinal conditions, thromboembolic or vascular disorders, bleeding disorders, immune suppression
- Currently active second primary malignancy

- Pregnancy or lactation

Treatments

Tivozanib hydrochloride was administered in 4-week cycles consisting of once-daily oral tivozanib hydrochloride 1.5 mg for 3 weeks followed by a 1-week rest period. Sorafenib was administered in 4-week cycles consisting of twice-daily oral sorafenib 400 mg for 4 weeks with no rest period.

Patients continued to receive their assigned treatment until they experienced disease progression, unacceptable toxicity, death or another reason to withdraw.

Chemotherapy, biological therapy (including cytokines, signal transduction inhibitors, monoclonal antibodies), immunotherapy, or any other therapy for RCC was prohibited. However limited radiotherapy was permitted with interruption of study drug during treatment.

Dose reductions and interruptions were recommended for study-drug related AEs grades 3 and 4, respectively. The sorafenib dose could be reduced to 400 mg once daily, then 400 mg once every other day. If toxicities resolved to ≤ Grade 1, the sorafenib dose could be re-escalated. If tivozanib or sorafenib was interrupted for Grade 4 toxicity; a lower dose was restarted as soon as toxicity improved to ≤ Grade 2. If study drug was interrupted for more than 2 weeks, the patient was discontinued from the study.

Specific protocol guidance was provided for the development of hypertension in patients taking tivozanib. Depending on the severity of hypertension, and the response to anti-hypertensive treatment, tivozanib could be continued at 1.5 mg (tivozanib hydrochloride) daily, interrupted and resumed at 1.0 mg (tivozanib hydrochloride) daily, or stopped. Specific protocol guidance was also provided in the event of skin toxicity with sorafenib.

Patients who completed 2 years on study with no PD were given the option to continue treatment in an extension protocol (AV-951-09-902).

Patients in the sorafenib arm of 951-09-301 who experienced radiographic evidence of PD were given the option to cross over to receive tivozanib in AV-951-09-902.

Patients randomised to tivozanib were discontinued from the study once progression was confirmed by IRR and continued treatment with standard of care as per local availability of therapy.

Objectives / endpoints

The study was designed to compare the PFS, OS, ORR, DR, safety and tolerability, PK and kidney-specific symptoms/health outcome measurements of subjects with advanced RCC randomised to treatment with tivozanib hydrochloride or sorafenib.

The primary efficacy endpoint was PFS by IRR assessment - defined as the time from randomisation to first documentation of PD or death due to any reason, whichever came first.

Secondary objectives included:

- Comparison of the OS of patients randomised to treatment with tivozanib hydrochloride or sorafenib, OS was defined as the time from the date of randomisation to date of death due to any cause and was analysed in the ITT population.

- Comparison of the ORR, DR and SD of patients randomised to treatment with tivozanib hydrochloride or sorafenib,

ORR was defined as the proportion of patients with CR or PR, relative to the total population of randomised patients. DR was defined as the time from the first documentation of objective tumour response according to RECIST to the first documentation of objective tumour progression or to death due to any reason. ORR, DR and duration of SD were analysed in the ITT population using both the Investigator and IRR assessments.

- Comparison of the safety and tolerability of tivozanib hydrochloride and sorafenib.
- Comparison of kidney-specific symptoms and health outcome measurements in patients randomised to treatment with tivozanib hydrochloride or sorafenib.
- Evaluation of the PK of tivozanib hydrochloride.
- Patient reported outcomes.

The following quality of life assessments were self-administered on the Day 1 visit of each cycle, and at the end of treatment visit:

- Functional Assessment of Cancer Therapy - General (FACT-G): a 27-question instrument to measure general quality of life in 4 domains - physical, social/family, emotional, and functional well-being.
- FACT - Kidney Symptom Index - Disease Related Symptoms (FKSI-DRS): a 9-question abbreviated version of the FKSI designed to specifically measure kidney cancer-related symptoms.
- European Quality of Life-5 Dimensions (EQ-5D): a general measure of health status that measures 5 descriptors of current health state - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

A tertiary objective was to study biomarkers in blood and archived tissue samples but this was never completed.
Patients underwent disease assessment at screening, following cycle 2 and every subsequent even-numbered cycle, with response determined by RECIST, Version 1.0.

Sample size

The median PFS in the sorafenib arm was hypothesised to be 6.7 months. Assuming a target HR of 0.70, equivalent to a 30% risk reduction (median of 6.7 months in the sorafenib control arm versus 9.7 months in the tivozanib arm) in PFS, the study would have more than 90% power to test the tivozanib regimen versus sorafenib using a two-sided 5% alpha log-rank test. A sample size of approximately 500 patients (250 patients per treatment arm) with a total number of 310 events (death or progression) was projected for this analysis. A dropout rate of 3% per treatment arm and accrual of approximately 40 patients per month would be assumed.

Randomisation

Patients were randomised in a 1:1 ratio to tivozanib hydrochloride or sorafenib. Randomisation was stratified by geographic region (North America/Western Europe, Central/Eastern Europe or rest of world); number of prior treatments for metastatic RCC (0 or 1); and number of metastatic sites/organs involved (1 or ≥ 2) as assessed by an independent radiologist. Randomisation was performed using an Interactive Voice Response System (IVRS). Treatments were randomly assigned to patients within the strata using a complete randomised block design.

A formal treatment cross-over was not built into the study design; however, patients randomised to sorafenib were given the option of crossing over to tivozanib hydrochloride in extension Study AV-951-09-902 if they developed radiographically documented PD as defined by RECIST and met other eligibility criteria. Patients randomised to tivozanib were discontinued from the study once progression was confirmed by IRR and continued treatment with standard of care as per local availability of therapy.

Blinding (masking)

This was an unblinded (open-label) study. However IRR was blinded to treatment allocation.

Statistical methods

The ITT population was defined as all randomised patients. For the ITT population, treatment group was designated according to initial randomisation, regardless of whether the patients received the assigned study drug. The ITT population was used for the analysis of the primary and secondary efficacy endpoints.

The per-protocol (PP) population was defined as all randomised patients who remained in the study for at least 8 weeks (2 cycles) (unless discontinued due to death or disease progression) and had no major protocol violations that would confound the effects of treatment in the judgment of the Sponsor medical monitor.

The primary efficacy analysis was to compare PFS between treatment groups in the ITT population. The primary analysis of PFS was to be performed when approximately 310 PFS events had occurred. This analysis was considered positive if the 2-sided stratified log-rank test for PFS, where the stratification factors (as entered into the IVRS) were number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥ 2), was significant at the 5% level. Region was not included in the analysis at the request of the FDA who was concerned about the number of stratification factors.

A number of sensitivity analyses were performed. Sensitivity analysis 1 used the investigator assessment of response and added in clinical PDs. For sensitivity analysis 2, initiation of new anti-cancer treatment was considered an event. For sensitivity analysis 3, discontinuation of therapy and initiation of new anti-cancer treatment were considered events. In these 2 analyses, also based on the IRR assessments, all deaths or PDs were events, even those occurring after 2 or more missed tumour assessments. Sensitivity analysis 4 used the IRR assessments and backdated any PD events that occurred immediately after missing or not evaluable (NE) assessments. If the PD occurred immediately after a NE assessment (or series of NE assessments), the PD date was the date of the first NE assessment preceding the PD. If the PD occurred immediately after a missing assessment (or series of missing assessments), the PD date was the date of the first missing assessment preceding the PD.

OS was defined as the time from the date of randomisation to date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive (as determined by a sweep conducted prior to the analysis) or the sweep date for the analysis, whichever was sooner. For the interim analysis of OS, patients known to have died between the sweep date (19 September 2011) and the snapshot (15 December 2011) were censored at the sweep date. For patients with no data beyond randomisation, survival times were censored on the date of randomisation.

Overall survival was compared between the 2 treatment groups using the stratified log-rank test, where the stratification matched that used in the primary analysis for PFS. The hazard ratio was estimated using the Cox proportional hazard (PH) regression model. The distribution of OS was estimated using the Kaplan-Meier method. The HR for treatment was estimated using the Cox proportional hazard regression model. The unstratified and stratified log rank tests, where the stratification included the factors over

which randomisation was stratified, were also performed. Kaplan-Meier plots of the survival distribution function by treatment group were produced.

The ORR and corresponding exact 2-sided 95% CIs were presented for each treatment group. The disease control rate (proportion of patients with CR, PR or SD) was also presented for each treatment group. For the overall analysis, the confirmed ORR was compared between the 2 treatment groups using the Cochran-Mantel-Haenszel test, where the stratification matched that used in the primary PFS analysis.

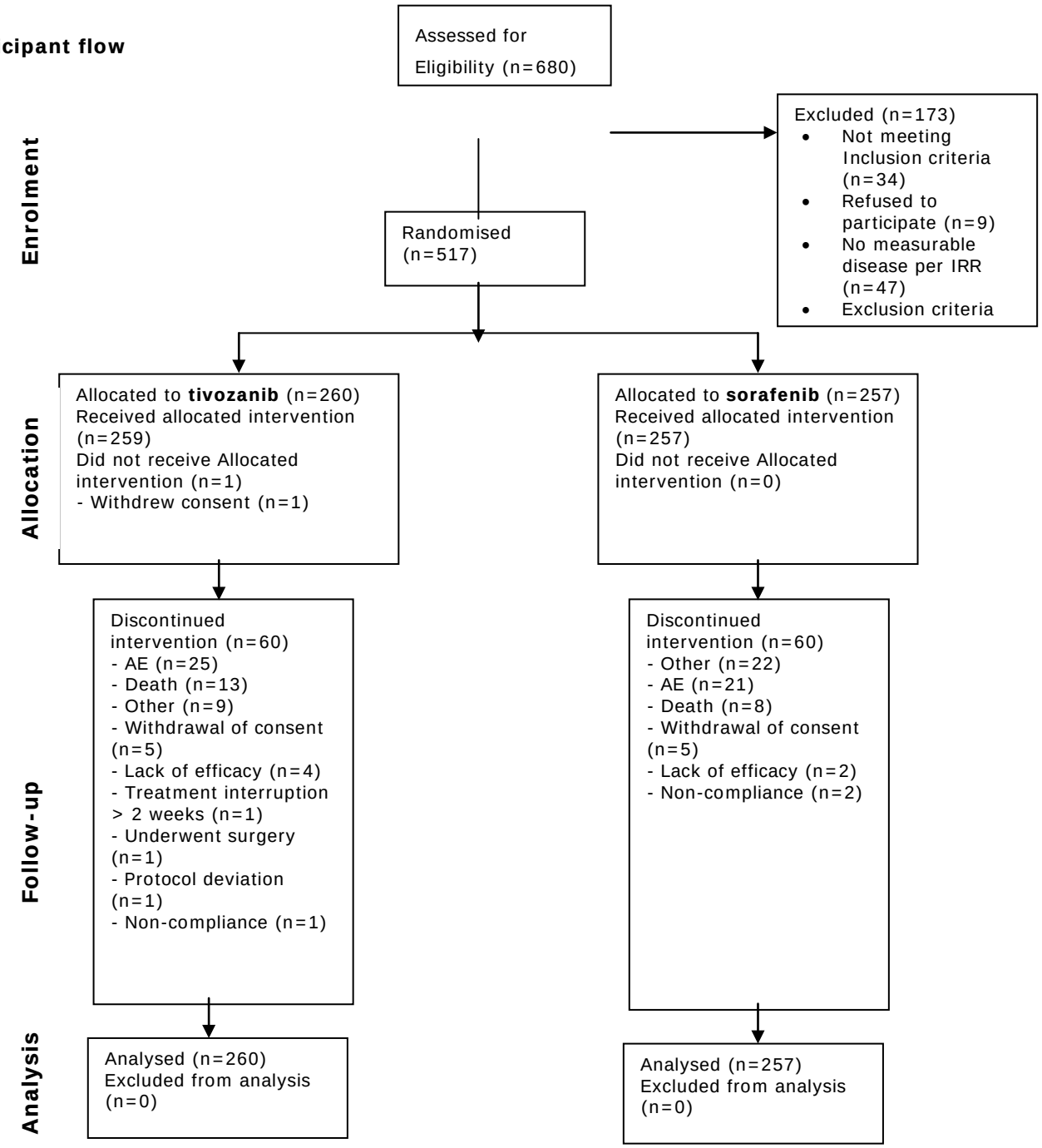
The estimate of the odds ratio for treatment (using the sorafenib arm as the reference treatment) and corresponding 95% CI were presented. The stratification factors were number of prior treatments (0 or 1); and number of metastatic sites/organs involved (1 or ≥ 2).

For the overall analysis, the confirmed ORR was compared between the 2 treatment groups using the Cochran-Mantel-Haenszel test, where the stratification matched that used in the primary PFS analysis. The estimate of the odds ratio for treatment (using the sorafenib arm as the reference treatment) and corresponding 95% CI were presented.

DR was calculated only for patients who had an objective tumour response (confirmed). Response was confirmed by repeat evaluations performed no less than 4 weeks after the criteria for response were first met. Duration of SD was defined as the time from randomisation to the first time the RECIST criteria for progression were met, taking as reference the smallest measurements recorded since study treatment started. DR and duration of SD data were censored on the day following the date of the last tumour assessment documenting absence of PD for patients who were given antitumour treatment other than study drug or for patients who were removed from study follow-up prior to documentation of objective tumour progression. DR and duration of SD were analysed in a similar manner as PFS and OS.

Results

Participant flow



Recruitment

Recruitment was highest in Central/Eastern Europe: 457 out of the 517 patients randomised (88.4%) were from sites in that region and mostly in Russia (90 patients in the tivozanib arm and 100 patients in the sorafenib arm) and in Ukraine (56 patients in the tivozanib arm and 45 patients in the sorafenib arm).

North America/Western Europe contributed 40 randomised patients (7.7%) and the rest of the world contributed 20 randomised patients (3.9%).

All patients were randomised between February 2010 and August 2010. The study dates were 11/02/2010 (first patient dosed) to 10/06/2013 (last patient completed).

Conduct of the study

The original protocol was dated 27/07/2009. There were 4 major protocol amendments, including the following changes:

Protocol amendment 1.0 *Dated 17/08/2009*
The length of time patients with documented stable disease or an objective response could continue to receive study drug was changed from “up to 1 year” to “up to 2 years” from the first dose as long as tolerability was acceptable. Patients with radiological evidence of progressive disease as assessed by the investigator, on either treatment arm, should continue treatment until PD was verified by an independent radiologist within 48 hours, except in the following situations: Greater than 50% increase in measurable disease per RECIST as assessed by the investigator; Appearance of new lesions, at least one of which measure > 20mm by CT scan or > 10mm by spiral CT scan as assessed by the investigator; Significant clinical deterioration that is indicative of progressive disease as assessed by the investigator.

Protocol amendment 2.0 *Dated 18/10/2010*
It was clarified that the number of metastatic sites/organs used in stratification was as determined by the independent radiologist. The exclusion criteria were amended to include all CNS metastases, unless previously treated and stable. All patients were to be followed until death from any cause.

Protocol amendment 3.0 *Dated 02/06/2011*
Text was added to specify that patients with radiological evidence of PD per local radiology assessment were to continue study drug until PD was verified by an independent radiologist and that images were to be submitted for independent review as soon as possible. The only exception was significant clinical deterioration indicative of progressive disease as assessed by the investigator. Tumour assessments were to be continued after discontinuation for patients who discontinued for reasons other than PD. After protocol amendment 3, all patients with evidence of PD as assessed by the investigator, on either treatment arm, were to continue treatment until PD was verified by an independent radiologist. Only patients with significant clinical deterioration indicative of PD as assessed by the investigator were exempt from verification by IRR review prior to discontinuation.

Protocol amendment 4.0 *26/09/2011*
It was clarified that patients who had PD, unacceptable toxicity, etc. were to be discontinued from receiving study drug, not necessarily from study participation. Patients could continue to be followed up for long-term response and survival.

Protocol violations and deviations

There were 13 eligibility violations in the tivozanib group compared to 14 in the sorafenib group. There were 24 occurrences of prohibited medicines (e.g. CYP 3A4 inducers and inhibitors, full dose anticoagulants) in the tivozanib group compared to 30 in the sorafenib group. Finally, there was one incidence of dosing beyond 30 days after confirmation of PD in the tivozanib group.

For patients in the tivozanib group, there was a lower occurrence of deviations associated with missed doses (20 occurrences vs 112 occurrences in the sorafenib group) and other study drug deviations (3 occurrences vs 45 occurrences in the sorafenib group).

Data cut-off for AV-951-09-301 was 10/07/2013 and for the extension 951-09-902 was 20/01/2015.

Baseline data

The baseline characteristics of patient enrolled in the pivotal study AV-951-09-301 are summarised in the tables below.

Table 16 Demographics (ITT population)

	Tivozanib (N=260)	Sorafenib (N=257)
Gender [n (%)]		
Male	185 (71.2)	189 (73.5)
Female	75 (28.8)	68 (26.5)
Age (years)		
Mean (STD)	58.2 (9.96)	58.4 (9.57)
Median	59.0	59.0
Range	23-83	23-85
Age group [n (%)]		
< 65 years	195 (75.0)	193 (75.1)
≥ 65 years	65 (25.0)	64 (24.9)
Race [n (%)]		
White	249 (95.8)	249 (96.9)
Asian	10 (3.8)	8 (3.1)
Black or African American	1 (0.4)	0 (0.0)
Ethnicity [n (%)]		
Not Hispanic or Latino	254 (97.7)	244 (94.9)
Unknown	4 (1.5)	4 (1.6)
Hispanic or Latino	2 (0.8)	9 (3.5)
Geographic Region[a] [n (%)]		
Central/Eastern Europe	229 (88.1)	228 (88.7)
North America/Western Europe	22 (8.5)	18 (7.0)
Rest of world	9 (3.5)	11 (4.3)

ITT = Intent-to-treat; STD = standard deviation
[a] Geographic region was a randomization stratification factor.

Table 17 Baseline characteristics (ITT population) Study AV-951-09-301

Characteristic	Tivozanib (N=260)	Sorafenib (N=257)
Weight (kg)		
Mean (STD)	80.70 (17.091)	80.08 (16.042)
Median	79.00	79.20
Range	44.0-137.0	43.0-138.8
Height (cm)		
Mean (STD)	171.41 (8.465)	171.33 (9.151)
Median	173.00	172.00
Range	145.0-190.0	145.0-203.0
Body mass index (kg/m^2)		
Mean (STD)	27.38 (5.123)	27.28 (5.037)
Median	26.95	26.50
Range	17.0-47.8	16.3-49.2
Baseline SBP [n (%)]		
SBP ≤ 140 mmHg	243 (93.5)	233 (90.7)
SBP > 140 mmHg	17 (6.5)	24 (9.3)
Baseline DBP [n (%)]		
DBP ≤ 90 mmHg	254 (97.7)	238 (92.6)
DBP > 90 mmHg	6 (2.3)	19 (7.4)
ECOG performance status [n (%)]		
0	116 (44.6)	139 (54.1)
1	144 (55.4)	118 (45.9)

Table 18 Cancer history (ITT population)

Parameter	AV-951-09-301 Tivozanib (n = 260)	AV-951-09-301 Sorafenib (n = 257)
Time since initial diagnosis, months		
n	246	242
Mean (SD)	29.9 (36.20)	35.7 (48.63)
Median	14.7	16.6
Q1, Q3	4.0, 40.8	4.4, 47.7
Range	0.5 - 168.6	1.0 - 264.3
Time since initial diagnosis, n (%)		
< 1 year	109 (41.9)	105 (40.9)
≥ 1 year	137 (52.7)	137 (53.3)
Time since most recent relapse or staging, months		
n	242	235
Mean (SD)	6.0 (13.13)	5.1 (8.20)
Median	2.1	2.0
Q1, Q3	1.3, 4.5	1.1, 5.1
Range	0.2 - 144.2	0.1 - 49.4
Pathological diagnosis, n (%)		
Clear cell	246 (94.6)	244 (94.9)
Unclassified or mixed type	0	0

Parameter	AV-951-09-301 Tivozanib (n = 260)	AV-951-09-301 Sorafenib (n = 257)
Papillary (chromophil)	0	0
Chromophobe	0	0
Collecting duct carcinoma (Bellini duct tumour)	0	0
Other/Clear cell component	14 (5.4)	13 (5.1)
Technique used to confirm diagnosis, n (%)		
Histology	258 (99.2)	256 (99.6)
Cytology	2 (0.8)	1 (0.4)
Stage at screening, n (%)		
Local recurrence	1 (0.4)	3 (1.2)
Stage IV	259 (99.6)	254 (98.8)
Revised MSKCC prognostic group††		
Poor	17 (6.5)	10 (3.9)
Intermediate	173 (66.5)	160 (62.3)
Favourable	70 (26.9)	87 (33.9)
Number of metastatic sites of disease, n (%)		
1 site	17 (6.5)	17 (6.6)
≥ 2 sites	243 (93.5)	240 (93.4)
Metastatic sites of the disease, n (%)		
Adrenal gland	78 (30.0)	57 (22.2)
Bone	61 (23.5)	52 (20.2)
Brain	8 (3.1)	8 (3.1)
Colon	2 (0.8)	1 (0.4)
Liver	67 (25.8)	49 (19.1)
Lung	212 (81.5)	204 (79.4)
Lymph node	182 (70.0)	166 (64.6)
Opposite kidney	33 (12.7)	34 (13.2)
Rectum	0	1 (0.4)
Soft tissue	41 (15.8)	31 (12.1)
Spine	8 (3.1)	2 (0.8)
Other	111 (42.7)	106 (41.2)
Number of prior treatments, n (%)		
0	181 (69.6)	182 (70.8)
1	78 (30.0)	75 (29.2)
2	0	0
3	0	0
Prior nephrectomy, n (%)‡‡		
Complete nephrectomy	249 (95.8)	247 (96.1)
Partial nephrectomy	11 (4.2)	10 (3.9)
Other	1 (0.4)	0
Unknown	0	0
Prior chemotherapy setting, n (%)		
Metastatic/unresectable	49 (18.8)	56 (21.8)
Adjuvant	23 (8.8)	21 (8.2)
Neoadjuvant	1 (0.4)	0
Other	7 (2.7)	6 (2.3)

Parameter	AV-951-09-301 Tivozanib (n = 260)	AV-951-09-301 Sorafenib (n = 257)
Unknown	5 (1.9)	3 (1.2)
Prior radiation indication, n (%)		
Palliative	20 (7.7)	18 (7.0)
Postoperative	12 (4.6)	13 (5.1)
Preoperative	3 (1.2)	1 (0.4)

The most frequent prior treatment for prior metastatic disease was interferon-alpha, which had been used as monotherapy in 75 (28.8%) patients in the tivozanib treatment group and 62 (24.1%) patients in the sorafenib group. Interferon-alpha was used in combination with one or more other anticancer agents in a further three patients in the tivozanib group and a further 15 patients in the sorafenib group. Two patients in the tivozanib group and two patients in the sorafenib group had received prior treatment with interleukin-2 with a further sorafenib patient receiving leukinferon (IFN plus a complex of cytokines) (See table below).

Table 19: Summary of prior medication for metastatic disease taken by patients in study AV-951-09-301

Treatment	Tivozanib N = 260	Sorafenib N = 257
Interferon-alpha*	75 (28.8%)	62 (24.1%)
Interferon-alpha/interferon-gamma	0	1 (0.4%)
Interferon-alpha + Trovax	1 (0.4%)	0
Interferon-alpha + vinblastine	1 (0.4%)	3 (1.2%)
Interferon-alpha + 5-FU + IMA901 (investigational multipeptide cancer vaccine) + IL-2	1 (0.4%)	0
Interferon-alpha + 5-FU	0	1 (0.4%)
Interferon-alpha + ABR217620 (fusion protein activating T-cells and targeting 5T4+ tumours)	0	2 (0.8%)
Interferon-alpha + bisphosphonate	0	1 (0.4%)
Interferon-alpha + capecitabine	0	1 (0.4%)
Interferon-alpha + cisplatin + cyclophosphamide + doxorubicin		1 (0.4%)
Interferon-alpha + IL-2	0	1 (0.4%)
Interferon-alpha + investigational tumour vaccine	0	1 (0.4%)
Interferon-alpha + medroxyprogesterone	0	2 (0.8%)
Interferon-alpha + tegafur	0	1 (0.4%)
Interleukin-2	1 (0.4%)	2 (0.8%)
Leukinferon (IFN plus complex of cytokines)	0	1 (0.4%)
Thalidomide	1 (0.4%)	0
Tamoxifen	1 (0.4%)	0
Etoposide + cisplatin	1 (0.4%)	0
Investigational drug antibodies	1 (0.4%)	0
Tuberculosis vaccine	1 (0.4%)	0
Immunotherapy (unspecified)	1 (0.4%)	0
Medroxyprogesterone	0	1 (0.4%)
Medroxyprogesterone + tamoxifen	0	1 (0.4%)
Autovaccination	0	1 (0.4%)

*this category includes only patients who received interferon as monotherapy

Table 20 Number of Metastatic Sites (Retrospective Independent Review)

Number of Metastatic Sites Involved	Tivozanib (N=260) n (%)	Sorafenib (N=257) n (%)
1	76 (29.2%)	88 (34.2%)
2	99 (38.1%)	106 (41.2%)
> 2	85 (32.7%)	63 (24.5%)

Table 21 Summary of Antihypertensive Medication at Baseline (ITT Population)

	Tivozanib (N=260) n (%)	Sorafenib (N=257) n (%)
Patients with 1 HTN medication on first dose	42 (16.2)	43 (16.7)
Patients with ≥ 2 HTN medications on first dose	36 (13.8)	44 (17.1)

ITT = Intent-to-treat; HTN = hypertension

Numbers analysed

All 517 patients who were randomised to study treatment were included in the ITT population, which was the primary analysis population. A total of 444 patients (223 in the tivozanib group and 221 in the sorafenib group) were included in the PP population.

Table 22 Patient Populations (All randomised patients) Study AV-951-09-301

	Tivozanib (N=260) n (%)	Sorafenib (N=257) n (%)
ITT population[a]	260 (100.0)	257 (100.0)
Safety population[a]	259 (99.6)	257 (100.0)
PP population[b,c]	223 (85.8)	221 (86.0)

ITT = Intent-to-treat; PP = Per protocol
[a] Percent of all randomized subjects.
[b] Percent of ITT population.
[c] Two subjects (Subject 433-001 in the tivozanib group and 433-010 in the sorafenib group) were included in the PP population in error as both received prohibited concomitant medications (steroids) during the study.

Outcomes and estimation

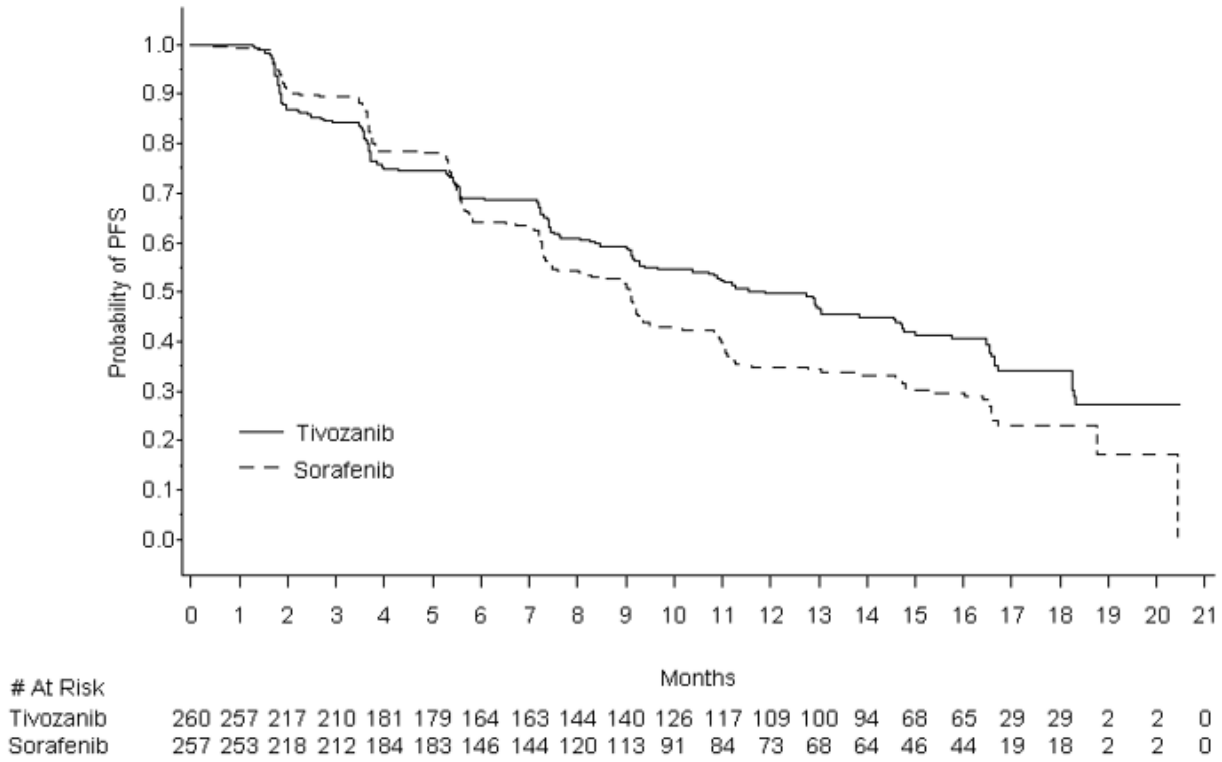
The primary endpoint was PFS as determined by IRR in the ITT population. In the primary analysis which was conducted after 310 events had occurred, median PFS was 11.9 months for tivozanib subjects compared to 9.1 months for sorafenib subjects. The hazard ratio (95% CI) was 0.797 (0.639, 0.993). The p-value was 0.042.

Table 23 PFS as Determined by IRR (ITT Population) Study AV-951-09-301

	Tivozanib (N=260)	Sorafenib (N=257)
Subjects who had disease progression or died, n (%)	153 (58.8%)	168 (65.4%)
Event by disease progression	139 (53.5%)	156 (60.7%)
Event by death without disease progression	14 (5.4%)	12 (4.7%)
Subjects with censored endpoints, n (%)	107 (41.2%)	89 (34.6%)
PFS (months), estimated quartile and 95% CI		
25%	4.0 (3.7, 5.6)	5.4 (3.8, 5.6)
50%	11.9 (9.3, 14.7)	9.1 (7.3, 9.5)
75%	NA (18.3, NA)	16.6 (14.8, 20.4)
Log-rank test statistic (p-value) for tivozanib as compared with sorafenib by primary stratified analysis[1]	4.123 (0.042)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by stratified Cox proportional hazards model	0.797 (0.639, 0.993)	
Log-rank test statistic (p-value) for tivozanib as compared with sorafenib by unstratified analysis	4.731 (0.030)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by unstratified Cox proportional hazards model	0.785 (0.630, 0.978)	
Log-rank test statistic (p-value) for tivozanib as compared with sorafenib by full stratified analysis[2]	3.478 (0.062)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by full stratified Cox proportional hazards model	0.810 (0.648, 1.012)	

[1]Primary stratified analysis includes the following stratification factors: as entered into the IVRS, number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥ 2);
[2]Full stratified analysis includes the following stratification factors: as entered into the IVRS, number of prior treatments (0 or 1), number of metastatic sites/organs involved (1 or ≥ 2), geographic region (Central/Eastern Europe vs others and rest of world vs others)

Figure 9 Kaplan-Meier Plot of PFS as Determined by IRR (ITT Population) Study AV-951-09-301



The updated PFS analysis by IRR, until the end of the study is in line with the primary analysis, conducted after 310 events had occurred.

In the ITT population the median PFS was 14.7 months by Investigator assessment at the end of Study AV-951-09-301.

Table 24 Progression-free survival as determined by investigator assessment (ITT, PP population)

	ITT Population		PP Population	
	Tivozanib (N=260)	**Sorafenib (N=257)**	**Tivozanib (N=223)**	**Sorafenib (N=221)**
Subjects who had disease progression or died, n (%)	144 (55.4%)	182 (70.8%)	125 (56.1%)	157 (71.0%)
Subjects with censored endpoints, n (%)	116 (44.6%)	75 (29.2%)	98 (43.9%)	64 (29.0%)
Median PFS (months) and 95% CI	14.7 (10.4, 16.6)	9.6 (9.0, 11.0)	14.8 (11.0, 16.7)	10.2 (9.1, 11.0)
Log-rank test statistic (p value) for tivozanib as compared with sorafenib by primary stratified analysis	8.635 (0.003)		9.034 (0.003)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by stratified Cox proportional hazards model	0.722 (0.580, 0.899)		0.698 (0.552, 0.884)	

Subgroup analyses: PFS

Geographical region (post-hoc)

This is post-hoc sub-group analysis by region, which groups centres from North America and the EU as 'North America + Europe':

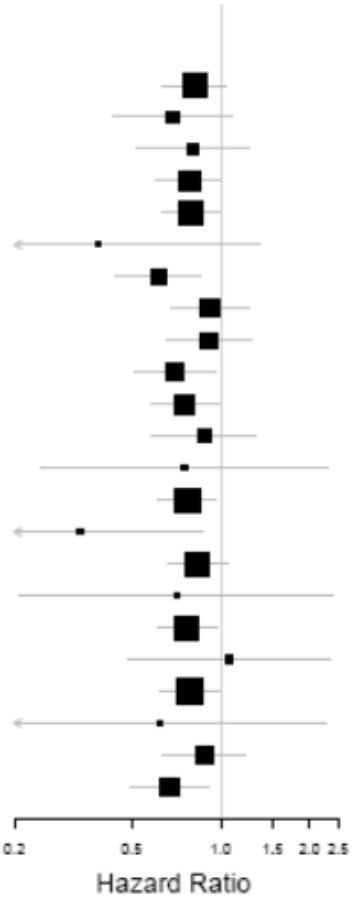
Table 25 Progression-Free Survival Assessment by Geographical Region - Study AV-951-09-301

	North America+Western Europe		North America+Europe		Ukraine+Russia	
	Tivozanib (N=22)	Sorafenib (N=18)	Tivozanib (N=98)	Sorafenib (N=88)	Tivozanib (N=146)	Sorafenib (N=145)
Patients who had disease progression or died, n (%)	8 (36.4)	11 (61.1)	55 (56.1)	58 (65.9)	91 (62.3)	95 (65.5)
Patients with censored endpoints, n (%)	14 (63.6)	7 (38.9)	43 (43.9)	30 (34.1)	55 (37.7)	50 (34.5)
PFS (months), estimated quartile and 95% CI						
25%	9.0 (1.4, NA)	3.5 (1.3, 8.5)	5.4 (3.6, 7.2)	13.9 (11.7, 18.4)	3.7 (3.5, 7.2)	5.4 (3.7, 5.7)
50%	NA (9.0, NA)	8.5 (3.5, 10.8)	12.9 (7.5, 16.7)	7.6 (7.2, 10.8)	11.9 (9.1, 14.7)	9.2 (7.5, 11.1)
75%	NA (NA, NA)	10.8 (8.0, NA)	18.6 (18.3, NA)	14.7 (11.0, 20.4)	22.5 (18.2, 22.5)	18.8 (16.0, 22.1)
Log-rank test statistic (p value) for tivozanib as compared with sorafenib by primary stratified analysis	4.007 (0.045)		7.112 (0.008)		0.173 (0.667)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by stratified Cox proportional hazards model	0.364 (0.131, 1.015)		0.597 (0.407, 0.877)		0.940 (0.703, 1.257)	

Demographic and baseline characteristics

Figure 10 Forest Plot of PFS Hazard Ratios by IRR for Pre-Specified Subgroups (ITT Population)

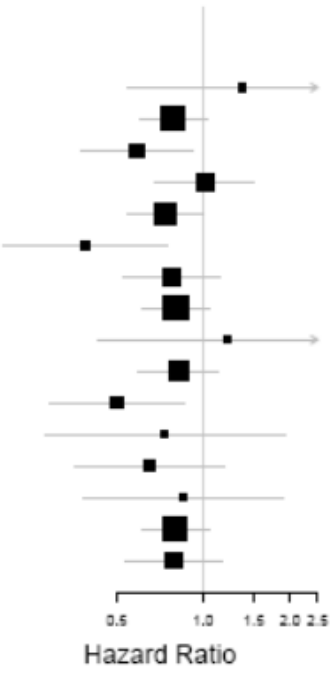
Subgroup	Tivozanib Event/N	Sorafenib Event/N	HR
<65 years	119/195	131/193	0.818
>=65 years	34/65	37/64	0.686
Female	40/75	42/68	0.805
Male	113/185	126/189	0.782
White	146/249	161/249	0.791
Non−White	7/11	7/8	0.384
ECOG status 0	57/116	92/139	0.617
ECOG status 1	96/144	76/118	0.92
<1 year since diagnosis	71/109	71/105	0.911
>=1 year since diagnosis	73/137	84/137	0.698
No prior systermic therapy for met disease	104/181	118/181	0.756
1 prior systemic therapy for met disease	48/78	50/76	0.877
1 metastatic site	5/16	8/17	0.753
>=2 metastatic sites	148/244	160/240	0.772
North America/Western Europe	8/22	11/18	0.335
Central/Eastern Europe	140/229	149/228	0.836
Rest of World	5/9	8/11	0.706
SBP at Baseline <= 140	143/243	151/233	0.772
SBP at Baseline > 140	10/17	17/24	1.067
DBP at Baseline <= 90	150/254	157/238	0.785
DBP at Baseline > 90	3/6	11/19	0.627
MSKCC Intermediate	79/118	70/101	0.879
MSKCC Favorable	72/140	98/155	0.67



Exploratory sub-group analyses were also pre-specified. These included the following prognostic groups: revised Memorial Sloan-Kettering Cancer Center (rMSKCC), composite Memorial Sloan-Kettering Cancer Center (cMSKCC), and Heng (2009).

Figure 11 Forest Plot of PFS Hazard Ratios by IRR for Exploratory Subgroups (ITT Population)

Subgroup	Tivozanib Event/N	Sorafenib Event/N	HR
Revised MSKCC Poor	15/17	7/10	1.361
Revised MSKCC Intermediate	107/173	108/160	0.786
Revised MSKCC Favorable	31/70	53/87	0.59
Baseline HENG Poor	59/78	42/59	1.012
Baseline HENG Intermediate	78/137	98/152	0.737
Baseline HENG Favorable	13/41	28/45	0.387
Prior cytokine therapy	48/79	54/80	0.775
No prior cytokine therapy	105/181	114/177	0.802
Composite MSKCC Naive−Poor	10/12	6/9	1.22
Composite MSKCC Naive−Intermediate	73/121	75/112	0.818
Composite MSKCC Naive−Favorable	21/48	37/60	0.498
Composite MSKCC Pre−treated−Poor	18/24	6/9	0.735
Composite MSKCC Pre−treated−Intermediate	20/31	27/39	0.654
Composite MSKCC Pre−treated−Favorable	10/23	17/28	0.849
Treatment Naive	102/175	112/174	0.797
Previously Treated	51/85	56/83	0.79



An exploratory analysis of PFS by diastolic BP sub-group (maximum on-study) was also presented.

Table 26 Exploratory Kaplan-Meier Analysis of Progression-Free Survival by Diastolic Blood Pressure Subgroup, IRR (ITT Population) - Study AV-951-09-301

	Diastolic Blood Pressure			
	Tivozanib		Sorafenib	
	Maximum On-Study DBP ≤ 90 mmHg (N=158)	Maximum On-Study DBP > 90 mmHg (N=101)	Maximum On-Study DBP ≤ 90 mmHg (N=169)	Maximum On-Study DBP > 90 mmHg (N=87)
Subjects who had disease progression or died, n (%)	106 (67.1)	47 (46.5)	116 (68.6)	51 (58.6)
Subjects with censored endpoints, n (%)	52 (32.9)	54 (53.5)	53 (31.4)	36 (41.4)
PFS (months), estimated quartile and 95% CI				
25%	3.8 (3.5, 5.6)	5.6 (3.7, 9.7)	3.8 (3.6, 5.4)	7.3 (6.7, 9.2)
50%	9.1 (7.5, 12.7)	18.3 (12.9, NA)	7.3 (5.7, 9.1)	11.0 (9.3, 16.4)
75%	16.7 (15.8, 18.3)	NA (NA, NA)	14.8 (11.1, 18.8)	NA (16.6, NA)
Log-rank test statistic (p value) within treatment group by unstratified analysis for maximum DBP > 90 as compared with maximum DBP ≤ 90 mmHg	11.72 (0.001)		10.59 (0.001)	
Hazard ratio (95% CI) within treatment group by unstratified analysis for maximum DBP > 90 as compared with maximum DBP ≤ 90 mmHg	0.553 (0.391, 0.781)		0.581 (0.417, 0.810)	

	Tivozanib vs Sorafenib	
	Maximum On-Study DBP ≤ 90 mmHg	Maximum On-Study DBP > 90 mmHg
Log-rank test statistic (p value) for tivozanib as compared with sorafenib by unstratified analysis	2.014 (0.156)	2.030 (0.154)
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by unstratified Cox proportional hazards model	0.826 (0.633, 1.077)	0.751 (0.504, 1.117)

Table 27 Pre-Specified Kaplan-Meier Analysis of Progression-Free Survival by Subgroup, Independent Radiological Review (ITT Population)

Subgroup	Tivozanib Event/N	Sorafenib Event/N	Hazard Ratio (CI)	Tivozanib Median PFS in Months (CI)	Sorafenib Median PFS in Months (CI)	Unstratisfied p-value
<65 Years	119/195	131/193	0.818 (0.638, 1.049)	11.0 (8.2, 13.0)	8.9 (7.3, 9.3)	0.112
≥ 65 Years	34/65	37/64	0.686 (0.429, 1.099)	14.7 (10.7, NA)	11.0 (8.3, 14.7)	0.114
Female	40/75	42/68	0.805 (0.521, 1.245)	12.9 (9.1, NA)	11.0 (7.5, 16.0)	0.327
Male	113/185	126/189	0.782 (0.606, 1.010)	11.5 (9.0, 14.7)	8.5 (7.3, 9.3)	0.058
White	146/249	161/249	0.791 (0.632, 0.990)	11.9 (9.3, 14.7)	9.1 (7.5, 10.8)	0.040
Non-white	7/11	7/8	0.384 (0.109, 1.357)	12.9 (3.5, 16.7)	5.5 (3.7, 7.2)	0.116
ECOG Status 0	57/116	92/139	0.617 (0.442, 0.860)	14.8 (11.3, NA)	9.1 (7.5, 11.0)	0.004
ECOG Status 1	96/144	76/118	0.920 (0.680, 1.245)	9.1 (7.5, 12.9)	9.0 (7.2, 10.9)	0.588
<1 yr since diagnosis	71/109	71/105	0.911 (0.655, 1.269)	8.4 (7.2, 12.9)	7.2 (5.5, 9.2)	0.581
≥1 yr since diagnosis	73/137	84/137	0.698 (0.509, 0.957)	14.8 (11.3, 16.7)	9.3 (8.1, 11.1)	0.024
No prior treatments	104/181	118/181	0.756 (0.580, 0.985)	12.7 (9.1, 15.0)	9.1 (7.3, 10.8)	0.037
1 prior treatment	48/78	50/76	0.877 (0.587, 1.309)	11.9 (8.0, 16.6)	9.1 (7.2, 11.1)	0.520
1 metastatic site	5/16	8/17	0.753 (0.246, 2.303)	NA (8.5, NA)	16.6 (8.1, NA)	0.617
≥2 metastatic sites	148/244	160/240	0.772 (0.617, 0.966)	11.3 (9.1, 13.8)	9.0 (7.3, 9.3)	0.023
North America/ Western Europe	8/22	11/18	0.335 (0.129, 0.875)	NA (9.0, NA)	8.5 (7.3, 10.8)	0.020
Central/ Eastern Europe	140/229	149/228	0.836 (0.664, 1.054)	11.3 (9.1, 14.6)	9.2 (7.3, 10.9)	0.129
Rest of World	5/9	8/11	0.706 (0.208, 2.404)	13.0 (1.8, 16.7)	6.4 (3.7, 9.0)	0.574
SBP at baseline ≤140 mmHg	143/243	151/233	0.772 (0.613, 0.971)	12.7 (9.3, 14.7)	9.1 (7.3, 10.8)	0.026
SBP at baseline > 140 mmHg	10/17	17/24	1.067 (0.486, 2.341)	7.2 (2.7, NA)	8.9 (7.2, 10.2)	0.871
DBP at baseline ≤90 mmHg	150/254	157/238	0.785 (0.627, 0.983)	11.5 (9.2, 14.7)	9.1 (7.3, 9.4)	0.033
DBP at baseline > 90 mmHg	3/6	11/19	0.627 (0.173, 2.279)	14.7 (9.1, NA)	9.5 (7.2, NA)	0.475
MSKCC Intermediate	79/118	70/101	0.879 (0.636, 1.215)	7.5 (5.6, 11.2)	7.3 (5.7, 9.1)	0.431
MSKCC Favorable	72/140	98/155	0.670 (0.494, 0.910)	16.5 (12.7, 18.3)	9.3 (8.5, 12.8)	0.010

NA=Not applicable
Note that MSKCC Poor is not included because the number of events was too small (2 events in 2 subjects for tivozanib, no events in 1 subject for sorafenib) to estimate the hazard ratio.

In the pre-specified subset of patients who had not received prior systemic therapy for metastatic disease (70% of the population), the median PFS in the tivozanib hydrochloride arm was 12.7 months (95% CI: 9.1 to 15.0) compared with 9.1 months (95% CI: 7.3 to 10.8) in the sorafenib arm with a p = 0.037 and a HR of 0.756.

In the predefined subgroup of one prior therapy for metastatic RCC, tivozanib showed a median PFS of 11.9 months vs. 9.1 months, HRR 0.877.

Secondary endpoints

Overall Survival (OS)

Table 28 Overall survival (ITT population) - Study AV-951-09-301

	Tivozanib N=260	Sorafenib N=257
Patients who died, n (%)[a]	133 (51.2)	121 (47.1)
Patients who survived, n (%)	127 (48.8)	136 (52.9)
OS (months), estimated quartile and 95% CI		
25%	12.1 (9.6, 14.9)	14.1 (12.0, 18.9)
50%	28.2 (22.5, 33.0)	30.8 (28.4, 33.3)
75%	NA (35.9, NA)	NA (NA, NA)
Log-rank test statistic (p-value) for tivozanib as compared with sorafenib by primary stratified analysis	1.189 (0.276)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by stratified Cox proportional hazards model	1.147 (0.896, 1.470)	
Log-rank test statistic (p-value) for tivozanib as compared with sorafenib by unstratified analysis	1.244 (0.265)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by unstratified Cox proportional hazards model	1.150 (0.899, 1.472)	

[a]Deaths occurred during 902 study period were included to this analysis

Table 29: Next Line Anticancer Medication Taken by Patients Post-Progression

Number of patients	TIV 260 n (%)	SOR 257 n (%)
Patients discontinuing first-line treatment	211	230
Patients with next line therapy	81 (38.4)	174 (75.7)
Tivozanib	NA	161
Other VEGF inhibitor	19	2
mTOR	23	4
Other	39	7
No therapy	130 (61.6)	56 (24.3)

Figure 12 Kaplan-Meier Plot of Overall Survival (ITT Population) - Study AV-951-09-301

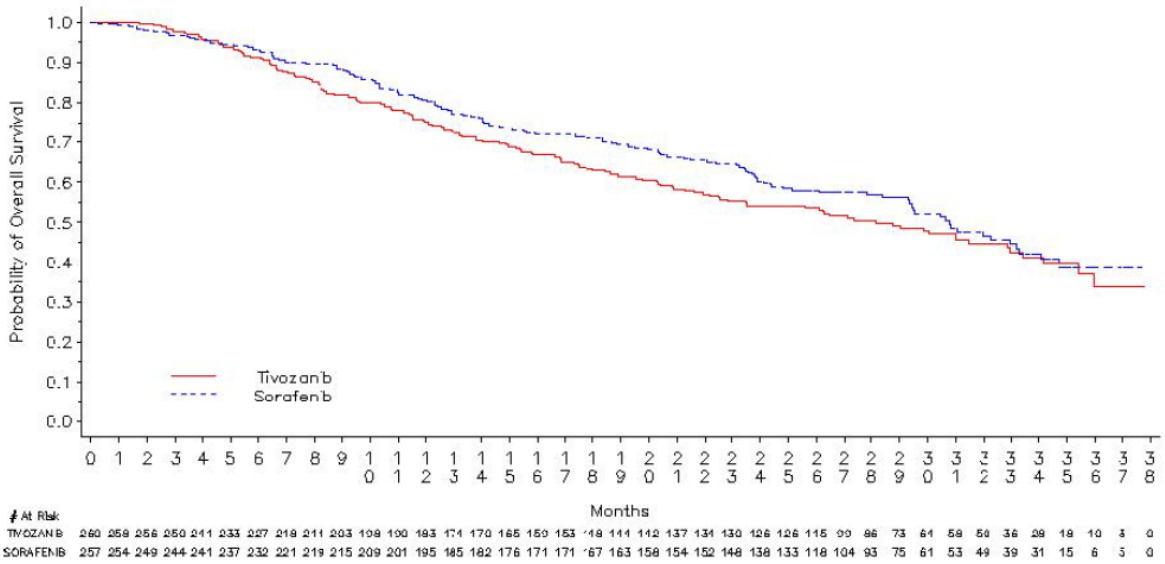


Table 30: Post Hoc Overall Survival Assessment by Geographical Region

	North America/Western Europe[a]		Central/ Eastern Europe[b]		Rest of World[c]	
	Tivozanib (N=22)	Sorafenib (N=18)	Tivozanib (N=229)	Sorafenib (N=228)	Tivozanib (N=9)	Sorafenib (N=11)
Patients who died, n (%)	7 (31.8)	12 (66.7)	124 (54.1)	107 (46.9)	2 (22.2)	2 (18.2)
Patients who were alive, n (%)	15 (68.2)	6 (33.3)	105 (45.9)	121 (53.1)	7 (77.8)	9 (81.8)
OS (months), estimated quartile and 95% CI						
25%	21.9 (4.6, NA)	14.3 (1.3, 24.4)	11.5 (9.2, 13.3)	13.9 (11.7, 18.4)	26.2 (5.1, NA)	34.1 (20.7, 34.1)
50%	NA (21.9, NA)	29.5 (14.3, 34.7)	26.3 (20.4, 31.4)	30.7 (26.1, NA)	NA (5.1, NA)	34.1 (20.7, 34.1)
75%	NA (NA, NA)	34.7 (29.5, NA)	NA (35.4, NA)	NA (NA, NA)	NA (5.1, NA)	34.1 (NA, NA)
Log-rank test statistic (p value) for tivozanib as compared with sorafenib by primary stratified analysis	2.225 (0.136)		2.611 (0.106)		0.577 (0.448)	
Hazard ratio (95% CI) for tivozanib as compared with sorafenib by stratified Cox proportional hazards model	0.497 (0.195, 1.269)		1.239 (0.955, 1.606)		2.503 (0.218, 28.787)	

NA=Not applicable
[a] Includes United States, Great Britain, Canada, France, and Italy
[b] Includes Russia, Serbia and Montenegro, Ukraine, Poland, Romania, Bulgaria, Hungary, and the Czech Republic
[c] Includes India and Chile

A post-hoc analysis, by grouping EU countries with North America as 'North America + Europe' was conducted.

Table 31 Second Line Therapy Use and Overall Survival by Region

Region	% Patients Receiving Second Line Therapy		OS Hazard Ratio (p-value)	Median OS (months)
	Tivozanib	Sorafenib		
ITT N=517	38.4	75.7	1.147 (p = 0.276)	T = 28.2 S = 30.8
NA and EU* N=186	55.6	79.5	0.846 (p = 0.433)	T = 32.9 S = 29.5
NA and EU5** N=40	84.2	82.4	0.497 (p = 0.136)	T = NA S = 29.5
RUS and UKR N=291	28.4	71.0	1.383 (p = 0.051)	T = 26.3 S = 32.0

* NA and = North America (US + Canada), UK, France, Italy, Bulgaria, Czech Republic, Hungary, Poland, Romania

** NA & EU5 = North America (US + Canada), UK, France, Italy

Post hoc analysis of PFS and OS data was performed on the 186 patients enrolled in North America and the European Union (US, Canada, Italy, France, UK, Bulgaria, Czech Republic, Romania, Poland, Hungary) in order to evaluate data by geographical stratification and retain the EU as a single region. This analysis revealed a median PFS in the EU/North America region of 12.9 months versus 7.6 months for sorafenib [p = 0.008] with a HR of 0.597.

Figure 13 Post Hoc Overall Survival Assessment for North America and Europe

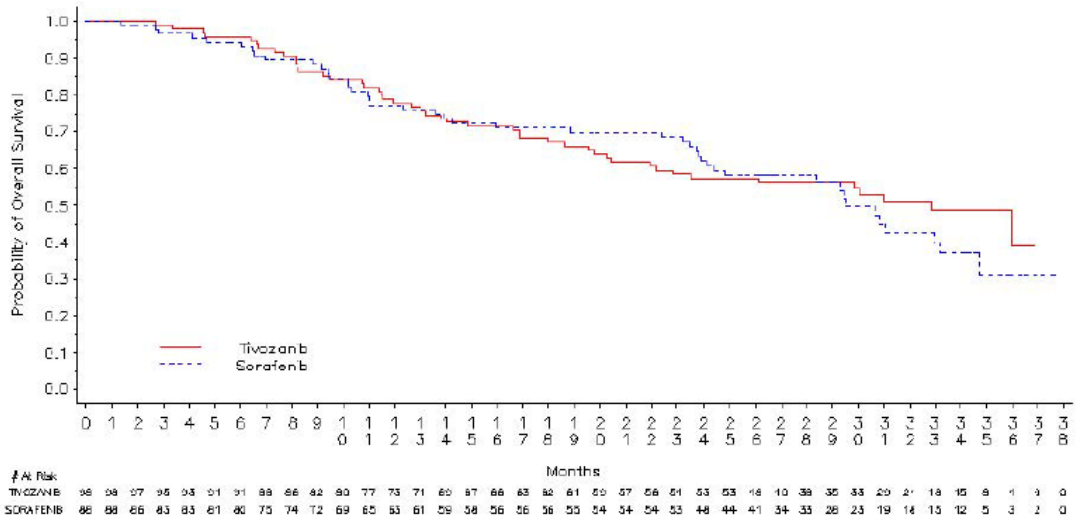


Table 32: Results of Cox Model Analysis for Overall Survival at the July 2013 analysis point

Parameter (reference)	Unadjusted comparison (1) HR (95% CI)	Unadjusted comparison + geography (2) HR (95% CI)	Adjusted for covariates (3) HR (95% CI)	Covariate adjusted + geography (4) HR (95% CI)	Covariate adjusted + new therapy + geography (5) HR (95% CI)
Primary exploratory variables					
Treatment (Sorafenib)	1.16 (0.91-1.48) P=0.25	1.16 (0.91-1.49) P=0.24	1.10 (0.86-1.41) P=0.43	1.10 (0.86-1.42) P=0.43	1.09 (0.80-1.48) P=0.60
Geography (all others)	-	1.14 (0.89-1.46)	-	1.01 (0.77-1.31)	1.00 (0.76-1.31)
New targeted therapy (none)	-	-	-	-	0.97 (0.71-1.34)
Covariates					
Age (≥65)	-	-	1.28 (0.96-1.71)	1.28 (0.95-1.71)	1.28 (0.95-1.72)
Sex (female)	-	-	1.11 (0.83-1.47)	1.11 (0.83-1.47)	1.11 (0.83-1.47)
Race (non-white)	-	-	3.61 (1.34-9.74)	3.60 (1.32-9.82)	3.60 (1.32-9.81)
ECOG PS (1)	-	-	0.67 (0.52-0.86)	0.67 (0.52-0.87)	0.67 (0.52-0.87)
Metastatic sites (≥2)	-	-	0.39 (0.19-0.78)	0.39 (0.19-0.78)	0.39 (0.19-0.78)
MSKCC (intermediate/poor)	-	-	0.45 (0.35-0.58)	0.45 (0.35-0.58)	0.45 (0.35-0.58)

Overall response rate (ORR)

Table 33 Summary of Overall Response, IRR (ITT Population)

	Tivozanib N=260	Sorafenib N=257
Confirmed Overall Response, n (%)		
Complete Response (CR)	3 (1.2)	2 (0.8)
Partial Response (PR)	83 (31.9)	58 (22.6)
Stable Disease (SD)	134 (51.5)	168 (65.4)
Progressive Disease (PD)	34 (13.1)	19 (7.4)
Not evaluable (NE)	6 (2.3)	10 (3.9)
Missing	0	0
Overall confirmed ORR (CR+PR), n (%)	86 (33.1)	60 (23.3)
95% CI for ORR	(27.4, 39.2)	(18.3, 29.0)
Primary stratified analysis		
Odds ratio	1.623	
95% CI for odds ratio	(1.101, 2.391)	
p-value	0.013	
Overall confirmed disease control rate (DCR) (CR+PR+SD), n (%)	220 (84.6)	228 (88.7)
95% CI for DCR	(79.6, 88.8)	(84.2, 92.3)

Duration of response

Median duration of response (DR) by IRR was 15.0 months for tivozanib compared to 12.9 months for sorafenib. The hazard ratio was 0.823 (90% CI: 0.488, 1.388). When investigator assessed, including extension study data, the difference in median DRs was increased: 24.3 months for tivozanib vs. 12.5 months for sorafenib.

Quality of life

Patient reported outcomes were measured by FACT-G total score and subscales (physical, social, emotional and functional well-being), FKSI-DRS, EQ-5D weighted health state index and EQ-5D VAS. In general the scores were comparable between treatment groups. A total of 258 out of 260 tivozanib patients and 254 out of 257 sorafenib patients completed the FACT-G Scale questionnaire at baseline. Total FACT-G Score was Mean (std) 77.05 (14.967) for tivozanib and 76.93 (15.949) for sorafenib. At the end of treatment 215 patients in the tivozanib arm and 214 patients in the sorafenib arm completed the questionnaire and the scores were Mean (std) 73.53 (17.781) and 73.04 (18.110) respectively, changes from baseline were -3.66 (14.995) for tivozanib and -4.82 (14.684) for sorafenib. The results were not statistically significant.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34 Summary of efficacy for trial AV-951-09-301

Title: A phase 3, randomised, controlled, multi-centre, open-label study to compare tivozanib (AV-951) to sorafenib in subjects with advanced renal cell carcinoma.			
Study identifier	AV-951-09-301		
Design	Open-label, randomised, controlled, multi-national, multicentre, parallel-arm study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2 years not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Tivozanib		Tivozanib hydrochloride 1.5 mg daily orally (3 weeks on, 1 week off), until disease progression or unacceptable toxicity, n=260 randomized
	Sorafenib		Sorafenib 400 mg BID orally. until disease progression or unacceptable toxicity, n=257 randomized
Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	PFS by independent radiological review
	Secondary:	Overall survival (OS)	
	Secondary:	Objective response rate (ORR)	ORR by independent radiological review
Database lock	10th July 2013 (though a snapshot was taken on 15th Dec 2011 for PFS)		
Results and Analysis			
Analysis description	**Primary Analysis (PFS)**		
Analysis population and time point description	Intention to treat After 310 PFS events (15th Dec 2011)		
Descriptive statistics and estimate variability	Treatment group	Tivozanib	Sorafenib
	Number of subject	260	257
	Median PFS (months)	11.9	9.1
	95% CI	9.3, 14.7	7.3, 9.5
Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups	Tivozanib compared with sorafenib
		Hazard ratio	0.797
		95% CI	0.639, 0.993
		P-value	0.042
Notes	The PFS analysis was repeated at database lock and the results were consistent with the primary analysis.		
Analysis description	**Secondary analysis (OS)**		

Analysis population and time point description	Intention to treat Deaths that occurred during 09-902 study period were included in this analysis. All subjects were followed up for a minimum of 2 years unless lost to follow up or died.		
Descriptive statistics and estimate variability	Treatment group	Tivozanib	Sorafenib
	Number of subject	260	257
	Median OS (months)	28.2	30.8
	95% CI	22.5, 33.0	28.4, 33.3
Effect estimate per comparison	Secondary endpoint (OS)	Comparison groups	Tivozanib compared with sorafenib
		Hazard ratio	1.147
		95% CI	0.896, 1.470
		P-value	0.265
Notes			
Analysis description	**Secondary analysis (ORR)**		
Analysis population and time point description	Intention to treat Whilst on randomised treatment		
Descriptive statistics and estimate variability	Treatment group	Tivozanib	Sorafenib
	Number of subject	260	257
	Confirmed overall response n (%)	86 (33.1)	60 (23.3)
	95% CI	27.4, 39.2	18.3, 29.0
Effect estimate per comparison	Secondary endpoint (ORR)	Comparison groups	Tivozanib compared with sorafenib
		Odds ratio	1.623
		95% CI	1.101, 2.391
		P-value	0.013

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

	Age 65-74 years (Older subjects number /total number)	**Age 75-84 years (Older subjects number /total number)**	**Age 85+ years (Older subjects number /total number)**
Controlled Trials	159/789	21/789	1/789
Non Controlled trials	70/266	10/266	1/266

Supportive studies

There are three studies to support the efficacy in advanced RCC: the Phase 3 extension study, and two Phase 2 studies.

Phase 3 extension study AV-951-09-902

This study was set up as an open-label extension protocol for the pivotal study (AV-951-09-301). Patients were enrolled and treated as follows:

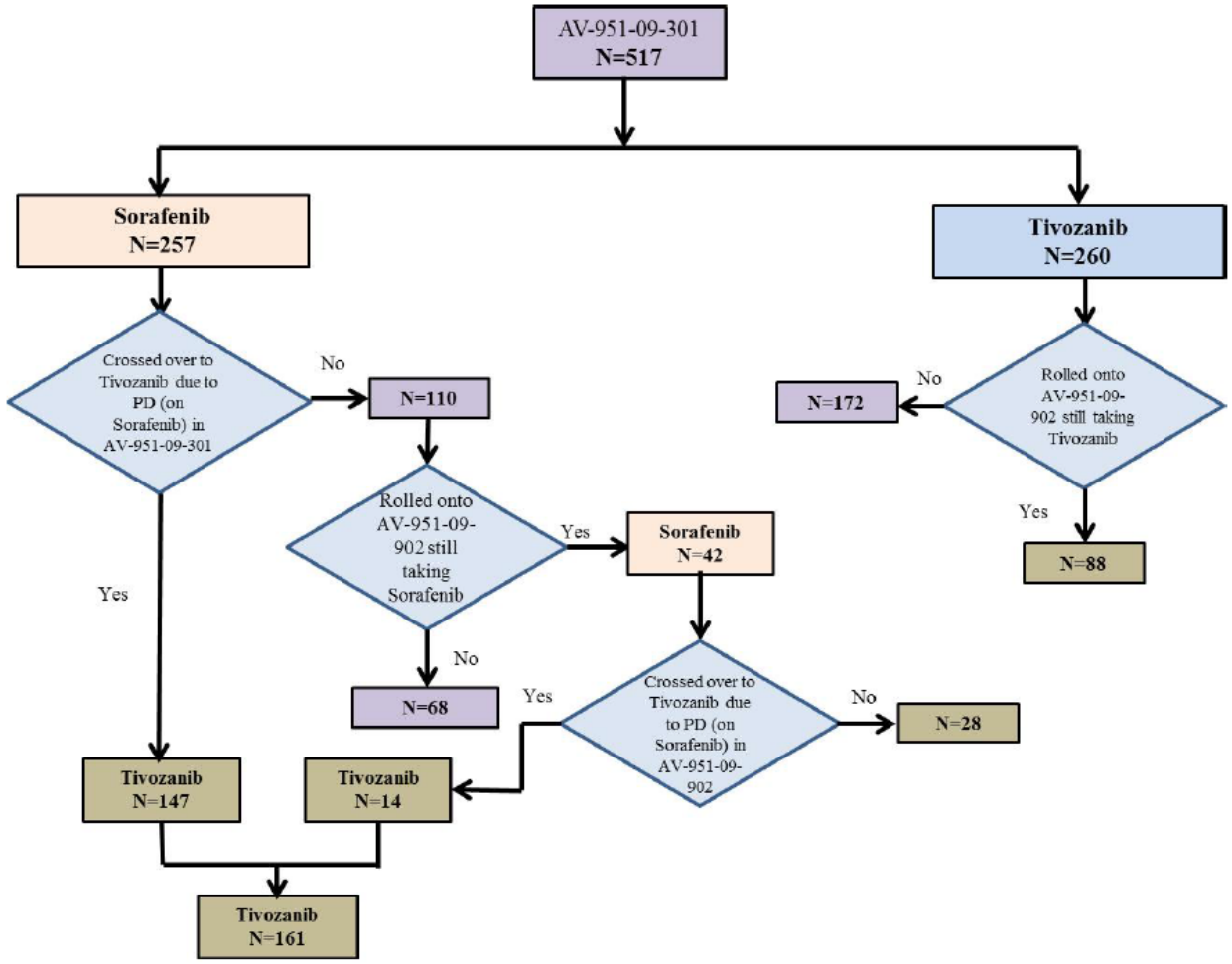
- Patients who were randomised to tivozanib and completed the pivotal study with no PD were continued on tivozanib
- Patients who had RECIST documented PD on tivozanib during the pivotal study were not enrolled, but were transferred to local standard of care
- Patients who were randomised to sorafenib and completed the pivotal study with no PD were continued on sorafenib
- Patients who had RECIST documented PD on sorafenib during the pivotal study were offered tivozanib
- Patients who continued sorafenib during the extension study were offered cross-over to tivozanib on progression

Exclusion criteria included: progression of CNS metastases, haematological or serum chemistry abnormalities, uncontrolled hypertension and treatment with another anti-cancer therapy.

The dosing regimens were as for the pivotal study. Treatment was continued until clinical or documented PD, or unacceptable toxicity. Disease and responses assessment were conducted by the investigator; there was no IRR.

The study dates were 24/05/2010 to 04/07/2014. A total of 277 patients were enrolled. Of these, 161 who were initially randomised to sorafenib received at least one dose of tivozanib in the extension study. This includes 14 patients who started the extension study on sorafenib, six of whom had documented PD in the pivotal study. Eighty-eight patients who were initially randomised to tivozanib received at least one dose of tivozanib in this study. Twenty-eight patients who were initially randomised to sorafenib received at least one dose of sorafenib in this study (but did not cross-over to tivozanib). The patient flow through both studies is illustrated below:

Patient flow AV-951-09-301/902 studies



Efficacy results

Median PFS by investigator assessment, including data from the pivotal and extension study for the ITT population, was 14.7 months for tivozanib patients compared to 9.7 months for sorafenib patients (p=0.006). The hazard ratio was 0.755 (95% CI: 0.617, 0.922).

For the 161 patients who crossed over to tivozanib, ORR was 18.0% (95% CI: 12.4%, 24.8%), all PR. Median duration of PR was 15.2 months. One hundred and eight patients (67.1%) had PD or died on study; median PFS was 11.0 months (95% CI: 7.3 to 12.7 months). Seventy-eight patients (48.4%) died on study; median OS from the start of the first dose in this study was 21.6 months (95% CI: 17.0 to 27.6 months).

For patients who remained on initial randomised tivozanib or sorafenib, the ORR was 55.7% (95% CI: 44.7%, 66.3%) and 57.1% (95% CI: 37.2%, 75.5%) respectively. Thirty-five (39.8%) patients on tivozanib treatment and 1 (3.6%) patient on sorafenib treatment had PD or died on this study.

Phase 2 study (AV-951-07-201)

This was a phase 2, placebo-controlled, randomised, discontinuation trial of tivozanib in patients with metastatic or recurrent RCC, or RCC not amenable to surgical intervention. This study enrolled subjects at 28 sites in Russia, Ukraine and India. The primary objectives of this study were to determine the safety of tivozanib, ORR at 16 weeks, and proportion remaining progression-free for 12 weeks following randomised assignment to tivozanib or placebo at 16 weeks.

Of the 274 subjects enrolled, 272 received tivozanib hydrochloride 1.5 mg daily (3 weeks on, 1 week off) during the initial 16-week open-label period. After 16 weeks, treatment assignment was determined by disease status (using RECIST criteria):

- Subjects with ≥25% tumour shrinkage continued dosing with open-label tivozanib for 12 weeks at current dose, unless PD or intolerable toxicity.
- Subjects with <25% tumour growth or shrinkage were randomly allocated to tivozanib at current dose or placebo, in a double-blind design, for 12 weeks at current dose, unless PD or intolerable toxicity. Those with PD had treatment unblended – those on tivozanib were discontinued, and those on placebo were offered tivozanib.
- Subjects with ≥25% tumour growth or other evidence of progression were discontinued.

All imaging studies were assessed retrospectively by IRR.

Efficacy results

At 16 weeks, following the initial open-label period, the ORR was 18.0% (95% CI: 13.6%, 23.1%) by IRR assessment. The PFS rate at 12 weeks post-randomisation (in subjects with <25% tumour growth or shrinkage) was 49.2% for tivozanib vs. 21.1% for placebo by IRR. The ORR for the entire study was 30.1% (95% CI: 24.8%, 36.0%) by IRR. The ORR for the entire study for subjects with clear cell nephrology and nephrectomy was 35.8% (95% CI: 32.4%, 44.3%) by IRR.

Phase 2 study (AV-951-10-202)

This was a phase 2, open-label, single-arm study of tivozanib in subjects with advanced RCC. One hundred and five subjects were enrolled from 21 sites in US and Canada. Subjects had unresectable locally recurrent or metastatic RCC and had undergone prior nephrectomy. Subjects were treatment naïve, or had received no more than one prior systemic therapy excluding VEGF or mTOR targeted therapy. Subjects received tivozanib 1.5 mg daily orally (3 weeks on, 1 week off). After 6 months on study drug without PD or unacceptable toxicity, subjects were given the opportunity to enter an extension protocol, AV-951-09-901, to continue receiving study drug. The primary efficacy endpoint was proportion of subjects who were progression-free at 6 months after first dose of study drug. Tumour assessments were performed by the investigators.

Efficacy results

At 6 months, PFS was 60.9% (95% CI: 50.1%, 70.9%). ORR was 24.8% (95% CI: 16.9%, 34.1%); there were 2 subjects with CR.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study AV-951-09-301 was a 2-year, open-label, randomised, controlled, multi-national, multicentre, parallel-arm study comparing tivozanib with sorafenib in patients with advanced RCC.

The study population had recurrent or metastatic RCC with a clear cell component and had undergone prior nephrectomy. Patients were treatment naïve or had received no more than one prior systemic treatment (immunotherapy including interferon-alfa or interleukin-2 based-therapy, chemotherapy, hormonal therapy or an investigational agent) for metastatic RCC. ECOG PS was 0 or 1. Patients were excluded if they had received any prior therapy with agents targeting the VEGF or mTOR pathway.

As the majority (around 75-90%) of renal cell carcinomas are histologically clear cell or have a clear cell component, even if the pivotal study had included patients with non-clear-cell RCC (nccRCC), the numbers would have been small. Patients with nccRCC were included in supportive studies 201 and 202. Although the numbers are small, there appears to be evidence of activity of tivozanib in nccRCC albeit at a reduced level compared to RCC.

The proposed indication does not specifically mention clear cell RCC. Given the evidence of activity in nccRCC, and the previous regulatory decisions regarding the indications for similar products, this is acceptable. Information on the population studied is included in SmPC section 5.1 which is sufficient.

The chosen dose of sorafenib is the approved dose in the EU for advanced RCC. During a scientific advice (SA) procedure, CHMP expressed concern that sunitinib rather than sorafenib was currently considered to be the most active tyrosine kinase inhibitor (TKI) in first-line RCC. However CHMP accepted the choice of sorafenib, with the comment that a demonstration of superiority would support a demonstration of efficacy.

Due to the incidence of DLTs in Study AV-951-03-b01 at the highest dose level tested (2.0 mg), the 1.5 mg dose of tivozanib hydrochloride was identified as the highest dose level with an acceptable safety/tolerability profile. This dose level was therefore determined as the RP2D (Eskens et al, 2011) and selected for further clinical studies. Following Study AV-951-03-b01 (with dosing cycles of 4 weeks of tivozanib hydrochloride followed by a 2-week rest period), the dosing regimen for RCC studies was altered to reduce the rest period to 1 week. In Study AV-951-03-b01, toxicities were rapidly reversible upon stopping treatment, supporting a shorter rest period. In addition, clinical data with sunitinib, another VEGFR inhibitor, demonstrated that some patients experienced recurrence of disease-related symptoms during a 14-day break in treatment (van der Veldt et al, 2008). For these reasons, the tivozanib hydrochloride dosing regimen was changed to 3 weeks of once-daily treatment followed by a 1-week rest period for the subsequent clinical study (AV-951-07-201), in an effort to maximise clinical benefit yet allow patients to recover from any treatment-related toxicity. This dosing regimen was also used for all subsequent RCC studies.

In the SmPC section 4.2 the recommended dose of tivozanib is expressed as 1340 microgram (as this is the amount of tivozanib free base equivalent to 1.5 mg salt) once daily for 21 days, followed by a 7-day rest period to comprise one complete treatment cycle of 4 weeks.

Patients who completed 2 years on study with no progressive disease (PD) were given the option to continue treatment in an extension protocol (09-902). In addition, patients who took sorafenib and experienced radiographic evidence of PD were given the option to cross over to receive tivozanib in study 09-902. Patients randomised to tivozanib were discontinued from the study once progression was confirmed by independent radiological review (IRR), and transferred to standard care.

The primary endpoint was PFS by independent radiological review (IRR). This was accepted as the primary endpoint during the CHMP SA procedure. As there was no IRR in extension study 09-902, the PFS using the IRR response assessment was limited to the end of Study 09-301. Key secondary endpoints included OS and ORR.

The ITT population was defined as all randomised patients, and was used for the analysis of the primary and secondary efficacy endpoints. This is agreed since in an open label study every subject randomised should be included in the analysis regardless of whether they took the treatment.

The ITT population was 517 patients (260 in the tivozanib arm and 257 in the sorafenib arm). Over 70% of the study population was male, in line with the known male preponderance for RCC. The median age was 59 years. This is younger than would be expected, given that RCC peaks in the 7th decade, and likely reflects the eligibility criteria. The majority of baseline characteristics, including cancer histories, were well-balanced between the groups. In each treatment arm, around 99% patients had metastatic disease at screening, and around 30% had a prior treatment for metastatic disease. A total of 78 (30.0%) patients in the tivozanib group were treated with IFN-α, alone or in combination with other anti-cancer agents, compared to 77 patients in the sorafenib group (30.0%). Very few received cytotoxic chemotherapy, 3 (1.2%) in the tivozanib arm compared to 6 (2.3%) in the sorafenib arm. There was no obvious imbalance.

The study was designed such that only patients randomised to sorafenib were permitted to cross over, which could potentially confound the overall survival results.

There was an over-representation of subjects from non-EU European countries in the randomised study population (56%). It is possible that it was easier to recruit in these countries because of limited availability of targeted therapies. Also, Investigators in many of these countries who had participated in the prior randomised discontinuation study were familiar with tivozanib and as a result, the study enrolled rapidly at the time of study initiation. However, this over representation was unanticipated by the study sponsor.

There was discordance of diagnosis between the investigator assessment and the IRR assessment in 27.3% in the tivozanib group and 27.6% in the sorafenib group. For patients with both IRR and investigator progression there was a discordance of date for 18.8% in the tivozanib group and 26.5% in the sorafenib group. Of these discordances around a half in each treatment arm were discordances where the IRR and the investigator had only been in disagreement for one assessment interval. The investigator assessments favoured tivozanib as they declared many more PDs on sorafenib than the IRR. This highlights the issue of investigator bias and the importance of using an IRR for the primary analysis.

Efficacy data and additional analyses

Pivotal study AV-951-09-301

9% of patients with RCC are expected to be ≥ 75 years at diagnosis (Altekruse SF et al SEER cancer statistics review, 1975-2007. NCI 08.01.2016). The over 75 year age groups are relatively under-represented in the RCC clinical efficacy studies, representing only 3.1% of the pooled study populations. However this is a general issue for clinical studies, due to the exclusion criteria. Under-representation of older patients is not expected to have implications for efficacy.

The primary endpoint was PFS as determined by IRR in the ITT population when 310 events had occurred. The median PFS (95% CI) was 11.9 months (9.3, 14.7) for tivozanib compared to 9.1 months (7.3, 9.5) for sorafenib; the hazard ratio (stratified Cox proportional hazards model) (95% CI) was 0.797 (0.639,

0.993) and p-value was 0.042. This updated analysis at study end is in line with the primary analysis. The pre-planned sensitivity analyses and subgroup analyses of PFS are in line with the primary outcome.

Internal inconsistency is noted in the large subgroups by geographical region. In the large subgroup of patients from Russia or Ukraine (56% of patients), the hazard ratio for PFS is 0.94 (0.70-1.26).No imbalance in prognostic factors was identified as a possible background cause for lack of PFS treatment effect in the large Russian/Ukrainian subgroup.

Post-hoc exploratory analyses according to the geographical groupings of Russia/Ukraine and North America/EU were performed where the applicant highlighted the geographical imbalance in baseline ECOG scores. The analysis showed that for patients with an ECOG score of 1, the hazard ratio is around 1 - in line with the Forest plot for pre-specified subgroups. For the patients on sorafenib, ECOG score makes no difference to PFS outcome, and therefore was not considered a prognostic factor. Therefore the imbalance in ECOG status between treatment groups could not explain the observed geographical imbalance in PFS. The median OS (95% CI) was 28.2 months (22.5, 33.0) for tivozanib compared to 30.8 months (28.4, 33.3) for sorafenib; the hazard ratio (stratified Cox proportional hazards model) (95% CI) was 1.147 (0.896, 1.470) and the p-value was 0.276. Since the study design allowed patients on sorafenib who had PD to receive tivozanib, there was potential for confounding and it was concluded that no clear difference in OS has been observed between the two treatment groups.

The ORR outcome by IRR favours tivozanib over sorafenib, 33% vs 23%. Median duration of response by IRR was 15.0 months for tivozanib compared to 12.9 months for sorafenib.

An increase in median PFS for tivozanib vs. sorafenib of 2.8 months is clinically relevant. Sorafenib is an active comparator, ORR and duration of response favour tivozanib, and data from phase 2 studies are supportive of the efficacy of tivozanib. Taking these factors into account, it is considered that the efficacy of tivozanib has been demonstrated.

Patient reported outcomes were generally comparable between treatment groups. For this un-blinded study, only limited conclusions can be drawn from patient-reported outcomes.

Supportive studies

The extension study (09-902) included 161 patients who crossed over from sorafenib to tivozanib. In this group, ORR was 18%. This provides some evidence of second-line activity of tivozanib in patients who have progressed on sorafenib.

For the Phase 2 randomised discontinuation study (07-201), the ORR by IRR was 18% after the 16 week open-label period. After randomised discontinuation, the PFS rate at 12 weeks (in subjects with <25% tumour growth or shrinkage) was 49% for tivozanib vs. 21% for placebo by IRR. This study selected a population of patients who were stable on tivozanib and then tested whether this stable disease was lost if treatment was withdrawn. It is important to note that this study does not test the efficacy of tivozanib versus placebo in the target population.

For the Phase 2 open-label single arm study (10-202), investigator-assessed ORR was 25% at 6 months. This is in line with the 33% rate of ORR by IRR for the pivotal study. The phase 2 studies provide supportive evidence of efficacy.

2.5.4. Conclusions on the clinical efficacy

An increase in median PFS for tivozanib vs. sorafenib of 2.8 months is clinically relevant and is supported by improvement in the ORR and duration of response and data from phase 2 studies.

2.6. Clinical safety

The integrated safety analyses were performed for the core RCC monotherapy studies (90-301, 07-201, 10-202, 12-205 and 09-902); the other monotherapy studies (03-B01, 08-105, 10-112) and the extension study (09-901). Supportive safety data is available from combination therapy studies and studies not sponsored by the Applicant.

Patient exposure

During the core RCC monotherapy studies, patients received tivozanib 1.5 mg daily (3 weeks on, 1 week off) which is the proposed dose. A total of 835 patients with RCC received tivozanib monotherapy, of which 674 were randomised to receive first-line tivozanib, and 161 crossed over to tivozanib after progressing on the comparator sorafenib. 157 patients with RCC have been exposed to tivozanib monotherapy for >6 and ≤12 months, 286 patients for > 12 months and 61 patients for > 24 months. During the procedure, the applicant provided an updated evaluation of safety from extension study 901.

An analysis of the relative dose intensity for 4 core RCC monotherapy studies (excluding Study AV-951-12-205) is presented in the following table. Relative dose intensity is defined as the actual dose relative to the presumed intended dose of 1.5 mg.

Relative Dose Intensity (Core RCC Monotherapy Studies*)

	Total Tivozanib (n = 797)	AV-951-07-201	AV-951-10-202	AV-951-09-902	AV-951-09-301	
		Tivozanib (n = 272)	Tivozanib (n = 105)	Tivozanib (n = 161)	Tivozanib arm (n = 259)	Sorafenib arm (n = 257)
Duration of exposure, days						
Quartile (95% CI)						
25%	106 (105, 120)	106 (99, 133)	104 (49, 105)	77 (50, 108)	159 (118, 187)	168 (113, 171)
50%	218 (190, 254)	259 (193, 304)	161 (160, 161)	224 (162, 282)	365 (280, 497)	288 (264, 337)
75%	534 (496, 602)	547.5 (445, 699)	161 (161, 162)	441 (385, 497)	834 (715, 951)	548 (448, 624)

Adverse events

Table 35 Most Frequently Reported Study Treatment-Related TEAEs (Occurring in ≥ 2.0% of First-line Tivozanib Hydrochloride Patients Overall) by System Organ Class and Preferred Term (Core RCC Monotherapy Studies)

System Organ Class Preferred Term	Total	AV-951-07-201	AV-951-10-202	AV-951-12-205	AV-951-09-902	AV-951-09-301	
	Tivozanib (n = 674) n (%)	Tivozanib (n = 272) n (%)	Tivozanib (n = 105) n (%)	Tivozanib (n = 38) n (%)	Tivozanib (n = 161) n (%)	Tivozanib arm (n = 259) n (%)	Sorafenib arm (n = 257) n (%)
Any Treatment-related Adverse Event	**469 (69.6)**	**182 (66.9)**	**65 (61.9)**	**19 (50.0)**	**86 (53.4)**	**203 (78.4)**	**231 (89.9)**
Vascular disorders	**286 (42.4)**	**122 (44.9)**	**37 (35.2)**	**13 (34.2)**	**35 (21.7)**	**114 (44.0)**	**87 (33.9)**
Hypertension	277 (41.1)	117 (43.0)	37 (35.2)	13 (34.2)	35 (21.7)	110 (42.5)	82 (31.9)
Gastrointestinal disorders	**182 (27.0)**	**53 (19.5)**	**28 (26.7)**	**12 (31.6)**	**28 (17.4)**	**89 (34.4)**	**104 (40.5)**
Diarrhea	107 (15.9)	33 (12.1)	14 (13.3)	7 (18.4)	17 (10.6)	53 (20.5)	74 (28.8)
Stomatitis	54 (8.0)	12 (4.4)	10 (9.5)	4 (10.5)	4 (2.5)	28 (10.8)	21 (8.2)
Nausea	35 (5.2)	6 (2.2)	7 (6.7)	1 (2.6)	5 (3.1)	21 (8.1)	13 (5.1)
Vomiting	16 (2.4)	2 (0.7)	2 (1.9)	1 (2.6)	4 (2.5)	11 (4.2)	6 (2.3)
Abdominal pain	15 (2.2)	6 (2.2)	0	0	2 (1.2)	9 (3.5)	7 (2.7)
Respiratory, thoracic and mediastinal disorders	**171 (25.4)**	**79 (29.0)**	**16 (15.2)**	**9 (23.7)**	**17 (10.6)**	**67 (25.9)**	**32 (12.5)**
Dysphonia	132 (19.6)	59 (21.7)	16 (15.2)	8 (21.1)	8 (5.0)	49 (18.9)	11 (4.3)
Dyspnea	31 (4.6)	16 (5.9)	1 (1.0)	1 (2.6	2 (1.2)	13 (5.0)	5 (1.9)
Cough	22 (3.3)	13 (4.8)	1 (1.0)	0	1 (0.6)	8 (3.1)	1 (0.4)

System Organ Class Preferred Term	Total	AV-951-07-201	AV-951-10-202	AV-951-12-205	AV-951-09-902	AV-951-09-301	
	Tivozanib (n = 674) n (%)	Tivozanib (n = 272) n (%)	Tivozanib (n = 105) n (%)	Tivozanib (n = 38) n (%)	Tivozanib (n = 161) n (%)	Tivozanib arm (n = 259) n (%)	Sorafenib arm (n = 257) n (%)
Skin and subcutaneous tissue disorders	**129 (19.1)**	**44 (16.2)**	**18 (17.1)**	**7 (18.4)**	**18 (11.2)**	**60 (23.2)**	**187 (72.8)**
Palmar-plantar erythrodysesthesia syndrome	65 (9.6)	11 (4.0)	12 (11.4)	6 (15.8)	16 (9.9)	36 (13.9)	137 (53.3)
General disorders and administration site conditions	**121 (18.0)**	**52 (19.1)**	**8 (7.6)**	**8 (21.1)**	**17 (10.6)**	**53 (20.5)**	**62 (24.1)**
Fatigue	63 (9.3)	22 (8.1)	4 (3.8)	6 (15.8)	8 (5.0)	31 (12.0)	28 (10.9)
Asthenia	53 (7.9)	28 (10.3)	1 (1.0)	2 (5.3)	8 (5.0)	22 (8.5)	22 (8.6)
Investigations	**64 (9.5)**	**15 (5.5)**	**7 (6.7)**	**2 (5.3)**	**15 (9.3)**	**40 (15.4)**	**54 (21.0)**
Blood thyroid stimulating hormone increased	15 (2.2)	0	1 (1.0)	0	3 (1.9)	14 (5.4)	5 (1.9)
Nervous system disorders	**53 (7.9)**	**17 (6.3)**	**5 (4.8)**	**3 (7.9)**	**9 (5.6)**	**28 (10.8)**	**20 (7.8)**
Headache	19 (2.8)	7 (2.6)	1 (1.0)	2 (5.3)	5 (3.1)	9 (3.5)	3 (1.2)
Musculoskeletal and connective tissue disorders	**47 (7.0)**	**23 (8.5)**	**3(2.9)**	**2 (5.3)**	**9 (5.6)**	**19 (7.3)**	**18 (7.0)**
Arthralgia	14(2.1)	5 (1.8)	2 (1.9)	1 (2.6)	3 (1.9)	6 (2.3)	4 (1.6)
Metabolism and nutrition disorders	**40 (5.9)**	**13 (4.8)**	**5 (4.8)**	**3 (7.9)**	**9 (5.6)**	**19 (7.3)**	**26 (10.1)**
Decreased appetite	22 (3.3)	0	5 (4.8)	3 (7.9)	7 (4.3)	14 (5.4)	21 (8.2)
Renal and urinary disorders	**26 (3.9)**	**9 (3.3)**	**1 (1.0)**	**0**	**1 (0.6)**	**16 (6.2)**	**8 (3.1)**
Proteinuria	24 (3.6)	9 (3.3)	1 (1.0)	0	1 (0.6)	14 (5.4)	6 (2.3)
Endocrine disorders	**21 (3.1)**	**0**	**6 (5.7)**	**0**	**5 (31)**	**15 (5.8)**	**8 (3.1)**

System Organ Class Preferred Term	Total Tivozanib (n = 674) n (%)	AV-951-07-201 Tivozanib (n = 272) n (%)	AV-951-10-202 Tivozanib (n = 105) n (%)	AV-951-12-205 Tivozanib (n = 38) n (%)	AV-951-09-902 Tivozanib (n = 161) n (%)	AV-951-09-301 Tivozanib arm (n = 259) n (%)	AV-951-09-301 Sorafenib arm (n = 257) n (%)
Hypothyroidism	19 (2.8)	0	6 (5.7)	0	5 (3.1)	13 (5.0)	5 (1.9)

PTs are included if they have an incidence of 2% or higher in the overall (first-line) Tivozanib column. Incidences for these PTs are provided for all studies. For each SOC and PT, patients are included only once, even if they experienced multiple events in that SOC or PT.

TEAEs were defined as any adverse event with onset during or after the first dose of the study.

Events designated as 'possibly related,' 'probably related,' or 'related' to study treatment by the investigator or missing this assessment were included.

AV-951-09-301 column included first line subjects data through AV-951-09-902 EOS. AV-951-09-902 column included only cross-over subjects second line data. Total Tivozanib column did not include Crossed over subjects data in AV-951-09-902.

TEAEs are reported using the MedDRA coding used for the individual studies. The following MedDRA versions were used to code TEAEs in the individual clinical study reports: AV-951-07-201: Version 7.1, AV-951-10-202: Version 15.0, AV-951-12-205: Version 15.0, AV-951-09-301: Version 15.0, AV-951-09-902: Version 17.0.

PT: preferred term; RCC: renal cell carcinoma; SOC: system organ class; TEAE: treatment-emergent adverse event; Tivozanib: tivozanib hydrochloride

The following table summarises the most frequently reported TEAEs in the core RCC monotherapy studies:

Table 36 TEAEs occurring in ≥ 10% of first-line tivozanib or sorafenib patients by PT, and corresponding Grade 3-4 incidences (pooled core RCC monotherapy studies and AV-951-09-301)

Total tivozanib (n=674) n (%)			**AV-951-09-301**			
			Tivozanib arm (n=259) n (%)		**Sorafenib arm (n=257) n (%)**	
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Any adverse event	620 (92)	397 (59)	238 (92%)	166 (64)	249 (97)	181 (70)
Hypertension	321 (48)	155 (23)	**116 (45)**	**68 (26)**	**91 (35)**	**46 (18)**
Dysphonia	181 (27)	<1%	**55 (21)**	**<1%**	**12 (5)**	**<1%**
Fatigue	174 (26)	37 (6)	53 (21)	14 (5)	41 (16)	9 (4)
Diarrhoea	172 (26)	15 (2)	**63 (24)**	**6 (2)**	**85 (33)**	**16 (7)**
Asthenia	120 (18)	36 (5)	44 (17)	10 (4)	44 (17)	7 (3)
Dyspnoea	110 (16)	25 (4)	31 (12)	5 (2)	22 (9)	5 (2)
Nausea	103 (15)	<1%	**34 (13)**	**<1%**	**19 (7)**	**<1%**
Back pain	101 (15)	17 (3)	**38 (15)**	**8 (3)**	**21 (8)**	**4 (2)**
Cough	86 (13)	<1%	23 (9)	<1%	18 (7)	<1%
Weight decreased	82 (12)	8 (1)	49 (19)	7 (3)	54 (21)	10 (4)
Stomatitis	81 (12)	<1%	30 (12)	<1%	23 (9)	<1%
PPE syndrome	74 (11)	10 (2)	**36 (14)**	**5 (2)**	**139 (54)**	**43 (17)**
Headache	71 (11)	<1%	23 (9)	<1%	11 (4)	<1%
Decreased appetite	70 (10)	<1%	28 (11)	<1%	24 (9)	<1%

Table 37: Tabulated list of adverse reactions observed in tivozanib treated patients (N=674) in the pooled five RCC monotherapy studies by MedDRA body system organ class (SOC), frequency and severity

System Organ Class	Adverse reaction	Overall adverse reactions n (%)	Overall adverse reactions frequency	≥ Grade 3 adverse reactions n (%)	≥ Grade 3 adverse reactions frequency
Infections and infestations	Fungal infection	3 (0.4%)	Uncommon	0	None reported
	Pustular rash	4 (0.6%)	Uncommon	1 (0.1%)	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia	6 (0.9%)	Uncommon	3 (0.4%)	Uncommon
	Anaemia	31 (4.6%)	Common	14 (2.1%)	Common
	Haemoglobin increased	4 (0.6%)	Uncommon	0	None reported
Endocrine disorders	Hypothyroidism	38 (5.6%)	Common	0	None reported
	Hyperthyroidism	5 (0.7%)	Uncommon	1 (0.1%)	Uncommon
	Goitre[1]	4 (0.6%)	Uncommon	0	None reported
Metabolism and nutrition disorders	Anorexia	21 (3.1%)	Common	0	None reported
	Decreased appetite	70 (10.4%)	Very common	4 (0.6%)	Uncommon
Psychiatric disorders	Insomnia	25 (3.7%)	Common	0	None reported
Nervous system disorders	Posterior Reversible Encephalopathy Syndrome (PRES)[2]	0	Rare	0	None reported
	Transient ischaemic attack	5 (0.7%)	Uncommon	2 (0.3%)	Uncommon
	Memory impairment[3]	6 (0.9%)	Uncommon	0	None reported
	Peripheral neuropathy[4]	34 (5.0%)	Common	1 (0.1%)	Uncommon
	Dizziness	39 (5.8%)	Common	1 (0.1%)	Uncommon
	Dysgeusia[5]	26 (3.9%)	Common	0	None reported
	Headache	71 (10.5%)	Very common	0	None reported
Eye disorders	Vision impairment[6]	17 (2.5%)	Common	1 (0.1%)	Uncommon
	Increased lacrimation	2 (0.3%)	Uncommon	0	None reported
Ear and labyrinth disorders	Vertigo	12 (1.8%)	Common	1 (0.1%)	Uncommon
	Tinnitus	9 (1.3%)	Common	0	None reported
	Ear congestion	4 (0.6%)	Uncommon	0	None reported
Cardiac disorders	Myocardial infarction (acute) / ischaemia[7]	10 (1.5%)	Common	7 (1.0%)	Common
	Pulmonary oedema	2 (0.3%)	Uncommon	2 (0.3%)	Uncommon
	Angina pectoris	10 (1.5%)	Common	2 (0.3%)	Uncommon
	Coronary artery insufficiency	3 (0.4%)	Uncommon	1 (0.1%)	Uncommon
	Tachycardia[8]	22 (3.3%)	Common	1 (0.1%)	Uncommon
	Electrocardiogram QT prolonged	1 (0.1%)	Uncommon	0	None reported
Vascular disorders	Haemorrhage[9]	24 (3.6%)	Common	5 (0.7%)	Uncommon
	Arterial thromboembolism[10]	21 (3.1%)	Common	16 (2.4%)	Common
	Venous thromboembolism[11]	7 (1.0%)	Common	5 (0.7%)	Uncommon
	Persistent severe hypertension[12]	7 (1.0%)	Common	6 (0.9%)	Uncommon
	Hypertension	321 (47.6%)	Very common	155 (23.0%)	Very common
	Flushing[13]	9 (1.3%)	Common	0	None reported

System Organ Class	Adverse reaction	Overall adverse reactions n (%)	Overall adverse reactions frequency	≥ Grade 3 adverse reactions n (%)	≥ Grade 3 adverse reactions frequency
Respiratory, thoracic and mediastinal disorders	Dyspnoea[14]	115 (17.1%)	Very common	26 (3.9%)	Common
	Epistaxis	16 (2.4%)	Common	1 (0.1%)	Uncommon
	Dysphonia	181 (26.9%)	Very common	1 (0.1%)	Uncommon
	Cough	86 (12.8%)	Very common	3 (0.4%)	Uncommon
	Rhinorrhoea	14 (2.1%)	Common	0	None reported
	Nasal congestion	9 (1.3%)	Common	0	None reported
Gastrointestinal disorders	Pancreatitis[15]	9 (1.3%)	Common	2 (0.3%)	Uncommon
	Duodenal ulcer	4 (0.6%)	Uncommon	0	None reported
	Dysphagia[16]	25 (3.7%)	Common	1 (0.1%)	Uncommon
	Vomiting	54 (8.0%)	Common	2 (0.3%)	Uncommon
	Gastrooesophageal reflux disease	14 (2.1%)	Common	0	None reported
	Abdominal pain[17]	101 (15.0%)	Very common	8 (1.2%)	Common
	Abdominal distension	11 (1.6%)	Common	0	None reported
	Nausea	103 (15.3%)	Very common	2 (0.3%)	Uncommon
	Diarrhoea	172 (25.5%)	Very common	15 (2.2%)	Common
	Stomatitis[18]	84 (12.5%)	Very common	4 (0.6%)	Uncommon
	Glossitis[19]	7 (1.0%)	Common	0	None reported
	Gingivitis[20]	13 (1.9%)	Common	2 (0.3%)	Uncommon
	Dyspepsia	42 (6.2%)	Common	0	None reported
	Constipation	44 (6.5%)	Common	1 (0.1%)	Uncommon
	Dry mouth	13 (1.9%)	Common	0	None reported
	Flatulence	16 (2.4%)	Common	0	None reported
Hepatobiliary disorders	ALT increased / AST increased[21]	26 (3.9%)	Common	9 (1.3%)	Common
	Gamma-glutamyltransferase increased	30 (4.5%)	Common	18 (2.7%)	Common
	Blood alkaline phosphatase increased	8 (1.2%)	Common	1 (0.1%)	Uncommon
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome / Hand foot skin reaction (PPE/HFS)	74 (11.0%)	Very common	10 (1.5%)	Common
	Skin exfoliation	12 (1.8%)	Common	1 (0.1%)	Uncommon
	Erythema[22]	9 (1.3%)	Common	0	None reported
	Urticaria	3 (0.4%)	Uncommon	0	None reported
	Pruritus[23]	26 (3.9%)	Common	0	None reported
	Dermatitis[24]	3 (0.4%)	Uncommon	0	None reported
	Alopecia	11 (1.6%)	Common	0	None reported
	Hyperhidrosis	5 (0.7%)	Uncommon	0	None reported
	Rash[25]	59 (8.8%)	Common	4 (0.6%)	Uncommon
	Acne[26]	11 (1.6%)	Common	0	None reported

System Organ Class	Adverse reaction	Overall adverse reactions n (%)	Overall adverse reactions frequency	≥ Grade 3 adverse reactions n (%)	≥ Grade 3 adverse reactions frequency
	Xeroderma	3 (0.4%)	Uncommon	0	None reported
	Dry skin	18 (2.7%)	Common	0	None reported
Musculoskeletal and connective tissue disorders	Arthralgia	46 (6.8%)	Common	3 (0.4%)	Uncommon
	Myalgia	22 (3.3%)	Common	3 (0.4%)	Uncommon
	Muscular weakness	6 (0.9%)	Uncommon	2 (0.3%)	Uncommon
	Musculoskeletal chest pain	10 (1.5%)	Common	1 (0.1%)	Uncommon
	Back pain	101 (15.0%)	Very common	17 (2.5%)	Common
Renal and urinary disorders	Proteinuria	59 (8.8%)	Common	14 (2.1%)	Common
	Blood creatinine increased	16 (2.4%)	Common	3 (0.4%)	Uncommon
General disorders and administration site conditions	Chest pain[27]	28 (4.2%)	Common	5 (0.7%)	Uncommon
	Pain[28]	98 (14.5%)	Very common	8 (1.2%)	Common
	Chills[29]	11 (1.6%)	Common	0	None reported
	Pyrexia	39 (5.8%)	Common	1 (0.1%)	Uncommon
	Peripheral oedema	28 (4.2%)	Common	0	None reported
	Mucosal inflammation	4 (0.6%)	Uncommon	0	None reported
	Asthenia	120 (17.8%)	Very common	36 (5.3%)	Common
	Fatigue	174 (25.8%)	Very common	37 (5.5%)	Common
Investigations	Amylase increased	19 (2.8%)	Common	13 (1.9%)	Common
	Lipase increased	30 (4.5%)	Common	23 (3.4%)	Common
	Blood thyroid stimulating hormone increased	17 (2.5%)	Common	0	None reported
	Weight decreased	82 (12.2%)	Very common	8 (1.2%)	Common

Adverse reactions from clinical studies are presented using frequencies for all-causality adverse events. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The following terms have been combined:

1 Goitre including goitre and toxic nodular goitre

2 PRES was not observed in patients treated with tivozanib in the five RCC monotherapy studies. One patient experienced Grade 4 PRES and hypertension in Study AV-951-09-901.

3 Memory impairment including amnesia and memory impairment

4 Peripheral neuropathy including hyperaesthesia, hypoaesthesia, mononeuropathy, neuropathy peripheral, peripheral sensory neuropathy and paraesthesia

5 Dysgeusia including ageusia, dysgeusia and hypogeusia

6 Vision impairment including reduced visual acuity, vision blurred and visual impairment

7 Myocardial infarction (acute) / ischaemia including acute myocardial infarction, ischaemia and myocardial infarction

8 Tachycardia including sinus tachycardia, supraventricular tachycardia, tachycardia and tachycardia paroxysmal

9 Haemorrhage including adrenal haemorrhage, anal haemorrhage, cervix haemorrhage uterine, duodenal ulcer haemorrhage, gingival bleeding, haematemesis, haemoptysis, haemorrhagic anaemia, haemorrhagic erosive gastritis, haemorrhagic stroke, mouth haemorrhage, pulmonary haemorrhage and respiratory tract haemorrhage

10 Arterial thromboembolism including acute myocardial infarction, arterial thrombosis, iliac artery thrombosis, ischaemic stroke, myocardial infarction and transient ischaemic attack

11 Venous thromboembolism including deep vein thrombosis, embolism venous and pulmonary embolism

12 Persistent severe hypertension including hypertensive crisis

13 Flushing including flushing and hot flush

14 Dyspnoea including dyspnoea and exertional dyspnoea

15 Pancreatitis including pancreatitis and pancreatitis acute

16 Dysphagia including dysphagia, odynophagia and oropharyngeal pain

17 Abdominal pain including abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and abdominal rigidity

18 Stomatitis including oral discomfort, oral disorder and stomatitis

18 Glossitis including glossitis and glossodynia

20 Gingivitis including gingival bleeding, gingival disorder, gingival pain and gingivitis

21 Alanine aminotransferase (ALT) increased / Aspartate aminotransferase (AST) increased including ALT increased and AST increased
22 Erythema including erythema, generalised erythema and palmar erythema
23 Pruritus including generalised pruritus and pruritus
24 Dermatitis including dermatitis and dermatitis bullous
25 Rash including rash, rash erythematous, rash generalised, rash maculo-papular, rash papular and rash pruritic
26 Acne including acne and dermatitis acneiform
27 Chest pain including chest pain and non-cardiac chest pain
28 Pain including bone pain, cancer pain, flank pain, groin pain, oral pain, pain, pain in extremity and tumour pain
29 Chills including chills and hypothermia

Serious adverse event / deaths / other significant events

Deaths

The incidence of AEs with an outcome of death in the pivotal study was increased in the tivozanib arm compared to the sorafenib arm (10.8% vs 5.8%). This is largely attributable to a higher incidence of deaths from neoplasm progression reported as adverse events in the tivozanib hydrochloride arm (9 patients, 3.5%) compared with the sorafenib arm (2 patients, 0.8%). The deaths that occurred > 30 days after drug discontinuation were comparable between tivozanib and sorafenib arms in the pivotal study. One death in the tivozanib arm was associated with hypertension following a suspected overdose (3 x 1.5 mg capsules). No information on cause of death is available for 2 deaths in the tivozanib arm of study 09-301.

TEAEs with an outcome of death (deaths within 30 days of the last dose of study drug) occurred in 47 of the 674 patients (7%) in the pooled tivozanib group of the core RCC monotherapy studies.

Serious adverse events

Overall in the core RCC monotherapy studies, the incidence of SAEs was 19.9%. In the pivotal study 09-301, the incidence was 28.6% in the tivozanib arm compared to 21.8% in the sorafenib arm. This is partly explained by an increase in SAEs related to disease progression.

In the pivotal study 09-301, the incidence of the SMQ Cerebrovascular ischaemia was 3.5% (9 patients) for tivozanib vs. 1.9% (5 patients) for sorafenib. There were 3 ischaemic strokes in the tivozanib arm compared to none in the sorafenib arm. The incidence of the SMQ Venous Embolic and Thrombotic Events may be increased for tivozanib compared to sorafenib, although the numbers are small. In the pivotal study 09-301, 6 patients (2.3%) on tivozanib and 2 patients (0.8%) on sorafenib reported TEAEs in this SMQ. There was one death due to PE, and 2 non-fatal PE cases, in the tivozanib arm and 2 deaths due to PE in the sorafenib arm. This may be an effect of VEGF pathway inhibition.

The incidence of haemorrhage events was increased for tivozanib vs. sorafenib in the pivotal study. 33 patients (12.7%) on tivozanib compared to 18 patients (7.0%) on sorafenib experienced haemorrhage TEAEs; there were 6 SAEs in the tivozanib arm compared to none in the sorafenib arm. Haemorrhage is a known risk for TKIs, including agents targeting the VEGF pathway, such as axitinib and bevacizumab.

In the pivotal study, the incidence of cardiac failure TEAEs was 1.5% (4 patients) on tivozanib and 1.6% (4 patients) on sorafenib. There were 5 deaths associated with cardiac failure in tivozanib-treated patients, of which 3 occurred in the tivozanib arm of the pivotal study. In the sorafenib arm there were 2 deaths associated with cardiac failure.

There was one event of posterior reversible encephalopathy syndrome (PRES) across the clinical development program.

Adverse events of special interest

Adverse events of special interest (AESI) were determined based on TEAEs observed within the tivozanib hydrochloride program as well as possible class effects seen with similar agents. Categories of AESI include:

- Hypertension
- Noninfectious encephalopathy/delirium (includes PRES)
- Arterial embolic and thrombotic events
- Venous embolic and thrombotic events
- Cerebrovascular ischaemia
- Hepatic disorders
- Haemorrhage
- Gastrointestinal perforation and fistula formation
- Thyroid dysfunction
- Acute pancreatitis
- Cardiac failure
- Acute renal failure
- Wound healing
- Proteinuria
- Hand Food Skin Reaction (Palmar-Plantar Erythrodysaesthesia, PPE)
- QT prolongation/Torsade de Pointes

Hypertension

In clinical studies with tivozanib hydrochloride, hypertension was the most commonly occurring TEAE. In almost half of the patients (39.8%), new or worsening hypertension was observed within the first 2 months of treatment. Whilst hypertensive TEAEs occurred frequently in treated patients, and often required treatment with hypertensive medications, it was an infrequent cause of tivozanib hydrochloride discontinuation. Across all the monotherapy studies in cancer patients receiving tivozanib hydrochloride, there have been 8 subjects with treatment-emergent hypertensive SAEs (5 patients in the core RCC monotherapy studies, 3 patients in the other monotherapy studies), including one fatal TESAE of uncontrolled hypertension in Study AV-951-09-301.

Noninfectious encephalopathy/delirium (includes PRES)

Of the approximately 1,100 cancer patients treated with tivozanib, PRES, also known as reversible posterior leukoencephalopathy syndrome (RPLS), was confirmed in one patient, after approximately 8 weeks on tivozanib.

Arterial embolic and thrombotic events

In clinical studies with tivozanib hydrochloride, arterial thromboembolic events including transient ischaemic attack, cerebrovascular accident, (acute) myocardial infarction and ischaemic stroke, have

been reported. Some of these events were associated with fatal outcome.

Venous embolic and thrombotic events

In clinical studies with tivozanib, venous thromboembolic events including pulmonary embolism, deep vein thrombosis and thrombophlebitis have been reported. Pulmonary embolism was associated with fatal outcomes in 0.4% of first-line tivozanib hydrochloride treated patients in the core RCC monotherapy studies. There were no cases in second-line tivozanib hydrochloride-treated patients.

Cerebrovascular ischaemia

The incidence of cerebrovascular ischaemia events was 3.5% in the tivozanib hydrochloride arm and 1.9% in the sorafenib arm in Study AV-951-09-301 and consistent across the studies.

Haemorrhage

In clinical studies with tivozanib hydrochloride, haemorrhagic events have been reported, including fatal events due to aortic aneurysm rupture and pulmonary haemorrhage.

Gastrointestinal perforation and fistula formation

There was a low incidence (1 patient, 0.1%) of tivozanib hydrochloride-treated patients with TEAEs relevant to gastrointestinal perforation and fistula formation in the core monotherapy studies. The incidence was similarly low in sorafenib-treated patients (1 patient, 0.4%).

Thyroid dysfunction

In clinical studies with tivozanib hydrochloride hypothyroidism has been observed to occur at any time during treatment with tivozanib hydrochloride, developing as early as within 2 months of treatment initiation. Risk factors for hypothyroidism include prior history of hypothyroidism and use of anti-thyroid medications. Thyroid function should be monitored before initiation of and periodically throughout treatment with tivozanib and hypothyroidism should be treated according to standard medical practice.

Acute pancreatitis

Acute pancreatitis was observed infrequently (1.3%) in first-line core RCC monotherapy studies. The findings are consistent in Study AV-951-09-301 (0.8% in the tivozanib hydrochloride arm and 0.4% in the sorafenib arm). The incidence is similar for that reported with sorafenib (0.7%) (Nexavar, 2007, EPAR), pazopanib (0.7%) (Votrient, 2015, SmPC) and sunitinib (<1.0%) (Sutent, 2015, SmPC). Based on the AE profile of VEGFR inhibitors, acute pancreatitis was considered an AESI; however, the data described in this section are such that the frequency and severity of this AESI do not warrant any special precautions.

Cardiac failure

In the first-line tivozanib hydrochloride core monotherapy studies, the incidence was low (1.0%) and similar to the sorafenib arm of Study AV-951-09-301 (1.6%).

Acute renal failure

Serious impairment of renal function due to VEGFR inhibition appears to occur infrequently, an impression borne out in the tivozanib hydrochloride clinical program. Acute renal failure TEAEs were reported in 0.7% of tivozanib hydrochloride-treated patients in the first-line core monotherapy RCC studies, similar to the sorafenib arm of Study AV-951-09-301 (0.4%).

Wound healing

In clinical studies, patients were excluded who had unhealed wounds, bone fractures, skin ulcers, inadequate recovery from surgery or patients who were undergoing major surgical procedure prior to

initiation of tivozanib hydrochloride and no cases of impaired wound healing have been reported during clinical studies.

Proteinuria

Proteinuria has been reported in clinical studies with tivozanib hydrochloride, so monitoring for proteinuria before initiation of and periodically throughout treatment is recommended.

Hand Food Skin Reaction (Palmar-Plantar Erythrodysaesthesia, PPE)

The incidence of hand foot skin reaction (which was searched for using the PT palmar-plantar erythrodysaesthesia syndrome) was 1.9% of the patients treated with tivozanib hydrochloride in Study AV-951-09-301 reported as Grade 3 events compared to 16.7% with sorafenib and which often led to dose reductions or interruptions for sorafenib.

QT prolongation/Torsade de Pointes

The SMQ QT Prolongation Torsade de Pointes / QT Prolongation identified 1 case of QT prolongation (PT was Electrocardiogram QT prolonged) in all core RCC monotherapy studies. The event was Grade 2, non-serious, considered unrelated to tivozanib and did not lead to a change in dosing. There were 2 (4.0%) additional events of QT prolongation reported as TEAEs in the other monotherapy studies (Study AV-951-10-112 the cardiac safety study). Neither event was considered serious or led to a change in dosing, both events were considered to be related to tivozanib.

Long-term adverse effects

An analysis comparing TEAE incidence in the first 2 months, after 2 to 12 months and ≥ 12 months of treatment was performed. This analysis included all first-line treatment for patients from the core RCC monotherapy studies (including time in extension Study AV-951-09-901), with an additional comparison between the 2 treatment groups of Study AV-951-09-301.

Only 230 first-line patients were evaluated for more than 12 months. Amongst these patients, 70.9% (163 patients) experienced the onset of at least one new or recurrent TEAE more than 12 months after the first dose of study drug. Most TEAEs increased in incidence in the second two periods evaluated, in line with the expected increase in background rates due to the increasing duration of exposure.

For the on-target TEAE of hypertension and dysphonia the trend was for a decrease in the onset of these TEAEs over time. Hypertension tends to occur primarily within the first 2 months of treatment.

There were no marked increases in TEAE incidence with long-term treatment.

Although the incidence of the remaining events of interest is low such that conclusions as to whether events are more likely to occur within the first 2 months of treatment versus between > 2 months and ≤ 12 months of treatment, it appears that patients who continue treatment for more than 1 year are not more likely to experience an event of interest.

Most of the fatal TEAEs were reported as disease progression. Of note, during the first 2 months of treatment 2 patients died of pulmonary embolism, between 2 and 12 months two patients died of myocardial infarction and >12 months 2 patients died of acute cardiac failure.

Laboratory findings

Grade 3/4 haematology abnormalities occurred in 6.0% of tivozanib-treated patients across the evaluated first-line core RCC monotherapy studies, and had a similar overall incidence in

tivozanib-treated patients (8.1%) and sorafenib-treated patients (5.4%) in the pivotal study. Low haemoglobin (<8.0 g/dL) was the most common abnormality. Thrombocytopenia was more common for tivozanib vs. sorafenib (19% vs 13%), but the ≥ Grade 3 (platelets < 50 X 10^9/L) incidence was low (0.4% vs 0% respectively).

Lipase increased (PT) was reported more commonly for sorafenib compared to tivozanib: 9.3% vs 4.6% in the pivotal study. The incidence of amylase increased (PT) was comparable: 4.2% vs 4.3%. The difference in lipase increased does not appear to be clinically important, since there were 2 reports of pancreatitis in the tivozanib arm compared to one report in the sorafenib arm.

Safety in special populations

MedDRA Terms	Age<65 years (n =494)	Age 65-74 years (n =155)	Age 75-84 years (n = 25)	Age 85+ years (n =0)
	n (%)	n (%)	n (%)	n (%)
Total with AEs	448 (90.7)	148 (95.5)	24 (96.0)	
Total with serious AEs	96 (19.4)	32 (20.6)	6 (24.0)	
Fatal	30 (6.1)	15 (9.7)	2 (8.0)	
*Hospitalisation/prolong existing hospitalisation**	*41 (21.1)*	*4 (7.1)*	*3 (33.3)*	
Life-threatening	Not collected	Not collected	Not collected	
Disability/incapacity	Not collected	Not collected	Not collected	
Other (medically significant)	Not collected	Not collected	Not collected	
AE leading to discontinuation of therapy	56 (11.3)	16 (10.3)	4 (16.0)	
Psychiatric disorders (SOC)	38 (7.7)	12 (7.7)	3 (12.0)	
Nervous system disorders (SOC)	111 (22.5)	48 (31.0)	13 (52.0)	
Accidents and injuries (SMQ)	11 (2.2)	9 (5.8)	2 (8.0)	
Cardiac disorders (SOC)	45 (9.1)	16 (10.3)	4 (16.0)	
Vascular disorders (SOC)	254 (51.4)	75 (48.4)	12 (48.0)	
Cerebrovascular disorder (PT)	0	0	0	
Infections and infestations (SOC)	99 (20.0)	27 (17.4)	4 (16.0)	
Anticholinergic syndrome (SMQ)	82 (16.6)	29 (18.7)	6 (24.0)	
Quality of life decreased (PT)	0	0	0	
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	8 (1.6)	4 (2.6)	1 (4.0)	
AEs (PTs) appearing more frequently in older patients				
Dysphonia	118 (23.9)	53 (34.2)	10 (40.0)	
Diarrhoea	112 (22.7)	53 (34.2)	7 (28.0)	
Fatigue	118 (23.9)	45 (29.0)	11 (44.0)	
Weight decreased	50 (10.1)	26 (16.8)	6 (24.0)	
Decreased appetite	43 (8.7)	22 (14.2)	5 (20.0)	
Hypothyroidism	21 (4.3)	13 (8.4)	4 (16.0)	

Immunological events

There was one report of hypersensitivity across all monotherapy studies, for a tivozanib-treated patient from study AV-951-10-202. This event was Grade 1-2 in severity, was not reported as a SAE, and did not lead to discontinuation of study drug.

Safety related to drug-drug interactions and other interactions

The Applicant has conducted an analysis according to concomitant use of PPI drugs. The sub-population using concomitant PPIs (n=53) consistently reported a higher incidence of TEAEs over the more common PTs, including hypertension (74% vs 41%) and dysphonia (38% vs 21%).

Discontinuation due to adverse events

In the pivotal study (09-301), discontinuations were comparable for the tivozanib arm vs the sorafenib arm: 14.7% vs 13.2%.

There was an excess of stroke events leading to discontinuation for tivozanib vs sorafenib in the pivotal study. There were 9 stroke events in the tivozanib arm: 3 ischaemic stroke, 3 events of cerebrovascular accident, 1 cerebral ischaemia, 1 haemorrhagic stroke and 1 hemiparesis. In the sorafenib arm there were 2 events of cerebrovascular accident.

Dose reduction and/or interruption of therapy due to AEs

The most frequent PT leading to dose reduction or dose interruption was hypertension across the core RCC monotherapy studies (32 reports; 4.7%). In the pivotal study, more patients had a dose reduction due to TEAEs in the sorafenib arm vs the tivozanib arm: 37.4% vs 11.6%. In addition, more patients reported TEAEs leading to drug interruption in the sorafenib arm vs. tivozanib arm: 37.0% vs 22.4%.

Table 38 TEAEs Leading to Dose Reduction and/or Drug Interruption (Occurring in ≥ 1.0% of First-line Tivozanib Hydrochloride Patients Overall) by Preferred Term (Core RCC Monotherapy Studies)

System Organ Class Preferred Term	Total Tivozanib (n = 674) n (%)	AV-951-07-201 Tivozanib (n = 272) n (%)	AV-951-10-202 Tivozanib (n = 105) n (%)	AV-951-12-205 Tivozanib (n = 38) n(%)	AV-951-09-902 Tivozanib (n = 161) n (%)	AV-951-09-301 Tivozanib arm (n = 259) n (%)	AV-951-09-301 Sorafenib arm (n = 257) n (%)
TEAEs Leading to Dose Reduction							
Hypertension	11 (1.6)	6 (2.2)	1 (1.0)	0	3 (1.9)	4 (1.5)	10 (3.9)
Fatigue	10 (1.5)	2 (0.7)	5 (4.8)	0	2 (1.2)	3 (1.2)	3 (1.2)
TEAEs Leading to Drug Interruption							
Hypertension	22 (3.3)	2 (0.7)	4 (3.8)	0	2 (1.2)	16 (6.2)	8 (3.1)
Diarrhea	15 (2.2)	2 (0.7)	6 (5.7)	0	1 (0.6)	7 (2.7)	9 (3.5)
Vomiting	9 (1.3)	0	4 (3.8)	0	3 (1.9)	5 (1.9)	6 (2.3)
Palmar-plantar erythrodysesthesia syndrome	8 (1.2)	0	3 (2.9)	0	2 (1.2)	5 (1.9)	45 (17.5)
Lipase increased	7 (1.0)	0	4 (3.8)	0	2 (1.2)	3 (1.2)	2 (0.8)
TEAEs Leading to Dose Reduction or Drug Interruption							
Hypertension	32 (4.7)	7 (2.6)	5 (4.8)	0	5 (3.1)	20 (7.7)	16 (6.2)
Diarrhea	21 (3.1)	5 (1.8)	6 (5.7)	0	3 (1.9)	10 (3.9)	20 (7.8)
Fatigue	12 (1.8)	3 (1.1)	5 (4.8)	1 (2.6)	3 (1.9)	3 (1.2)	6 (2.3)
Palmar-plantar erythrodysesthesia syndrome	11 (1.6)	0	3 (2.9)	0	5 (3.1)	8 (3.1)	60 (23.3)
Vomiting	10 (1.5)	0	4 (3.8)	0	3 (1.9)	6 (2.3)	6 (2.3)
Asthenia	8 (1.2)	1 (0.4)	1 (1.0)	1 (2.6)	2 (1.2)	5 (1.9)	5 (1.9)
Lipase increased	8 (1.0)	0	4 (3.8)	0	2 (1.2)	4 (1.5)	9 (3.5)
Dyspnea	7 (1.0)	1 (0.4)	4 (3.8)	1 (2.6)	0	1 (0.4)	2 (0.8)

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The overall clinical safety assessment of tivozanib hydrochloride is based on data from the randomised controlled pivotal study, AV-951-09-301, and extension study AV-951-09-902 and supported by data from the other core RCC monotherapy studies.

Most patients in the 5 core RCC monotherapy studies (627, 75.0%) have been exposed to single-agent tivozanib hydrochloride at a starting dose of 1.5 mg for ≤ 12 months, and a subset of patients from AV-951-07-201, AV-951-09-302 (first-line tivozanib hydrochloride treated patients into Study AV-951-09-902) as well as patients from extension study, AV-951-09-902 (second-line tivozanib hydrochloride treated patients), were exposed for > 24 months. It should be noted that the number of patients exposed to first line treatment with tivozanib hydrochloride for more than 24 months was higher than that for first line sorafenib.

The study population consisted mainly of white, Central/Eastern Europe males. Age and Gender based analyses showed no major differences between male or female and <65 vs. >65 years old patients. A subgroup analysis of white vs. non-white patients was also done, but the small percentage of non-white patients (less than 6%) precludes any definitive conclusions regarding a relationship between race and TEAEs.

The most common TEAEs (occurring in ≥ 20% of patients) observed in the RCC population treated with tivozanib hydrochloride as first-line therapy were hypertension, dysphonia, fatigue and diarrhoea. Most TEAEs were of NCI CTCAE Grades 1-3 and were manageable. The most common ≥ Grade 3 TEAEs were hypertension, fatigue and asthenia. Following second-line tivozanib hydrochloride therapy in Study AV-951-09-902, hypertension, fatigue, diarrhoea and asthenia occurred with lower incidences than in the first-line core monotherapy studies but were still the most common events.

The most common TEAEs leading to dose reduction or interruption in the RCC population treated with first-line tivozanib hydrochloride were hypertension and diarrhoea. The overall incidence of TEAEs leading to dose reductions and dose interruptions was lower in tivozanib hydrochloride-treated patients than in sorafenib-treated patients. The incidence of TEAEs leading to discontinuation was similar in both treatment groups. The excess of dose interruptions and reductions in the sorafenib arm mainly due to PPE suggests that tivozanib may be more tolerable than sorafenib. There were 32 reports (4.7%) of hypertension leading to dose reduction or dose interruption across the core RCC monotherapy studies. The incidence of ischaemic strokes, venous embolic and thrombotic events, and haemorrhage were low, but marginally increased for tivozanib compared to sorafenib.

In the pivotal study, more patients had a dose reduction due to TEAEs in the sorafenib arm vs the tivozanib arm: 37.4% vs 11.6%. In addition, more patients reported TEAEs leading to drug interruption in the sorafenib arm vs. tivozanib arm: 37.0% vs 22.4%. The differences were mainly due to an excess of PPE cases in the sorafenib arm, for which there was specific protocol guidance. Advice on dose reduction and interruption for hypertension is included in the SmPC section 4.4.

In the Phase 3 pivotal trial (AV-951-09-301), the overall incidence of AEs with an outcome of death in the tivozanib hydrochloride group was 10.8% (28 of 259 patients) compared with 5.8% (15 of 257) in the sorafenib group. This is largely attributable to a higher incidence of deaths from neoplasm progression reported as adverse events in the tivozanib hydrochloride arm (9 patients, 3.5%) compared with the sorafenib arm (2 patients, 0.8%).

Adverse events of special interest (AESIs) were determined based on TEAEs observed within the tivozanib hydrochloride program as well as possible class effects seen with similar agents. TEAEs with an outcome of death (deaths within 30 days of the last dose of study drug) occurred in 47 of the 674 patients (7%) in the pooled tivozanib group of the core RCC monotherapy studies.

The overall incidence of the following AESIs was higher in patients in the tivozanib hydrochloride-treated arm than in the sorafenib-treated arm in Study AV-951-09-301 (all first-line data into Study AV-951-09-902): hypertension (47.5% versus 37.4%), arterial embolic and thrombotic events (4.6% versus 3.1%), venous embolic and thrombotic events (2.3% vs 0.8%), cerebrovascular ischaemia (3.5% vs 1.9%), haemorrhage (12.7% versus 7.0%), hyperthyroidism (1.5% vs 1.2%), hypothyroidism (5.4% versus 2.3%), acute pancreatitis and acute renal failure (each 0.8% versus 0.4%) and proteinuria (9.3% versus 8.6%). The overall incidence of the following AESIs was higher in patients in the sorafenib-treated arm than in the tivozanib hydrochloride-treated arm in Study AV- 951-09-301 (all first-line data into Study AV-951-09-902): non-infectious encephalopathy/delirium including PRES (0.8% versus 1.2%), hepatic disorders (8.1% versus 10.1%), cardiac failure (1.5% versus 1.6%) and HFSR (PPE; 13.9% versus 54.1%). Rare cases of GI perforation and fistula formation, wound healing complications, and acute renal failure were observed.

Based on the tivozanib hydrochloride clinical development program, the following safety concerns have been included as either an important identified or an important potential risk in the RMP (data are provided from SMQs and PTs): hypertension (47.5% in the tivozanib hydrochloride arm of Study AV-951-09-301 versus 37.4% in the sorafenib arm), arterial embolic and thrombotic events (4.6% versus 3.1%), venous embolic and thrombotic events (2.3% versus 0.8%), congestive heart failure (1.5% versus 1.6%); haemorrhage (12.7% versus 7.0%), proteinuria (9.3% versus 8.6%), and hand-foot skin reaction (13.9% versus 54.1%) identified as important identified risks; and hepatic effects (8.1% versus 10.1%), wound healing complications (0.4% in both arms), QT prolongation (none in Study AV-951-09-301), GI perforation and fistula formation (0.4% in both arms), PRES (1 patient in Study AV-951-09-301), reproductive and developmental toxicity (none reported), overdose (0.4% versus 0.4%), and toxicities, such as persistent severe hypertension, arising from concomitant administration of tivozanib with medicinal products that inhibit transporters (none reported) identified as important potential risks in the RMP.

Hypertension was the most frequently occurring TEAE observed in the tivozanib hydrochloride clinical program. There was a higher incidence of hypertension in the tivozanib hydrochloride arm than in the sorafenib arm in the pivotal study. One of the best documented and most frequently observed on-target effects of agents that target the VEGF pathway, the class of drug to which tivozanib hydrochloride belongs, hypertension is related to the effect of these drugs on the vasculature. Hypertension is a known risk factor for the occurrence of cardiovascular disease, atherosclerotic disease and cerebrovascular accidents. Hypertension in tivozanib hydrochloride patients was managed with anti-hypertensive medications as directed in the study protocols and infrequently led to dose modification; it is considered a manageable risk. It is recommended that blood pressure should be well controlled prior to initiating tivozanib hydrochloride therapy and that patients should be monitored for hypertension and treated as needed with antihypertensive therapy according to standard medical practice. In the case of persistent hypertension despite use of antihypertensive medications, the dose of tivozanib hydrochloride should be reduced or the treatment interrupted and re-initiated at a lower dose once the blood pressure is controlled, according to clinical judgment. Discontinuation of treatment should be considered in case of severe and persistent hypertension, posterior reversible encephalopathy syndrome, or other complications of hypertension. If tivozanib hydrochloride is interrupted, patients receiving antihypertensive medications should be monitored for hypotension (See SmPC section 4.4 and RMP).

One patient (diagnosed with serious carcinoma) from parent Study AV-951-10-112 treated with tivozanib reported PRES in the extension Study AV-951-09-901 following hypertension (see SmPC section 4.8). PRES is a neurological disorder that may present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. An MRI test is necessary to confirm the diagnosis of PRES. Tivozanib therapy should be discontinued in patients developing PRES. The safety of reinitiating tivozanib therapy in patients previously experiencing PRES is

not known. Risk factors for PRES/RPLS include uncontrolled hypertension and noncompliance with antihypertensive treatment (see SmPC section 4.4, 4.8 and RMP). This class effect has been included in the RMP as an important potential risk.

Arterial thromboembolic events (ATEs) have occurred (see SmPC section 4.4, 4.8 and RMP). Risk factors for ATE include malignant disease, age > 65 years, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, and prior thromboembolic disease. Tivozanib must be used with caution in patients who are at risk for, or who have a history of these events (such as myocardial infarction, stroke).

Venous thromboembolic events (VTEs) have been reported including pulmonary embolism and deep vein thrombosis (see SmPC section 4.4, 4.8 and RMP). Risk factors for VTEs include major surgery, multiple trauma, prior VTEs, advanced age, obesity, cardiac or respiratory failure, and prolonged immobility. It is recommended that treatment decision, in patients who are at risk for VTEs, should be based on individual patient benefit/risk assessment.

A risk of prolonged QT/QTc was foreseen based on the findings of the cardiac safety study 10-112, and an evaluation of possible QT/QTc-related events in the RCC monotherapy studies. QT/QTc interval prolongation has been reported (see SmPC section 4.8 and 5.1). QT/QTc interval prolongation may lead to an increased risk for ventricular arrhythmias. The risk is adequately reflected in the SmPC (section 4.4 and 4.8) and it is recommended that tivozanib is used with caution in patients with a history of QT interval prolongation or other relevant pre-existing cardiac disease and those receiving other medications known to increase the QT interval. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range is recommended.

Cardiac failure has been reported; signs or symptoms of cardiac failure should be periodically monitored throughout treatment with tivozanib (see SmPC section 4.4 and 4.8). Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of tivozanib therapy, plus treatment of potential underlying causes of cardiac failure e.g. hypertension.

In the pivotal study the percentage of patients in the tivozanib hydrochloride arm with Grade 3 or higher elevations in ALT and AST was 2-fold less than in the sorafenib arm (ALT: 0.8% vs 3.5%; AST: 1.9% vs 3.9%). No Hy's Law cases of hepatotoxicity were observed. The risk of liver toxicity is adequately reflected in the SmPC (section 4.2, 4.4, 4.8 and 5.2). Patients should be monitored for liver enzyme elevations (ALT, AST, alkaline phosphatase and bilirubin) before initiation of and periodically throughout treatment with tivozanib hydrochloride.

PPE was reported at a higher incidence by sorafenib-treated patients than tivozanib hydrochloride-treated patients in the pivotal study (54.1% vs 13.9%). This was also true for the incidence of ≥ Grade 3 events (16.7% vs 1.9% respectively). This resulted in a lower incidence of dose reductions (5 in the tivozanib hydrochloride arm vs 43 in the sorafenib arm) and a lower incidence of dose interruptions (5 versus 45, respectively) due to PPE in Study AV-951-09-301. Management of patients experiencing PPE may include topical therapies for symptomatic relief with consideration of temporary interruption and/or reduction in treatment dose or, in severe or persistent cases, permanent discontinuation of treatment.

Dysphonia, another "on target" TEAE, was more common in the tivozanib hydrochloride arm than in the sorafenib arm of the pivotal study (21.2% vs 4.7%). All dysphonia events were mild to moderate. No TESAE was reported. TEAEs of dysphonia did not lead to study drug discontinuation but led to dose reduction or interruption in 1 patient in the sorafenib arm of the pivotal study.

"Off target" TEAEs that were more common in the sorafenib arm than in the tivozanib hydrochloride arm included HFSR (PPE; 54.1% vs 13.9%), alopecia (21.4% vs 2.3%) and diarrhoea (33.1% vs 24.3%). A

greater rate of study drug discontinuations and dose reductions and interruption were seen in sorafenib patients compared with tivozanib hydrochloride-treated patients as a result of these TEAEs.

Other common TEAEs were similar in both arms, including fatigue, asthenia, and weight decrease (all approximately 15% to 20%). Fewer Grade 3 or higher TEAEs occurred in the tivozanib hydrochloride arm than in the sorafenib arm (64.1 vs 70.4%).

Two patients received excessive doses of tivozanib during the monotherapy studies. A patient with a history of hypertension experienced aggravated uncontrolled hypertension that was fatal after taking 3 doses of 1340 microgram tivozanib in one day (total 4020 microgram). No adverse reaction was experienced by the second patient who took 2 doses of 1340 microgram tivozanib in one day (total 2680 microgram). Blood pressure should be well controlled prior to initiating tivozanib and patients should be monitored for hypertension during treatment (see SmPC section 4.4, 4.9 and RMP).

In vitro studies have shown that tivozanib is neither a substrate nor inhibitor of the multidrug efflux pump P-gp. However, the potential for tivozanib to be a substrate of transporters other than P-gp has not been studied (see SmPC section 5.2). Other transporters that may be affected by tivozanib include BCRP, BSEP, MDR1, MRP2, OATP1B1, OATP1B3 and OCT1 transporters. Patients treated with tivozanib and co-administered medicinal products that are known to inhibit transporters may be at increased risk of toxicities. Toxicities, such as persistent severe hypertension, arising from concomitant administration of tivozanib with medicinal products that inhibit transporters is an important potential risk of tivozanib. The applicant is requested to perform in vitro studies to evaluate tivozanib as a substrate of OCT1, OATP1B1, OATP1B3, P-gp, BCRP, BSEP and MRP2.

As VEGF is a key regulator of angiogenesis and as seen from nonclinical data, it is not unexpected that exposure to tivozanib hydrochloride could result in adverse effects during pregnancy. There have been no cases observed in the clinical development program but as studies in animals have shown reproductive toxicity, reproductive and developmental toxicity is considered an important potential risk (See SmPC section 4.6 and 5.3). It is currently unknown whether tivozanib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method (see SmPC section 4.5 and 4.6). As there is no information on the potential of tivozanib excretion in human milk, use during lactation is included in the RMP as “missing information” (see also SmPC section 4.6).

In addition, whilst the following are also recognised VEGF class effects, the assessment of the frequency and severity did not warrant inclusion in the RMP as either an important identified or an important potential risk; fatigue (20.5% versus 16.3%), asthenia (17.0% versus 17.1%), and hypothyroidism (5.4% versus 2.3%).

The data show a slightly more favourable safety profile of tivozanib compared with sorafenib in terms of lower incidence of specific ADRs (e.g. PPE), and lower dose reductions and dose interruptions for tivozanib hydrochloride-treated patients compared to sorafenib-treated patients. However in an open-label study, treatment comparisons require caution. The reduced incidence of PPE syndrome and diarrhoea is an advantage for tivozanib compared to sorafenib, although counteracted to some extent by increased incidences of dysphonia and hypertension. The safety profile is in accordance with that expected from nonclinical studies and known class effects (see SmPC section 4.4 and 4.8) and is manageable with dose reductions as described in the SmPC section 4.2. There is sufficient long-term data, as 286 patients were on-treatment over 12 months.

Co-administration with herbal preparations containing St. John’s wort (*Hypericum perforatum*) is contraindicated (see discussion on interactions under Clinical Pharmacology, SmPC section 4.3 and 4.5).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In general, the safety profile is in line with that expected for a specific VEGF inhibitor and appears acceptable. The most common ADRs appear manageable and adequate recommendations are included in the SmPC. Serious adverse reactions include ischaemic events, venous thromboembolism, haemorrhage and cardiac failure, although the risks are in line with other TKIs including VEGF inhibitors.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Hypertension Arterial embolic and thrombotic events Venous embolic and thrombotic events Congestive heart failure (CHF) Haemorrhage Proteinuria Hand-foot skin reaction (HFSR)
Important potential risks	QT prolongation Hepatic effects GI perforation and fistula Posterior reversible encephalopathy syndrome (PRES) Reproductive and developmental toxicity Wound healing complications Overdose Toxicities, such as persistent severe hypertension, arising from concomitant administration of tivozanib with medicinal products that inhibit transporters
Missing information	Use during lactation

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
EUSA/GBL/01/2017-03 (Protocol No.: EUSA-02-24Jan2017) *In vitro* interaction studies of tivozanib with human BSEP, BCRP, MDR1 and MRP2 efflux (ABC) transporters, and with OATP1B1, OATP1B3 and OCT1 uptake transporters. (Category 3 study)	1. To evaluate tivozanib as a substrate of the human BCRP, BSEP, MDR1 and MRP2 efflux transporters in the vesicular transport substrate assay. 2. To evaluate tivozanib as a substrate of the human OATP1B1, OATP1B3 and OCT1 uptake transporters in the uptake transporter substrate assay.	Toxicities, such as persistent severe hypertension, arising from concomitant administration of tivozanib with medicinal products that inhibit transporters	Planned	Final report: Q4 2017

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypertension	• Warning in Section 4.4 of the SmPC that hypertension is expected with tivozanib. Monitoring of blood pressure is recommended with advice on treatment provided.	None
	• Section 4.8 of the SmPC lists hypertension as the most important serious adverse reaction with a frequency of very common, persistent severe hypertension (including hypertensive crisis) with a frequency of common and describes the hypertension adverse reactions reported in clinical studies.	
	• Section 4.9 of the SmPC warns of the need to monitor and treat hypertension in cases of suspected overdose.	
	• Section 2 of PL warns that Fotivda can increase blood pressure and recommends monitoring of blood pressure during treatment.	
	• Section 3 of PL warns of increased risk of high blood pressure in cases of overdose.	
	• High blood pressure is included as a very common side effect and very high blood pressure is included as a common side effect in Section 4 of PL.	
	• Prescription only medication	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Use is restricted to physicians experienced in the treatment of RCC	
Arterial embolic and thrombotic events	• Section 4.4 of SmPC warns that tivozanib must be used with caution in patients at risk of or with a history of arterial embolic/thrombotic events.	None
	• Section 4.8 of SmPC lists arterial thromboembolism, acute myocardial infarction/ischaemia, and angina pectoris as common adverse reactions, transient ischaemic attack as an uncommon adverse reaction and describes the arterial thromboembolic adverse reactions reported in clinical studies.	
	• Warning that treatment with Fotivda may increase risk of thrombosis included in Section 2 of PL.	
	• Rapid heart rate, tightness of chest, heart attack/reduced blood flow to heart, blood clot in an artery (blood vessel) and blood clot in the lung are listed as common side effects in Section 4 of PL.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Venous embolic and thrombotic events	• Warning that treatment of patients at risk for VTEs should be based on individual risk/benefit assessment is included in Section 4.4 of SmPC.	None
	• Section 4.8 lists venous thromboembolism as a common adverse reaction and describes the venous thromboembolism adverse reactions reported in clinical studies.	
	• Warning that treatment with Fotivda may increase risk of thrombosis included in Section 2 of PL.	
	• Section 4 of PL lists blood clot in the lung and blood clot in a deep vein as common side effects.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Congestive heart failure (CHF)	• Recommendation that signs of cardiac failure should be continually monitoring during treatment included in Section 4.4 of SmPC.	None
	• Section 4.8 of SmPC lists pulmonary oedema as an uncommon adverse reaction	
	• Section 2 of PL includes a warning to report potential symptoms of heart failure (shortness of breath or ankle swelling) immediately.	
	• Section 4 of PL lists heart failure and swelling in the lungs caused by fluid build-up as uncommon side effects	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Haemorrhage	• Section 4.4 of SmPC includes a warning to use with caution in patients at risk for or with a history of bleeding and recommends interruption of tivozanib therapy if any bleeding requires medical intervention.	None
	• Section 4.8 of SmPC lists haemorrhage as a common adverse reaction and describes the haemorrhage adverse reactions reported in clinical studies.	
	• Warning of potential increased risk of bleeding included in Section 2 of PL.	
	• Bleeding, coughing up blood, vomiting up blood, and nose bleed included as common side effects and bruising easily and bleeding into the skin included as uncommon side effects in Section 4 of PL	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Proteinuria	• Section 4.4 of SmPC recommends monitoring for proteinuria before and during treatment and what action to take if proteinuria develops.	None
	• Proteinuria is listed as a common adverse reaction in Section 4.8 of SmPC.	
	• Recommendation that a doctor monitor the amount of protein in the urine is included in Section 2 of PL.	
	• Increased amount of protein in the urine is included as a common side effect in Section 4 of PL.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Hand-foot skin reaction (HFSR)	• Warning that HFSR has been reported in clinical studies with tivozanib is included in Section 4.4 of SmPC.	None
	• HFSR is listed as a very common adverse reaction in Section 4.8 of SmPC.	
	• Section 2 of PL includes a warning about the symptoms of HFSR.	
	• HFSR is listed as a very common side effect in Section 4 of the PL.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Important potential risks		
QT prolongation	• Section 4.4 of SmPC recommends that tivozanib be used with caution in patients who have or may develop prolongation of QTc.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Electrocardiogram QT prolonged is listed as an uncommon adverse reaction in Section 4.8 of SmPC and describes the QT prolongation adverse reactions reported in clinical studies.	
	• Section 5.1 of SmPC includes a discussion of QTcF changes observed in Study AV-951-10-112.	
	• Section 2 of PL recommends heart monitoring in patients with arrhythmia during treatment.	
	• Section 4 of PL lists abnormal electrocardiogram (ECG) and rapid and/or irregular heart beat as uncommon side effects	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Hepatic effects	• Section 4.2 of SmPC provides guidance on monitoring ALT, AST, bilirubin and AP levels prior to and during treatment and recommends on dosing instructions and use in patients with hepatic impairment.	None
	• Section 4.4 of SmPC recommends that ALT, AST, bilirubin and AP levels be monitored before and during treatment with tivozanib. Tivozanib should not be used in patients with severe hepatic impairment, and that caution is advised in patients with mild and moderate hepatic impairment, with a dose modification recommended for patients with moderate hepatic impairment.	
	• In Section 4.8 of SmPC gamma-glutamyltransferase increased, AST/ALT increased and blood alkaline phosphatase increased are listed as common adverse reactions.	
	• In section 5.2 of SmPC there is a description of tivozanib exposure in patients with mild, moderate and severe hepatic impairment leading to dosing instructions and use in patients with hepatic impairment.	
	• Section 2 of PL recommends regular monitoring of liver function and that it may be necessary to reduce the frequency of dosing in patients with liver problems.	
	• In Section 4 of PL abnormal blood test results for liver are listed as common side effects.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
GI perforation and fistula	• Section 4.4 of SmPC recommends periodic monitoring for GI perforation or fistula and warns that Fotivda should be used with caution in patients at risk of these.	None

	• Diarrhoea, stomatitis, nausea and abdominal pain are listed as very common adverse reactions in Section 4.8 of SmPC. Vomiting, dyspepsia, constipation, flatulence, gastrooesophageal reflux disease, dysphagia, pancreatitis, abdominal distension, glossitis, gingivitis and dry mouth are listed as common adverse reactions in Section 4.8 of SmPC. • Duodenal ulcer is listed as an uncommon adverse reaction in Section 4.8 of SmPC.	
	• Section 2 of PL includes warning to monitor for symptoms of GI perforation or fistula.	
	• Section 4 of PL lists gastrointestinal symptoms as very common, common and uncommon side effects and peptic ulcer in the small intestines as an uncommon side effect.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Posterior reversible encephalopathy syndrome (PRES)	• Section 4.4 of SmPC lists one case of PRES reported in a patient treated with tivozanib and warns that treatment must be discontinued in patients developing PRES.	None
	• PRES is included as a rare adverse reaction in Section 4.8 and describes the symptoms of PRES.	
	• A warning to immediately report symptoms of PRES is included in Section 2 of PL.	
	• Section 4 of PL lists PRES as a rare side effect.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Reproductive and developmental toxicity	• Section 4.5 of SmPC advises that women using hormonal contraceptives should add a barrier method.	None
	• Section 4.6 of SmPC warns that effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least one month after completing therapy and that a barrier method of contraception should be used. • Section 4.6 of SmPC warns that tivozanib should not be used during pregnancy and advises women of child bearing potential to use adequate contraception during treatment. • Section 4.6 of SmPC warns of a potential effect on male and female fertility.	
	• Preclinical studies assessing reproductive toxicity and effects on fertility are discussed in Section 5.3 of SmPC.	
	• Section 2 of PL includes a warning not to take Fotivda when pregnant and to use effective contraception. • Section 2 of PL mentions a potential effect on fertility.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Wound healing complications	• Section 4.4 of SmPC recommends that tivozanib therapy is interrupted in patients undergoing major surgical procedures.	None

	• Section 2 of PL includes a warning that treatment may need to be interrupted when undergoing surgery.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Overdose	• Section 4.9 of SmPC provides advice on the management of overdose including monitoring for hypertension and that blood pressure should be well controlled before and during therapy.	None
	• Section 3 of PL advises on overdose and symptoms of high blood pressure that may occur associated with overdose.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Toxicities, such as persistent severe hypertension, arising from concomitant administration of tivozanib with medicinal products that inhibit transporters	• Section 5.2 advises that tivozanib is not a substrate of P-glycoprotein and that the potential for tivozanib to be a substrate of other transporters has not been studied.	None
	• Section 2 of PL advises patients to inform their doctor or pharmacist of other medicines they are or have been taking.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	
Missing information		
Use during lactation	• Section 4.6 of SmPC states that the potential for excretion of tivozanib in human milk is unknown and includes a warning not to breast-feed during treatment with tivozanib.	None
	• Section 2 of PL includes a warning not to breast-feed during treatment with Fotivda.	
	• Prescription only medication	
	• Use is restricted to physicians experienced in the treatment of RCC	

Routine risk minimisation measures are considered sufficient to manage the risks of this medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of tivozanib hydrochloride monohydrate with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers tivozanib hydrochloride monohydrate to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fotivda (tivozanib hydrochloride monohydrate) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Renal cell carcinoma (RCC) accounts for 2% to 3% of all adult malignancies. Patients with localised disease at diagnosis have a 5-year survival rate of approximately 85% compared with 10% in those with metastatic disease at diagnosis (25% to 30% of patients).

In RCC, overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) promotes neoangiogenesis, which contributes to the development and progression of RCC.

3.1.2. Available therapies and unmet medical need

In metastatic RCC, targeted therapy is now the first-line standard of care. VEGF inhibitors (e.g. axitinib, bevacizumab), multi-target tyrosine kinase inhibitors (e.g. sorafenib, sunitinib, pazopanib) and mTOR inhibitors (e.g. temsirolimus) are already approved in the EU for the first-line treatment of advanced RCC.

3.1.3. Main clinical studies

The clinical efficacy of tivozanib is supported by an open-label, randomised, controlled pivotal study (09-301). Supportive efficacy data comes from two phase 2 studies (10-202, 07-201) and one extension study (09-902).

3.2. Favourable effects

For the primary endpoint of progression-free survival (PFS) by independent radiological review (IRR) in the intention to treat population at study end, the median PFS (95% CI) was 11.9 months (9.3, 14.7) for tivozanib compared to 9.1 months (7.3, 9.5) for sorafenib. The hazard ratio (stratified Cox proportional hazards model) (95% CI) was 0.797 (0.639, 0.993). The p-value was 0.042. The pre-planned sensitivity analyses and subgroup analyses of PFS are in line with the primary outcome.

The overall response rate (ORR) outcome by IRR favours tivozanib over sorafenib, 33% vs 23%. Median duration of response by IRR was 15.0 months for tivozanib compared to 12.9 months for sorafenib.

Some supportive evidence of efficacy is available from the Phase 2 and extension studies. For the Phase 2 randomised discontinuation study (07-201), the ORR by IRR was 18% after the 16 week open-label period. After randomised discontinuation, the PFS rate at 12 weeks (in subjects with <25% tumour growth or shrinkage) was 49% for tivozanib vs. 21% for placebo by IRR. For the Phase 2 open-label single arm study (10-202), investigator-assessed ORR was 25% at 6 months.

3.3. Uncertainties and limitations about favourable effects

The pivotal study only enrolled patients with RCC that included a clear cell component. Patients with nccRCC were included in supportive studies 201 and 202. Although the numbers are small, there appears to be evidence of activity of tivozanib in nccRCC albeit at a reduced level compared to ccRCC. Given the evidence of activity in nccRCC restricting the indication to ccRCC was not considered justified.

3.4. Unfavourable effects

The extent of clinical trial exposure at the claimed dose in the relevant disease population was adequate.

Adverse events (AEs) reported frequently for tivozanib include hypertension (48%), dysphonia (27%), fatigue (26%), diarrhoea (26%) and asthenia (18%). These preferred terms and frequencies are in line with the known safety profiles of other TKIs for the treatment of advanced RCC including VEGF inhibitors. Hypertension was the commonest reported AE. The higher incidence for tivozanib vs. sorafenib is expected, since tivozanib specifically targets the VEGF pathway, and the mechanism is believed to be related to VEGF pathway inhibition. The incidence is in line with that reported for axitinib, another selective inhibitor of VEGF-1, -2 and -3, in a second-line advanced RCC population. Dysphonia, believed to be a VEGF inhibitor effect, is also more common in tivozanib patients compared to sorafenib patients.

The lower incidence of diarrhoea with tivozanib, including grade 3-4 events, may represent an advantage for tivozanib compared to sorafenib. The incidence of PPE syndrome was significantly lower for tivozanib compared to sorafenib (13.9% in the tivozanib arm versus 54.1% in the sorafenib arm).

Less common but more serious effects include hepatic disorders, arterial thrombotic events, venous embolic and thrombotic events, haemorrhage and cardiac failure. The incidences are in line with other TKIs. A risk of QT/QTc prolongation cannot be ruled out based on the available data, recommendations for periodic monitoring through ECG and maintenance of electrolytes in the normal range is recommended in the SmPC (see SmPC section 4.4 and RMP).

3.5. Uncertainties and limitations about unfavourable effects

In vitro studies demonstrated that no unchanged tivozanib is excreted in the urine, and it is suggested that tivozanib is primarily hepatically eliminated. CYP3A4 has been identified as one of the metabolic pathways. However the contribution of different elimination mechanisms and routes has not been fully assessed. The Applicant will perform the evaluation of tivozanib as a substrate of OCT1, OATP1B1, OATP1B3, P-gp, BCRP, BSEP and MRP2 and the need for further interaction studies will be assessed (see RMP).

Significant cardiovascular disease (including uncontrolled hypertension), thromboembolic or vascular disorders, or bleeding disorders were exclusion criteria for the pivotal study. Therefore the risk of serious events may be increased with real world use and needs to be reviewed within the PSURs. Special populations such as older and non-white patients have not been studied adequately; more information is expected to come through the PSURs. Use during lactation is an area of missing information in the RMP.

3.6. Effects Table

Table 39. Effects Table for Fotivda (vs. sorafenib) in the first-line treatment of advanced RCC (data cut-off: 15th December 2011).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median PFS	PFS by independent radiological review in ITT population after 310 events	Months (95% CI)	11.9 (9.3, 14.7)	9.1 (7.3, 9.5)	(p=0.0.039).	Study AV-951-09-301
ORR	ITT population, whilst on randomized treatment	%	33.1	23.3	p= 0.013	Study AV-951-09-301
DOR	Median (by IRR)	months	15.0	12.9		Study AV-951-09-301
Unfavourable Effects						
Any	Grade 3-4	Unit	tivozanib	control	Uncertainties / strength of evidence	references

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hypertension	PT Grade 1-4	%	45	35		Study AV-951-09-301
Hypertension	PT Grade 3-4	%	26	18		Study AV-951-09-301
Dysphonia	PT Grade 1-4	%	21	5		Study AV-951-09-301
Fatigue	PT Grade 1-4	%	21	16		Study AV-951-09-301
Diarrhoea	PT Grade 1-4	%	24	33		Study AV-951-09-301
PPE syndrome	PT Grade 1-4	%	14	54		Study AV-951-09-301
PPE syndrome	PT Grade 3-4	%	2	17		Study AV-951-09-301

Abbreviations: PFS = progression-free survival; OS = overall survival; ORR = overall response rate; PT = preferred term; SMQ = standard MedDRA queries

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

An increase in median PFS for tivozanib vs. sorafenib of 2.4 months is clinically relevant. Sorafenib is an active comparator and there are supportive data from Phase 2, and ORR and duration of response favour tivozanib. Taking these factors into account, the observed primary PFS outcome provides adequate evidence of the efficacy of tivozanib in the first-line treatment of advanced RCC.

In general, the safety profile is in line with that expected for a specific VEGF inhibitor. The most frequent ADRs are manageable, although they will affect quality of life. The reduced incidence of PPE syndrome is an advantage for tivozanib compared to sorafenib, although on the other hand there were increased incidences of dysphonia and hypertension. However, the excess of dose interruptions and reductions in the sorafenib arm mainly due to PPE suggests that tivozanib may be more tolerable than sorafenib.

3.7.2. Balance of benefits and risks

An increase of 2.4 months in median PFS for tivozanib vs. sorafenib as an active comparator is clinically relevant and supported by data from Phase 2, and ORR and duration of response. The safety profile is in line with that expected for a specific VEGF inhibitor.

The benefit – risk balance of tivozanib in the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC is positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Fotivda in the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC, is positive.

The divergent position is appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Fotivda is not similar to Torisel within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Fotivda is favourable in the following indication:

First line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

The divergent position to the majority recommendation is appended to this report.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tivozanib hydrochloride monohydrate is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendix

1. Divergent position to the majority recommendation

DIVERGENT POSITION DATED 22 June 2017

Fotivda EMEA/H/C/004131

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of a marketing authorisation for Fotivda for the following reason(s):

This application is supported by a single pivotal study. This was a 2-year, open-label, randomized controlled trial comparing tivozanib with sorafenib in 517 patients with advanced RCC who had received no prior targeted therapy. No specific concerns are raised regarding the pivotal trial methodology. However, the study was designed such that only patients randomized to sorafenib were permitted to cross over. This has the potential to confound the overall survival (OS) results. The primary endpoint was progression-free survival (PFS) as determined by independent radiological review (IRR) in the ITT population.

In our view, the clinical efficacy of tivozanib has not been sufficiently established. The results of the single pivotal trial are not compelling and it is also of concern that a large proportion of patients started a new anti-cancer therapy before progression. Considering the open-label design of the single pivotal study, OS needs to be reassuring (in line with scientific advice and EMA guidance). However, all performed OS analyses have failed to show any OS benefit, and thus OS results do not support the PFS results.

Additionally, there is a lack of internal consistency in the PFS result with regard to geographical region, with the lack of efficacy in Russia and the Ukraine which cannot be attributed just to treatment cross-over since the hazard ratio for the PFS was already close to 1. A post-hoc analysis showed that for patients with an ECOG score of 1, the hazard ratio is around 1. This post-hoc analysis also suggests that for the patients on sorafenib, ECOG score makes no difference to PFS outcome, and therefore may not be a prognostic factor after all. The applicant's conclusion that the observed geographical imbalance in PFS is a reflection of imbalance in ECOG status between treatment groups could be questioned since these countries were not considered different to the rest of Central/Eastern Europe at randomisation so any separation at this point in time could be seen as data driven. It is therefore our opinion that the lack of internal consistency remains.

In conclusion, the efficacy of tivozanib is not considered robustly demonstrated. Although the safety of tivozanib is acceptable, we consider a positive benefit-risk balance for tivozanib not sufficiently demonstrated.

Agnes Gyurasics

Alar Irs

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Svein Rune Anderson (Norway)