EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 June 2010
EMA/CHMP/248579/2010
Evaluation of Medicines for Human Use

CHMP assessment report

Votrient

International Nonproprietary Name: pazopanib

Procedure No. EMEA/H/C/001141

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Glaxo Group Limited submitted on 27 February 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Votrient, 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 EMEA/CHMP on 27 October 2008.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier 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 tests or studies.

The applicant Glaxo Group Limited submitted on 27 February 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Votrient, which was designated as an orphan medicinal product EU/3/06/382 on 29 June 2006.

Votrient was designated as an orphan medicinal product in the following indication: treatment of renal cell carcinoma (RCC). The calculated prevalence of this condition was 3.5 per 100,000 EU population.

In connection with the review of the orphan designation criteria by the Committee on Orphan Medicinal Products (COMP) at its meeting of 7-8 April 2010, the Applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products on 7 April 2010.

The applicant applied for the following indication: "Votrient is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC)."

Information on Paediatric requirements
Pursuant to Article 7, the application included an EMA Decision P/47/2008 for the following condition:

- treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney)

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 application contained a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol Assistance:
The applicant received Protocol Assistance from the CHMP on 14 December 2006. A revised Final Protocol Assistance letter following clarification was received on 22 February 2007, which subsequently received follow-up Protocol Assistance on 20 September 2007.

The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status:
Votrient has been given a Marketing Authorisation in the USA on 19/10/2009.
A new application was filed in the following countries: Switzerland, Australia, New Zealand, Canada, Brasil, Russia, South Africa, South Korea, Turkey, India, Hong Kong, Chile, Indonesia, Malaysia.
The product was not licensed in any country at the time of submission of the application.

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

Rapporteur: Jens Ersbøll **Co-Rapporteur:** Barbara van Zwieten-Boot

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 27 February 2009.
- The procedure started on 25 March 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2009.
- During the meeting on 20-24 of July 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 September 2009.
- The summary report of the inspection carried out at the following site GlaxoSmithKline Priory Street Ware Herts. SG12 0DJ, UK, between 13-17 June 2009, was issued in September 2009
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 November 2009.
- During the CHMP meeting on 16-19 November 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 21 December 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 January 2010.
- Following the CHMP request, a Scientific Advisory Group (SAG) meeting took place on 8 January 2010 to provide advice on the list of questions adopted by the CHMP at its November 2009 meeting.
- The Rapporteurs circulated the Updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 and 14 January 2010.
- The CHMP adopted two reports on similarity of Votrient with Nexavar (sorafenib)/Torisel (temsirolimus) and Afinitor (everolimus) in June 2009 and January 2010.
- During the meeting on 15-18 February 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Votrient on 18 February 2010. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 17 February 2010.
- On 7 April 2010 the applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products.
- On 15 April 2010, the European Commission informed the EMA that a conditional marketing authorisation as recommended by the CHMP opinion could not be granted because the CHMP recommendation was based on Article 2(3) of Regulation (EC) No 507/2006, i.e. medicinal product designated as orphan medicinal product in accordance with Article 3 of Regulation (EC) No 141/2000.
- During the meeting on 19-22 April 2010, the CHMP adopted a revised positive opinion for granting a conditional Marketing Authorisation to Votrient on 22 April 2010 based on Article 2(1) of Regulation (EC) No 507/2006, i.e. medicinal product which aims at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Approximately 59,000 new renal cell carcinoma (RCC) cases and 27,000 RCC related deaths occur each year in the European Union (EU). The incidence of RCC increases with age and nearly three-quarters of the patients diagnosed between the ages of 50 and 79. The incidence of RCC is higher in men than in women. Approximately 60% of all RCC cases are diagnosed at the localized stage, usually due to incidental findings on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). The incidence of advanced stage and unstaged disease, however, is increasing and approximately 20% of RCC patients have metastatic disease at initial diagnosis and roughly 20% to 40% of patients diagnosed with localized tumor subsequently develop metastases.

The current standard of care for RCC is nephrectomy followed by systemic therapy for metastatic disease. The median survival for subjects with metastatic disease treated with conventional (cytokine-based) therapy is 10-13 months. The systemic treatments of advanced RCC have improved in recent years following a better understanding of the biology of RCC and development of several targeted agents including sunitinib, sorafenib, temsirolimus, everolimus and bevacizumab. Overexpression of proteins targeted by these agents including VEGF, VEGFRs, and PDGFR has been identified in the vast majority of subjects with clear cell RCC. These features are associated with increased angiogenesis, advanced tumor stage, aggressive phenotype, and poor survival and are therefore currently considered valid targets for the treatment of RCC.

This is a Centralised Marketing Authorisation Application under article 8(3) of Directive 2001/83/EC for pazopanib (Votrient) 200 mg and 400 mg film-coated tablets. Pazopanib was granted Orphan Drug Designation for RCC, based on the criterion of significant benefit, on 21 June 2006 (Orphan Medicinal Product Number: EU/3/06/382).

In connection with the review of the orphan designation criteria by the Committee on Orphan Medicinal Products (COMP) at its meeting of 7-8 April 2010, the Applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products on 7 April 2010.

Pazopanib is an oral angiogenesis inhibitor targeting the tyrosine kinase activity associated with vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, platelet-derived growth factor receptor (PDGFR)-α, and PDGFR–β, and stem cell factor receptor (c-KIT). The recommended dose of pazopanib is 800 mg once daily.

The claimed therapeutic indication is:

'Votrient is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC)'

The approved indication is:

'Votrient is indicated for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.'

The EMA has waived the obligation to submit the results of studies with Votrient in all subsets of the paediatric population in renal cell carcinoma as the condition does not normally occur in the paediatric population.

The applicant has received central Protocol Assistance by the CHMP on clinical issues in December 2006. In their response to the main clinical issue the CHMP suggested the conduction of an active comparator study. Clarification advice was received on 22 February 2007 maintaining the recommendation to conduct of an active controlled study. A second follow-up advice was given in September 2007 on the design of study VEG108844 (a head to head comparative, non-inferiority study with sunitinib) and on study VEG110324 (a study evaluating the effect and safety of pazopanib in patients who have failed or not tolerated another available TKI therapy).

2.2 Quality aspects

Introduction

Composition
Votrient is presented as immediate release film-coated tablets containing 200 mg or 400 mg pazopanib free base as the active substance.
Both strengths are capsule shaped tablets, plain on one side and debossed with an identifying code on the other side. The 200 mg strength tablets are pink, while the 400 mg strength are white tablets.
Other ingredients for the core tablets include microcrystalline cellulose, sodium starch glycolate, povidone K30 and magnesium stearate. The film coating consists of titanium dioxide, hypromellose, macrogol and polysorbate 80. The film coating of the 200 mg strength also contains red iron oxide.
Both strengths are packaged in white HDPE bottles with child resistant closures.

Active Substance

The chemical name of pazopanib is 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide monohydrochloride. It is a white to slightly yellow, non-

hygroscopic, crystalline substance. Evidence of structure of the active substance has been shown by elemental analysis, 1^{H}-NMR, ^{13}C-NMR, MS and IR, while the molecular structure has been determined by XRD. The crystal structure has been determined by single crystal X-ray crystallography. The solid state form selected is Form 1. It has been shown that the proposed manufacturing process consistently produces Form 1 and that no conversion occurs during stability. Pazopanib is very slightly soluble in aqueous solutions, being practically insoluble above pH 4. In order to improve its solubility, the active substance is micronized.

- Manufacture

Pazopanib is synthesized in a four step process using acommercially available starting material. The choice of the starting material as well as the route of synthesis has been appropriately justified. The applicant has used risk assessment and Design of Experiments to identify the critical process parameters that affect the critical quality attributes of the active substance as well as to establish the operating ranges that will ensure the desired product quality.
A detailed discussion has been provided concerning the potential impurities arising from the starting materials, reagents or the route of synthesis. Two of these impurities are controlled in the active substance specifications. No single structurally known organic impurity is limited above the limit of max.0.15% , which would require specific toxicological qualification.
The solvents used in the synthesis have been shown to be efficiently removed during the purification and drying operations and appropriate specifications have been set to control their presence.

- Specification

The active substance specification includes tests for appearance, particle size (laser diffraction) identification (IR, chloride counter ion), assay (HPLC), related impurities (HPLC), total viable aerobic count, bacterial endotoxins, residual solvents (GC), loss on drying (Ph. Eur), water content (Karl-Fisher) and heavy metals (Ph. Eur). A QbD approach has been followed for the development of the analytical method for the determination of assay and related substances by gradient HPLC. Different tools such as fishbone diagram, Failure mode and effects analysis (FMEA), DoE and Measurement system analysis (MSA) have been used to set up a design space for these methods. The rest of the analytical procedures employed to test the active substance have been developed using a traditional development approach.
Batch analysis data have been provided for three production-scale batches, which were manufactured according to the proposed synthetic route at the commercial site and tested by the proposed analytical methods. All batches met the predefined specifications showing the proposed synthetic route is reproducible and can consistently produce active substance of the intended quality.

- Stability

Data from four production scale batches stored for up to 24 months at long term and accelerated conditions in accordance with the ICH guidelines have been presented. Samples wee tested for assay, description, particle size, water content and impurities employing the analytical methods used for release that have been demonstrated to be stability indicating.
In addition results from photostability and forced degradation studies have been provided, performed in accordance with the ICH requirements.
In all cases no significant changes were observed at long-term, accelerated or stress conditions.

Medicinal Product

- Pharmaceutical Development

The design of the formulation focussed on the following needs:

- To minimize the number of tablets per dose.
- To develop two strengths in order to be able to adjust the dosing to an intermediate dose.
- To minimize the tablet size, for improved patient compliance.
- To include physically and chemically compatible components.
- To enable the application of a robust and reproducible manufacturing process.
- To develop one tablet core formulation for both strengths, thus resulting in dose proportional tablets for the two strengths.
- To comply with compendial and any other relevant quality standards at manufacture and over the proposed shelf-life.
- To result in a dosage form that is al least stable during two years when stored at temperatures up to 30°C.

Throughout the development of both the active substance and the finished product the applicant used the principles described in ICH Q8 and ICH Q9 Guidelines. More specifically the applicant used risk

assessment methodologies such as Failure Mode and Effects Analysis (FMEA) and Best Route Innovation Technology Evaluation and Selection Techniques (BRITEST) to establish those process parameters and material attributes that are likely to have the greatest impact on product quality. The identified parameters and attributes were then further studied using Design of Experiments to identify their effect on product quality and to establish the operating ranges that would ensure the desired product quality.

The active substance can be classified as a Class II active substance (high permeability, low solubility) according to the Biopharmaceutics Classification System (BCS). This implies that particle size is expected to impact dissolution and thus bioavailability. Therefore the active substance is micronized in order to improve its solubility and to provide a more consistent particle size input to the granulation process. In addition, considerable attention was paid to the development of a discriminating dissolution method.

Based on risk assessment, the following attributes of the active substance were identified as critical for the finished product quality; solubility, particle size distribution, identity, form, and impurities. Multivariate analysis (MVA) was conducted to evaluate the variability in the input active substance used for the manufacture of clinical trial batches. In all cases the manufacturing process could manage the variability in the active substance attributes providing finished product with consistent performance.

For the formulation development standard pharmacopoeial excipients were selected that are commonly used in these kinds of formulations. Based on the scientific and prior knowledge of the excipients used in pazopanib tablets and on the risk assessment, no excipient attributes were identified as high risks to product quality.

A standard wet granulation method was used for the manufacture of the finished product. Extensive development studies were performed to establish the critical process parameters that affect finished product quality.. A design space has been proposed for dissolution of the pazopanib tablets.

The pazopanib tablets are packaged in HDPE plastic bottles. The plastic packaging materials components comply with European Directive 2002/72/ EC for use in contact with food. The HDPE bottle materials of construction comply with Ph.Eur. 3.1.3 on Polyolefines.

- Manufacture of the Product

The manufacturing process is a standard wet granulation process and consists of the following steps: granulation; milling; drying; blending and compression. The tablets are then film-coated.
All critical process parameters have been identified and controlled by appropriate in process controls.
For control verification the use of continuous verification has been proposed rather than conventional validation. In light of the enhanced knowledge presented in the dossier for the process and the finished product and this was considered acceptable.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification (UV and HPLC), assay (HPLC), uniformity of dosage units (USP), microbial content and dissolution. All tests included in the specification have been satisfactorily described and validated.
Batch analysis data from 3 primary batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were carried out on 3 primary batches of tablets according to the ICH requirements. The batches included in the stability programme were manufactured using the proposed commercial composition and manufacturing process. Samples were stored at 25°C/60 % RH and 30°C/65 % RH for 24 months and in 40°C/75 % RH for 6 months.

The parameters tested were description, identity, assay, impurities, uniformity of dosage units and dissolution. The analytical methods used were the same as for release testing and they have been adequately validated in order to be able to detect deterioration of the tablet quality.
Tablets were also exposed to ICH photostability conditions. No significant changes were observed in description, pazopanib content, impurities content or dissolution, and all results comply with specification.

Stress testing during 12 months at 5°C/ambient humidity and 3 months at 50°C/ambient humidity revealed no evidence of significant levels of degradation products. Also description, pazopanib content, and dissolution rate did not change and remained well within the specification.

Based on the stability data a shelf-life of 24 months will be applied to the product, with no special storage conditions requirements.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of pazopanib is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3 Non-clinical aspects

Introduction

All pivotal studies were conducted in accordance with GLP regulations. Exploratory or range finding studies were not in accordance with GLP regulations.

Non-clinical studies were primarily conducted using the monohydrochloride salt of pazopanib (GW786034B). All pivotal safety studies were conducted using the micronized monohydrochloride salt of pazopanib, which is the form proposed for use in humans. Some preliminary studies used the parent compound (GW786034) and the dihydrochloride salt of pazopanib (GW786034A). Additionally, radiolabelled salts of pazopanib were used: ^{14}C-pazopanib monohydrochloride and ^{14}C-pazopanib dihydrochloride.

Pharmacology

- Primary pharmacodynamics

Potency and selectivity in cell-free assays

The *in vitro* activity of pazopanib was evaluated using the recombinant kinase domain of various kinases. In cell free assays, pazopanib inhibited substrate phosphorylation catalysed by human recombinant VEGFR-1, VEGFR-2 and VEGFR-3 with IC_{50} values of 10, 30 and 47 nM (see Table 1). Moreover, FGFR1 and Tie2 were inhibited with IC_{50} values of 140 nM and 4.5 µM, respectively. Other receptor tyrosine kinases involved in angiogenesis were inhibited at low pazopanib concentrations, such as PDGFRα (IC_{50}= 71 nM) and PDGFRβ (IC_{50}≈140 nM).

Table 1. Pazopanib IC_{50} (µM) obtained with recombinant human kinase domains

Enzyme	Study rr2002-00010-01	Study rh2003-00076-00
VEGFR-1	0.010	0.013
VEGFR-2	0.030	0.012
VEGFR-3	0.047	-
PDGFRα	-	0.071
PDGFRβ	0.195	0.084
Tie-2	4.52	-
FGFR1	-	0.14
FGFR3	-	0.13
FGFR4	-	0.8*
c-RAF/MEK/ERK	14.5	-

**estimated*

The affinity of pazopanib against various human recombinant kinases was evaluated *in vitro* and compared to the available agents, sunitinib and sorafenib. The results are presented in Table 2.

Table 2. Summary of Inhibition of Purified Kinases by Pazopanib, Sunitinib and Sorafenib

Enzyme	Ki^{app} * (nM)		
	Pazopanib	**Sunitinib**	**Sorafenib**
VEGFR-1	15	229	10
VEGFR-2	8	51	4
VEGFR-3	10	30	6
PDGFRα	30	28	2
PDGFRβ	14	7	5
Flt-3	230	0.6	22
c-KIT	2.4	0.5	15
B-Raf (Wild Type)	68	470	1.9
B-Raf V600E	160	3000	6.1
C-Raf	109	2000	1.9

* K_i^{app} = apparent inhibition constant

Pazopanib inhibited substrate phosphorylation catalysed by recombinant mouse, rat and dog VEGFR-2 with IC_{50} values of 42, 17 and 17 nM, respectively. No species difference with respect to VEGFR-2 affinity was present. The affinity towards monkey VEGFR-2 was not evaluated.

Inhibition of receptor tyrosine kinase activity in cells

To confirm the biochemical activity of pazopanib in a cell-based assay, tyrosine autophosphorylation of VEGFR-2 after VEGF stimulation was determined in human umbilical vein endothelial cells (HUVEC). HUVEC stimulated with 10 ng/mL VEGF exhibit an increase in tyrosine phosphorylation of VEGFR2. Treatment of cells with pazopanib inhibited this increase in receptor autophosphorylation in a dose-dependent manner (IC_{50} = 7 nM).

The cellular activity of pazopanib, sunitinib and sorafenib against VEGFR-2, c-Kit, PDGFR-β, and Flt-3 receptors was evaluated in a ligand-induced receptor autophosphorylation assay using HUVEC, NCI-H526 (human small cell lung carcinoma), human foreskin fibroblast (HFF) and RS4;11 cells (human B-cell acute lymphoblastic leukemia). As shown in Table 3, all three inhibitors exhibit similar potency in suppressing activation of VEGFR-2 and PDGFR-β. However, sunitinib showed 10-fold greater potency than pazopanib and 100-fold greater potency than sorafenib against c-Kit activation. Sunitinib and sorafenib both potently inhibited wild-type Flt-3 receptor activation with IC_{50} of 1nM, whereas pazopanib was 1000-fold less active against Flt-3 with IC_{50} ≥1μM. These results are generally consistent with the observed differences in binding affinities (please refer to Table 2).

Table 3. Inhibition of ligand-induced receptor autophosphorylation in cell lines expressing the target molecule

Enzyme	IC_{50} (nM)		
	Pazopanib	**Sunitinib**	**Sorafenib**
VEGFR-2 (HUVEC)	8	5	10
PDGFRβ (HFF cells)	3	2	7
Flt-3 (RS4;11 cells)	≥1 μM	1	1
c-KIT (NCI-H526 cells)	26	0.3	290

Inhibition of cellular proliferation

Pazopanib selectively inhibited the proliferation (BrdU incorporation) of VEGF-stimulated human umbilical vein endothelial cells (HUVEC) (IC_{50} = 21 nM) while it had a less potent inhibitory effect of HUVEC proliferation stimulated by the pro-angiogenic growth factor basic-FGF (b-FGF) (IC_{50} = 721 nM).

In a 3-day cell proliferation assay, treatment with sunitinib and sorafenib induced dose-dependent inhibition of MV4-11 cell growth with IC_{50} of 5 and 4 nM, respectively, whereas pazopanib was much less potent with an IC_{50} of 1.4 μM. MV4-11 cells harbour the Flt-3 internal tandem duplications mutation, which results in constitutive activation of Flt-3. These results are consistent with the reduced

potency of pazopanib in Flt-3 receptor autophosphorylation assays compared to sunitinib and sorafenib.

Pazopanib was evaluated for its ability to inhibit the growth of a variety of human tumour cell lines, HT-29 (colon), MDA-MB-468 (breast), PC3 (prostate), and A375P (melanoma) and normal human fibroblasts (HFF) growing in serum containing media. Pazopanib inhibited proliferation of HFF with an IC_{50} of 1.01 µM and had no effect on the proliferation of the 4 tumour cell lines at the highest concentration tested (30 µM).

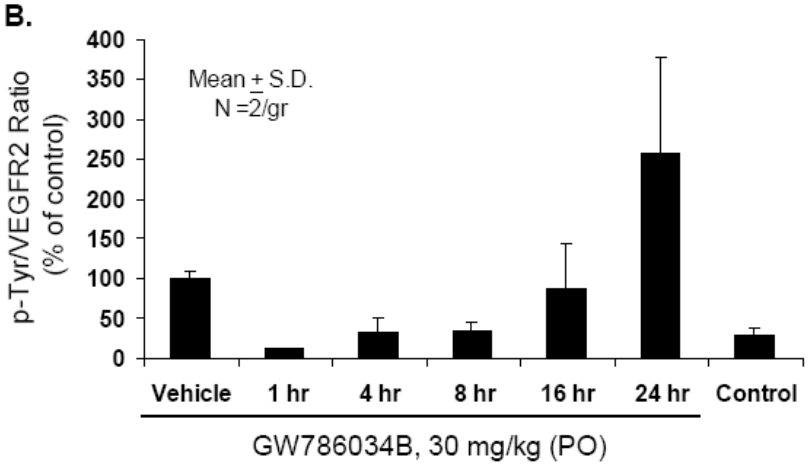
To further investigate whether pazopanib can directly modulate the proliferation of tumour cells, the compound was tested in a cell proliferation assay in a panel of 282 human cell lines. Of these, 281 were tumour cell lines derived from various tissue types, and 1 was a non-transformed breast cell line. IC_{50} values across the cell panel ranged from 0.01 to >10 µM. Only 7 cell lines showed an IC_{50} <1 µM: GDM1 (AML); ARH-77 (myeloma); NCI-H716 (colon carcinoma); G402 (kidney leiomyoblastoma); CGTH-W-1 (thyroid carcinoma); A204 (rhabdomyosarcoma) and CML-T1 (CML). Hence, pazopanib is a weak or inactive inhibitor of proliferation in the majority of human cell lines tested *in vitro*. The anti-tumour activity of pazopanib is, therefore, most likely derived from its anti-proliferative effect on endothelial cells.

The effects of the three VEGFR TKIs on human bone marrow progenitor growth induced by multiple growth factors (GM-CSF, Flt-3 ligand, the c-KIT ligand SCF) and combinations of these were investigated. The resultant IC_{50} values showed that sunitinib is a more potent inhibitor of growth factor induced bone marrow progenitor growth than pazopanib and sorafenib. Moreover, sorafenib appeared to be a more potent inhibitor of Flt-3 and Flt-3/SCF stimulated growth than pazopanib. The IC_{50} values for pazopanib varied from 173 nM (GM-SCF + SCF) to 8984 nM (Flt-3).

One of the circulating metabolites of pazopanib inhibited VEGF-induced endothelial cell proliferation with similar potency to that of pazopanib. The other 3 circulating metabolites showed at least 10- to 20-fold less activity than pazopanib. However, in bFGF-stimulated endothelial cells, all the metabolites except one were more potent (IC_{50}=0.79 to 5.5 µM) than pazopanib (IC_{50}>10 µM).

Inhibition of VEGFR activity *in vivo*

Mice treated with PO pazopanib were at different times post-dosing IV administered with $VEGF_{121}$ (15 µg/mouse). Subsequently, the lungs were harvested 5 minutes later and analysed for phosphorylated and total VEGFR-2 levels. The densitometric analysis of the Western blots are shown in Figure 1 below. A single oral dose of 30 mg/kg pazopanib inhibited VEGFR-2 phosphorylation for 8 but not 16 hours. This finding is consistent with the short half-life of pazopanib in mice (4-5 hours). Moreover, decreased VEGFR-2 phosphorylation was observed in murine lungs when VEGF was given 2 hours following PO administration of 10, 30 and 100 mg/kg pazopanib. Overall, the study results suggest that approximately 40 µM pazopanib is required for optimal inhibition of VEGFR2 phosphorylation in mice.



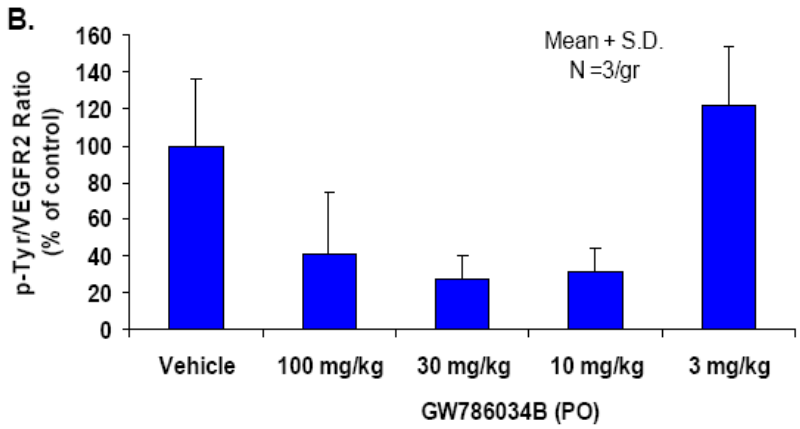


Figure 1. Desitometric analysis of Western blots represented as percent control for p-Tyr/VEGFR-2 ratio following PO administration of pazopanib (monohydrochloride salt GW786034B).

Pazopanib given PO at ≥30 mg/kg inhibited bFGF- and VEGF-induced angiogenesis in a variety of animal models including the Matrigel plug and corneal micropocket models of angiogenesis in Swiss nude or C57B1/6 mice. Pazopanib also showed generally dose-dependent inhibition of aberrant ocular angiogenesis in laser-induced choroidal neovascularization in C57B1/6J mice (≥8 mg/kg, PO) and Brown Norway rats (2.25 mg/kg, eye drops) as well as corneal neovascularization in a suture-induced model in New Zealand white rabbits (≥0.1 mg/eye/day, eye drops).

Anti-tumour activity in human tumour xenografts in mice

The anti-tumour activity of 21 to 46 days of PO pazopanib treatment was investigated in various human tumour xenograft models in mice. A summary of these findings is presented in Table 4. The tumour cell lines were propagated in either Swiss nude, CD-1 nude or SCID mice (n=5-8 mice/group). The tumour cells were injected SC and pazopanib treatment started when tumour volume reached between 100-350 mm^3 in size (advanced stage).

Table 4. Pazopanib effect on tumour growth in various human tumour xenograft models.

Cell Line	Dose Regimen	Effect on Tumour Growth
HT29*	0, 10, 30, 100 mg/kg QD or BID for 21 days	65-82% inhibition at 100 mg/kg QD and BID
Colo-205	0, 30, 100 mg/kg BID for 21 days	No inhibition at 100 mg/kg
HN5*	0, 10, 30, 100 mg/kg QD or BID for 21 days	≥90% inhibition at 100 mg/kg QD and BID
A375P*	0, 10, 30, 100 mg/kg QD or BID for 21 days	44-64% inhibition at 100 mg/kg QD and BID
PC3*	0, 10, 30, 100 mg/kg QD or BID for 21 days	0-58% inhibition at 100 mg/kg QD and BID
BT474	0, 30, 100 mg/kg QD for 21 days	64-78% inhibition at 100 mg/kg
NCI-H322	0, 30, 100 mg/kg QD for 21 days	56-88% inhibition at 100 mg/kg
CAKI-2	0, 10, 30, 100 mg/kg QD for 24 days	99% inhibition at 100 mg/kg
A498	0, 10, 30, 100 mg/kg QD for 24 days	64% inhibition at 100 mg/kg
ACHN	0, 10, 30, 100 mg/kg QD for 46 days	46% inhibition at 100 mg/kg
786-O	0, 10, 30, 100 mg/kg QD for 31 days	30% inhibition at 100 mg/kg
CAKI-1	0, 10, 30, 100 mg/kg QD for 21 days	No inhibition at any dose
OVCAR-3	0, 10, 30, 100 mg/kg BID for 22 days	81% inhibition at 100 mg/kg
SKOV3	0, 30, 100 mg/kg BID for 21 days	41% inhibition at 100 mg/kg

* = overall results obtained with pazopanib monohydrochloride and pazopanib dihydrochloride.
HT29, Colo-205 = Human colon carcinoma. HN5 = Human head and neck carcinoma overexpressing ErbB1. A375P = Human melanoma. PC3 = Human prostate carcinoma. BT474 = Human breast ductal carcinoma overexpressing ErbB2. NCI-H322 = Human non-small cell lung carcinoma moderately expressing ErbB1 and ErbB2. CAKI-1, CAKI-2, ACHN, A498 and 786-O = Human renal cell carcinoma. OVCAR-3, SKOV3 = Human ovarian carcinoma. QD = Once daily dosing. BID = Twice daily dosing.

The anti-tumour activity of pazopanib was compared with sunitinib and sorafenib in two mouse xenograft models of human colon cancer (Colo-205 and HT-29). CD-1 nude mice with similar sized tumours (~250-350 mm^3) were PO treated with pazopanib (30, 100 mg/kg BID), sunitinib (20, 40, 80 QD) or sorafenib (15, 30, 60 mg/kg QD) for 21 days (n=8 mice/group). Pazopanib showed ~70% and sorafenib ~40% inhibition of tumour growth compared to sunitinib.

- Secondary pharmacodynamics

Pazopanib was tested at a concentration of 10 µM in a battery of 49 radioligand-binding assays to evaluate its binding interactions with various physiological receptors and ion channels. These included adenosine, adrenergic, cholinergic, dopamine, endothelin, glutamate, histamine, opioid, purinergic, serotonin, steriod, sigma, and leukotriene receptors: monoamine transporter sites (dopamine, norepinephrine, serotonin); and ion channels (calcium, chloride ($GABA_A$), potassium (Kv), and sodium). Pazopanib did not significantly (>50%) inhibit the binding of any of the radioligands to their respective binding sites with the following exceptions: adenosine A3 (73% inhibition), adrenoceptors α2 (58%) & β1 (107%), histamine H_2 (82%), muscarinic M_1 (62%), serotonin 5-HT_{1A} (71%), 5-HT_{5A} (85%), and 5-HT_7 (53%).

Subsequently, it was further evaluated whether pazopanib caused β-adrenergic mediated changes in force of contraction or rate in spontaneously beating isolated rat atria. Cumulative doses of pazopanib were associated with dose-related increases in atrial force which were not blocked with propranolol (around 45% increase at 30 µM and 10% increase at 3 µM). Pre-incubation of tissue with pazopanib reduced the maximum contractile response to the β-adrenoceptor agonist isoproterenol, hence a β

adrenoceptor mediated effect cannot be excluded. There was little change in atrial rate with pazopanib (-5% at 30 µM).

The activity of pazopanib was evaluated in a panel of 242 kinases. Sunitinib and sorafenib were tested for comparison. Compounds were first evaluated at two fixed concentrations, 0.3 µM and 10 µM. At 10 µM, a total of 94 kinases were inhibited >50% by pazopanib, while 147 and 82 kinases were inhibited by sunitinib and sorafenib, respectively. A sub-set of 61 kinases that were inhibited >50% at 0.3 µM by at least one drug was selected for IC_{50} determination. Pazopanib inhibited 31 kinases with an IC_{50} <1 µM, while sunitinib and sorafenib inhibited 53 and 25 kinase, respectively, with some overlap. Amongst the kinases inhibited by pazopanib (IC_{50}<1 µM), which are not directly involved in tumour angiogenesis are Abl (IC_{50}=624 nM), Aurora-A (64 nM), c-kit (48 nM), c-Raf (92 nM), DDR2 (474 nM), KDR (15 nM), Lck (379 nM), MLK1 (21 nM), PTK5 (97 nM), Ret (232 nM), Tao2 (383 nM), TAO3 (181 nM), TrkA (937 nM), and Yes (667 nM).

- Safety pharmacology programme

The results from the safety pharmacology studies are summarized in Table 5.

Table 5. The safety pharmacology studies conducted with pazopanib (monohydrochloride salt) and its dihydrochloride salt (GW786034A).

Organ System Evaluated (Study Report No.) GLP-status	Species/ Number	Method of Administration/ Dose/ Compound	Results	NOAEL
CENTRAL NERVOUS SYSTEM				
Neurobehavioral evaluations* (0470087) GLP	SD rats, 6□/group	PO/3, 10, 100, 300 mg/kg/ pazopanib	No treatment-related effects	**300 mg/kg**
CARDIOVASCULAR SYSTEM				
hERG current (FD2008-00125-00) GLP	Stably transfected HEK293 cells/ 5-6 cells/ concentration	*In vitro*/ 1.241 and 4.137 µM/ pazopanib	Non concentration-dependent □ hERG current (~ □19% at both concentrations)	**ND**
Action potential parameters (APD_{60}, APD_{90}, RMP, MRD and UA) (FD2002-00060-00) GLP	Cardiac purkinje fibres isolated from beagle dogs/4 fibres	*In vitro*/ 40 and 80 nM/ pazopanib	No treatment-related effects	**80 nM**
Cardiovascular function, i.e., blood pressure, heart rate (CD2002-00002-00) Non-GLP	Anaesthetised SD rats/3□	IV (1-min infusion)/ 1, 3, 10 mg/kg/ GW786034A	No treatment-related effects	**10 mg/kg IV**
Cardiovascular function, i.e., blood pressure, heart rate, ECG and body temperature (CD2002-0009-00) GLP	Telemetered Cynomolgus monkey/ 4□	PO/ 5, 50, 500 mg/kg/ pazopanib	No treatment-related effects	**500 mg/kg PO**
Cardiovascular function, i.e., blood pressure, heart rate, ECG (CD2006-00750-00) GLP	Telemetered Cynomolgus monkey/ 4□ (main) & 3□ (TK)	IV (1-min infusion)/ 3.75 mg/kg/ pazopanib	Reversible □ heart rate (7-26%) Satellite group: AUC=41 µg·h/mL Cmax = 55 µg/mL	**ND**
RESPIRATORY SYSTEM				

Organ System Evaluated (Study Report No.) GLP-status	Species/ Number	Method of Administration/ Dose/ Compound	Results	NOAEL
Respiratory function (tidal volume, respiratory rate, minute volume) (RD2001-01691-00) GLP	SD rat, 6/group	PO/3, 10, 100, 300 mg/kg/ pazopanib	No treatment-related effects	**300 mg/kg**

** Behaviour, skeletal muscle tone, reflexes, rectal body temperatures, and overt autonomic, gastrointestinal, and neurological effects were monitored pretreatment (approximately 24 hours before dosing), approximately 3 hours after dosing (predicted t_{max}), and approximately 24 hours after dosing*
$APD_{60 \text{ or } 90}$ - Action potential duration at 60% and 90% repolarisation
HEK – human embryonic kidney
MRD - Maximum rate of depolarisation
ND – Not determined
RMP - Resting membrane potential
UA - upstroke amplitude

- Pharmacodynamic drug interactions

The effect of combining PO pazopanib with various antineoplastic agents was evaluated in xenograft models (data not shown).

A study was performed to investigate whether pre-treatment of tumour bearing mice with an anti-angiogenic agent had an effect on the delivery of chemotherapeutic agents to the tumours (data not shown).

Pharmacokinetics

The analytical methods used were appropriately validated. The validation studies were not conducted in compliance with GLP. However, they were performed at facilities used for operating in accordance with the principles of GLP.

- Absorption

The pharmacokinetics of pazopanib and/or its dihydrochloride salt has been studied in several animal species (see Table 6 for results in cynomolgus monkey). The terminal elimination half-life was comparable among the animal species ($t_{½}$=2-6 h) but significantly lower than observed in humans ($t_{½}$=21-51 h). The peak plasma concentration following PO administration was generally observed within 4 hours post-dosing in all species including humans. High inter- and intra-species variability was observed in the oral bioavailability. A high bioavailability (>70%) was observed in a few individual animals. The oral bioavailability of pazopanib is comparable between species (e.g., 21% [range 14-39%] in humans vs. 30% in monkeys).

Table 6. Pharmacokinetic data obtained in cynomolgus monkeys.

N	4♂ (cross-over)			4♂	4♂ (cross-over)		4♂	3/sex
Compound	GW786034A (dihydrochloride salt)			Pazopanib	Pazopanib		Pazopanib	Salt form not specified
Route	PO - fed prior to dosing or 8 h post-dosing	PO - fed 8 h post-dosing	IV - fed 4 or 8 h post-dosing	PO	PO	IV 60-min infusion	PO	PO
Dose (mg/kg)	5	50	5	50	10	2	50	50 mg/kg/day for 7

								days
C_{max} (µg/mL)	5.5 (fed) 8 (fasting)	34	-	30	0.001	0.01	33	16.01 (day 1) 21.19 (day 7)
T_{max} (h)	0.5 (fed) 1.4 (fasting)	2	-	0.9	7.4	1	1.75	-
$AUC_{0-\infty}$ (h·µg/mL)	22.7(fed) 28.4 (fasting)	-	47 (4 h) 59 (8 h)	141	20	29	177	63 (day 1) 95 (day 7)
$T_{½}$ (h)	5.5 (fed) 4.9 (fasting)	6.2	5.5 (4 h) 4.7 (8 h)	6.6	NC	175	-	-
MRT (h)	-	-	-	-	17.4	3.35	-	-
V_{ss} (L/kg)	-	-	0.285 (4 h) 0.283 (8 h)	-	NC	0.268	-	-
Cl (mL/min/kg)	-	-	2 (4 h) 1.6 (8 h)	-	NC	1.35	-	-
F (%)	53 (fed) 49 (fasting)	30	-	30[b]	16.1	-	-	-

[b] Calculated based on the AUC obtained following IV administration of 5 mg/kg to fasting animal (fed 4 hours post-dosing) in study RD2001-01169-00

- Distribution

Following IV administration, pazopanib displayed a volume of distribution which was less than the total body water in all species including humans (rats: 72-88%, dogs: 49%, monkeys: 39-41%, and humans: 22-31% relative to total body water of the respective species).

In dogs, a rapid drop in plasma levels was observed after feeding of the animals regardless of the route of administration (PO or IV). Food intake had no significant effect on pharmacokinetic parameters in monkeys.

Following single PO administration, radioactive pazopanib-related material was widely distributed throughout the body of rats. In rat, tissues exhibited their highest radioactivity concentration at a time point similar to time for peak plasma concentration (T_{max}) suggesting rapid distribution. Radioactivity was not observed in most tissues 3 days post-dosing in agreement with the short half-life in rats. The exception was melanin-containing tissues (i.e., eye, pigmented skin and meninges) which suggest that a selective association of pazopanib-related material with melanin-containing tissues takes place. Moreover, following ocular administration, melanin-containing tissues of the rabbit eye showed relatively high concentrations in both the dosed and, to a smaller extent, in the non-dosed eye, confirming the association of pazopanib-related material to melanin-containing tissues following both local and systemic exposure.

Pazopanib was highly bound (>99.5%) to plasma proteins in all species including humans. Pazopanib was very highly bound to human serum albumin (>99%) and highly bound to human α 1-acid glycoprotein (>95%). Furthermore, *in vitro* data indicated that pazopanib binding to albumin was affected by the presence of fatty acids (e.g., palmitate) and some drugs (e.g., warfarin).

A comparative assessment of steady state systemic exposure (AUC and C_{max}) of circulating metabolites has been performed following PO administration of pazopanib to mice (100 mg/kg/day), rats (3 & 30 mg/kg/day), monkeys (50 mg/kg/day) and humans (800 mg/day). Significant exposure to the main three active circulating metabolites has been obtained in the pivotal repeat-dose toxicity studies in mice, rats and/or monkeys (up to 10-fold) and these active metabolites are considered qualified. Significant exposure to a forth active metabolite (M24) has not been demonstrated.

- Metabolism and elimination

The extent of metabolism of pazopanib was low in human liver microsomal and hepatocyte incubations as well as in most of the preclinical species. Pazopanib was more extensively metabolized by rabbit and dog hepatocytes than by those from the other species studied. Following PO administration, unchanged pazopanib was the predominant component in faeces from all species including humans.

The routes of metabolism observed in human liver microsomes and hepatocytes were mono-oxygenation, di-oxygenation, and possibly oxidation to a carboxylic acid. Glucuronidation of a mono-oxygenated metabolite was also detected in human hepatocytes. There were no unique human phase I metabolites observed in either liver microsomal or hepatocyte incubations. However, a phase II metabolite, i.e., a glucuronide potentially derived from a carboxylic acid metabolite, was observed only in human hepatocytes. Its presumed precursor was identified *in vivo* as a significant component (<19%) in bile from bile duct cannulated monkeys. In conclusion, the combined *in vitro* and *in vivo* metabolic data indicated no major species differences in metabolism

The predominant route of elimination of radioactivity in rat, monkey and human following oral administration was via faeces with a minor contribution eliminated in urine. No significant difference in elimination or mass balance was observed between males and females. The metabolites of pazopanib were also eliminated largely via feces. The fecal metabolites together accounted for 1.45%, 14% and 10% of administered dose in rats, monkeys and humans, respectively; whereas, the urinary metabolites together accounted for less than 1% of the administered doses in all three species

After administration of a single oral dose of ^{14}C-pazopanib, the majority of the dose was excreted via the faeces in rat (52 to 61%) and monkey (85 to 87%), with lesser amounts in the urine (15 to 17% and 2.3%, respectively. Biliary excretion accounted for 8 and 23% of the administered radioactivity in rats and monkeys, respectively. Most of the dose was eliminated within 48 hours post dose with high total recovery. A summary of the results is shown in Table 7.

Table 7. Excretion of radioactivity following oral administration in rat, monkey and human

Species	**Number Gender**	**Dose (mg/kg)**	**Urine (% dose)**	**Feces (% dose)**	**Bile (% dose)**	**Total (% dose)**
Rat	3M	10	15.0	60.6	-	89.8
Rat	3F	10	16.6	51.5	-	93.7
Rat*	3M	10	25.0	43.1	7.5	92.3
Monkey	3M	5	2.1	85.0	-	88.5
Monkey	3F	5	2.8	86.7	-	92.5
Monkey*	3M	5	2.3	60.0	22.9	91.4
Human	3M	433 mg	2.6	82.2	-	84.9

* Bile duct-cannulated

- Pharmacokinetics drug interactions

In human liver microsomes *in vitro*, pazopanib showed moderate to marked inhibition of CYP enzymes [1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 with IC50 values ranging from 7.9 µM (2C9) to 18 µM (2D6)]. There was no evidence for time- or NADPH-dependent inhibition. However, in humans pazopanib was not an inhibitor of 2C9, 2C19 and 1A2, and was a weak inhibitor of CYP3A4 and CYP2D6; repeat doses of pazopanib (800 mg) resulted in a less than 2-fold increase in plasma AUC of the probe substrates. Similarly, coadministration of pazopanib with paclitaxel (metabolized by CYP3A4 and CYP2C8) resulted in less than 2-fold increase in paclitaxel exposure relative to administration of paclitaxel alone. Pazopanib showed moderate interaction with human PXR, suggesting a potential for CYP3A4 induction in humans.

In cultured human hepatocytes, pazopanib also showed some potency to induce CYP3A4 and CYP2B6. However, there was no significant CYP enzyme induction following repeat oral dosing in rats (up to 300 mg/kg/day) or monkeys (up to 500 mg/kg/day) for 4 weeks. In humans, coadministration of pazopanib 800 mg once daily with paclitaxel or midazolam resulted in less than 2-fold increase in exposure of these two CYP3A4 substrates indicating no net induction of CYP3A4 by pazopanib. In vitro, pazopanib is also an inhibitor of human UGT1A1 with an IC50 value of 1.2 µM.

Pazopanib was shown to be a substrate for the transporters P-gp, BCRP and organic anion transporting polypeptide (OATP1B1) *in vitro*. Pazopanib was not an inhibitor of human BCRP-mediated transport *in vitro*.

Toxicology

- Single dose toxicity

Single-dose toxicity studies are summarized in Table 8:

Table 8. Results from the single-dose toxicity studies.

Species/ Sex/Number/ Group	**Dose/Route**	**Approx. lethal dose / observed max non-lethal dose**	**Major findings**
Beagle dogs 2 males/dose	0, 150, 450 mg/kg PO	>450 mg/kg	Not described. Part of an exposure study. Pazopanib was well-tolerated
Rat (SD)/3/sex/dose	0, 1.1, 5.4 mg/kg IV Mean AUC_{0-24} ☐51.8, 226 µg.h/ml ☐68.5, 257 µg.h/ml	>5.4 mg/kg	No findings (clinical observations; body weight, haematology, coagulation, clinical chemistry, macroscopic and microscopic observations)

Seven daily doses up to 1000 mg/kg/day were well tolerated by monkeys (no deaths) by nasogastric intubation. No treatment-related effects were observed (survival, clinical observations, body weight, food consumption, macroscopic and microscopic observations). In the rat micronucleus test, doses of up to 2000 mg/kg were given on two consecutive days without adverse clinical signs.

- Repeat dose toxicity (with toxicokinetics)

The main findings in the repeated dose toxicity studies performed for pazopanib are summarised in Table 9.

Table 9: Overview of repeated dose toxicity studies for pazopanib

Number/Sex /Group	**Dose/Route**	**Duration**	**NOEL/ NOAEL (mg/kg/day)**	**Major findings**
Mouse 24M/dose	751, 1384, 5143 mg/kg/day oral (diet)	7 days	N.D.	(in-life observations) ≥**751**: ↓ BW **=5143**: 14 mortalities; poor health status; ↓ body temp; piloerection; irregular respiration; whole body pallor; hunched posture; dark eyes; closed lids (dose not palatable)
Mouse 24M/dose	207, 448 mg/kg/day oral (diet)	7 days	448	No **in-life** treatment-related findings.

Number/Sex /Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Mouse 6/sex/dose (9 for TK)	200, 1000, 2000 mg/kg/day oral gavage	14 days	N.D.	**=200:** 1 mortality (cause unknown) ≥**200**: ↓ BW; occasional piloerect coat; growth plate hypertrophy in stifle joint ≥**1000**: mineralization in heart due to calcium deposition; nephropathy: tubular dilation, basophilia and degeneration, tubular regeneration; growth plate hypertrophy in sternum/bone marrow **=2000**: 1 mortality (animal was misdosed).
Mouse 12/sex/dose	100, 300, 1000 mg/kg/day oral gavage	13 weeks	N.D.	≥**100**: Broken and overgrown nails; pale incisors; ↑ Hb (M); ↓ erythrocytes (F); ↑ MCH, MCV, basophils (M), monocytes; slight microcytosis; ↑ ALT, AST (M); ↓ cytoplasmic rarefaction of hepatocytes; absence or sparsity of corpora lutea; ↑ ovarian cysts ≥**300**: Broken, thin and overgrown teeth, ↑ RBC distribution width; ↑ lymphocytes, basophils; kidney cortex (F): basophilic tubules, inflammatory cell infiltration, glomerular atrophy, pigment and mineralization; liver: hepatocyte hypertrophy (M), centrilobular aggregates of granular macrophages (M), pigmented macrophages; effects on digits (M) **=1000**: ↓ BW (F); ↑ neutrophils, large unstained cells; moderate microcytosis; ↑ ALT, AST; pale, thickened and distended bowel; liver (F): hepatocyte hypertrophy, eosinophilic foci, adenoma (1); cartilage thickening and partial fusion of femur growth plate, osteoarthrosis (F); cartilage degeneration of sternum growth plate (M); crystalline material accumulation in mesenteric lymph node
Rat 6F/dose (for TK)	30, 100, 300 mg/kg/day oral gavage	4 days	N.D.	≥**30**: ↑ MCHC; ↓ MCV; ↓ reticulocytes; ↑ ALT, AST; ↑ total bile acid; ↓ thymus weight ≥**100**: hypertrophic chondrocyte expansion growth plate of femur/tibia/sternum; ↓ capillaries in growth plate of femur/tibia; necrosis of corpora lutea in ovaries
Rat 15/sex/dose (3 for TK)	3, 10, 30, 100, 300 mg/kg/day oral gavage	4 wks/6 wks recovery	30	≥**100**: Hypertrophy of the epiphyseal growth plate in femur/stifle; Depletion of round spermatids (Stage I - V tubules) **=300**: 1 mortality (M); ↑ ALT, AST (F), ALP (F); ↑ reticulocytes; ↓ testis weight; Hypertrophy of the epiphyseal growth plate in sternebrae; Hypocellularity of metaphyseal bone marrow (M) **Recovery**: excessive growth/brittleness of teeth; broken/missing nails

Number/Sex /Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Rat 20M/dose	10, 30, 300 mg/kg/day oral gavage	4 wks/10 wks recovery	10	≥**30**: Incisors: multifocal dentine and enamel degeneration; dental and enamel thinning; focal amelioblastic and ondotoblastic atrophy; focal ondotoblastic necrosis **=300**: Incisors: periodontal oedema; multifocal dental pulp necrosis **Recovery**: all effects resolved, except minimal dentine degeneration
Rat 12/sex/dose (6 for TK)	3, 30, 300 mg/kg/day oral gavage	13 weeks	3	≥**3**: minimal basophil hypertrophy in pituitary gland ≥**30**: teeth: ↓ dentine thickness, degeneration, atrophy/necrosis ameloblastic and ondoblastic layer, pulp necrosis; overgrown nails; growth plate hypertrophy; kidney: tubular degeneration/regeneration, CPN; cortical hypertrophy of adrenals; minimal lymphangiectasis and sinus histiocytosis **=300**: 1 mortality; ↓ BW; discoloured/enlarged adrenals; dilated duodenum; trabecular atrophy, hypocellular marrow; chondroid change in bone; severe necrosis and moderate angiectasis of adrenals; testes atrophy; effects on duodenum; hypospermia; mammary gland atrophy; ↓ globule leukocytes in trachea and larynx
Rat 18/sex/dose	3, 30, 300 mg/kg/day oral gavage	26 weeks	N.D.	≥**3**: ↑ MCV, MCH (F); ↑ ALT (M); ↓ testis weight; CPN; angiectasis and hemorrhage of adrenal cortex; basophilic hypertrophy in pituitary (M); ≥**30**: 1 mortality; ↓ BW and food consumption; ↓ platelets (M), RBC; ↑ Hb (M), MCV, MCH (M); ↑ lymphocytes (F); ↑ APPT; ↑ serum bile acids, urea nitrogen, globulin, chol, inorganic phosphorus; ↓ albumin ↑ urine protein excretion; trabecular atrophy; hypocellular marrow; basophilic hypertrophy in pituitary; ↓ globule leukocytes in tachea; effects on teeth; testes and ovary atrophy; **=300**: ↑ triglycerides; ↓ TP; ↑ urine volume (F); ↓ urine creatinine excretion (M); ↑ adrenal weight; growth plate hypertrophy femur; periosteal chondroid change; dyskeratosis in digits; bowel effects; crystaline pigment in MLN; acinar atrophy in pancreas; aspermia, hypospermia and cribform change in epididymis;
Dog 1/sex/dose	50, 100, 150 mg/kg/day oral gavage	4 days	N.D.	≥**50**: loose/yellow feces; myeloid hyperplasia bone marrow; cortical tubular-cell vacuolation (F) ≥**100**: emesis (F); hypertrophy zona fasciculate in adrenal gland **=150**: salivation (M)

Number/Sex /Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Monkey 1/sex/dose	100, 300, 1000 mg/kg/day oral (nasogastric)	8 days	1000	No treatment-related effects
Monkey 3/sex/dose	5, 50, 500 mg/kg/day oral gavage	4 weeks	500	No treatment-related effects
Monkey 4/sex/dose	5, 50, 500 mg/kg/dose oral gavage	52 weeks	50	**=500**: 2 mortalities (M); diarrhoea; ↓ BW; crystalloid material (test article) in duodenum, jejunum and MLN; ↓ TP, albumin (F)

N.D.: not determined, BW: body weight, Hb: haemoglobin, MCH: mean cell haemoglobin, MCV: mean cell volume, RBC: red blood cells, ALT: alanine aminotransferase AST: aspartate aminotransferase, ALP: alkaline phosphatase, APPT: activated partial thromboplastin time, TP: total protein, Chol: cholesterol, CPN: chronic progressive nephropathy, MLN: mesenteric lymph node

- Genotoxicity

Pazopanib was tested in a standard battery of genotoxicity studies. Pazopanib was found to be non-mutagenic and non-clastogenic when tested in a bacterial cell (Ames) assay, human peripheral lymphocyte chromosome aberration assay and rat micronucleus assay (at concentrations or doses up to 5000 µg/plate, 200 µg/mL or 2000 mg/kg, respectively) (see Table 10).

Table 10: Overview of genotoxicity studies for pazopanib

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria (miniwell) RD2001/01168/00 Non-GLP	*S. typhimurium*: TA98, TA100, TA1535, TA1537	TA98 and 100: up to 400 µg/plate +/- S9 TA1535 and 1537: up to 800 µg/plate +/- S9	Positive in TA1535 without S9 at 100 and 800 µg/plate
Gene mutations in bacteria RD2002/00279/00 Non-GLP	*S. typhimurium*: TA98, TA100, TA1535, TA1537	Up to 5000 µg/plate +/- S9	Negative
Gene mutations in bacteria RD2002/00280/00 Non-GLP	*S. typhimurium*: TA100, TA1535	Up to 5000 µg/plate +/- S9	Negative
Gene mutations in bacteria RD2002/00887/00 GLP	*S. typhimurium*: TA98, TA100, TA1535, TA1537 *E. coli*: WP2 *uvrA* pKM101	Up to 5000 µg/plate +/- S9	Negative
Chromosome aberrations in mammalian cells RD2002/00238/00 GLP	Human peripheral blood lymphocytes	2.50 to 300 µg/ml +/- S9	Negative
Chromosomal aberrations in vivo RD2002/00227/00 GLP	SD rat, micronuclei in bone marrow	0, 1250, 2000 mg/kg/day 7M/dose	Negative

- Carcinogenicity

No studies were submitted.

- Reproduction Toxicity

Pazopanib's effect on male and female fertility was evaluated in two separate rat studies. Moreover, embryo-foetal development was evaluated in rats and rabbits. The results are given in Table 11.

Table 11. Reproductive studies conducted with pazopanib.

Species; Number Female/ group Dose	**Dosing period**	**Major findings**	**NOAEL (mg/kg &AUC)**
Rat SD 25 females /dose 0, 3, 30, 300 mg/kg bw/day PO	Males: Untreated Females: 2 weeks prior to and during cohabitation. D0-D6 Post coitum (pc). Sacrifice at GD20	**BW:** All: D0-D7 pc: BW gain☐ 300: BW gain D7-D20 pc☐ with food consumption☐ D14-D20. **Fertility:** 300: Fertility index, implantation☐ ≥30: live fetuses☐, resorption, pre-implantation loss☐ **Foetal:** ≥30: BW☐	NOAEL systemic: ND NOAEL fertility, early embryonic dev.: 3 mg/kg/day
Rat SD 25 males /dose 0, 3, 30, 100 mg/kg bw/day PO	Males were terminated following 105-108 days of treatment. After 10 days and 63-65 days of treatment, males were cohabitated with untreated females (sacrificed D20)	≥30 (D0-63): fractured incisors, soft stool, smeared fur, ☐BW, BW gain, food consumption Testis histopathology: ☐testes weight, testicular sperm concentrations, sperm production rate, epididymidis weight 100: sperm motility☐ **Fertility:** No effects	NOAEL for fertility (100mg/kg/day) and for male repro organ (3mg/kg/day) Systemic and fertility 3 mg/kg /day
Rat SD 6/dose 0, 3, 10, 30, 100, 300 mg/kg/day **PO**	GD: 6-17.	**Maternal effects:** 300: BW gain GD 6-9☐ food consumption☐ ≥10 BW gain markedly reduced with BW loss at end of gestation **Foetal:** ≥10: mean litter proportion of early and total resorptions☐ ≥30: All animals completely resorbed litters. Some animals with brown material around vaginal area D15-19 10: gravid uterus weight☐ (not measured at higher doses)	NOAEL Maternal and foetal : 3 mg/kg /day
Rat SD 22/dose 0, 1, 3, 10 mg/kg/day PO	GD: 6-17	**Maternal effects:** 10; BW gain☐ **Foetal:** 10: live foetus/litter☐, resorption/litter☐ BW☐, cardiovascular malformations (retrooesophageal right subclavian arteries (4 foetuses in 4 litters), missing innominate arteries (5 foetuses in 5 litters), common truncus (1 foetus) 3: right-sided aortic arch (1 foetus) ≥3: delayed ossification	NOAEL **maternal:** 3 mg/kg bw/day NOAEL **foetal:** 1 mg/kg bw/day
NZW rabbits (non-pregnant) 4/dose 0, 100, 300, 1000 mg/kg bw/day PO	13 days	1000: BW, food consumption☐ 300: 2 found dead, 1 euthanized. Prior to death BW, food consumption☐ 100: BW, food consumption☐	ND
NZW rabbits 6/dose	GD:7-19	**Maternal effects** 100: All euthanized D18 pc. after BW,	Maternal and foetal NOAEL

Species; Number Female/ group Dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
0, 3, 10, 30, 100 mg/kg bw/day		food consumption☐ 30: One abortion, Food consumption☐ **Foetal effects:** ≥10: early resorptions☐, postimplantation loss☐ (not significant at 10, but above historical controls) All doses: BW☐	3 mg/kg bw/day

BW-Body weight

- Local tolerance

The dermal toxicity and dermal irritation of pazopanib have been investigated in rabbits from acute exposure up to 28 days and in minipigs for 7 days. The dermal toxicity/irritation was not more pronounced than the vehicle. Systemic exposure was below the level of detection of the analytical methods used.

Eye toxicity/irritation was investigated in rabbits (acute to 28 days exposure) and in dogs (acute exposure to 26 weeks). In the rabbit, pazopanib powder was a slight irritant, whereas no ocular or other findings were observed in the rabbit or dog with solution formulations.

- Other toxicity studies

Antigenicity
The potential of pazopanib to induce hypersensitivity was investigated in the local lymph node assay with a maximal concentration of 25% w/w. Pazopanib was not sensitizing in the local lymph node assay test

Metabolites
The metabolites are deemed qualified based on the exposure in the toxicity studies. The circulating metabolites of pazopanib inhibited VEGF-induced endothelial cell proliferation with similar or 10- to 20-fold lower potency to that of pazopanib. However, in bFGF-stimulated endothelial cells, all the metabolites except one were more potent (IC_{50}=0.79 to 5.5 μM) than pazopanib (IC_{50}>10 μM)

Studies on impurities
Several genotoxic impurities have been identified by the applicant. The level of all these impurities is below the TTC level (below 1.7 ppm corresponding to 1.36 μg/day at the maximum recommended dose of 800 mg pazopanib) except for one. Following treatment with the maximum recommended clinical dose of pazopanib, the daily intake of this impurity is 0.1 mg/day (corresponding to 115 ppm), i.e., around 67-fold higher than the TTC level. The impurity tested negative in the Ames test, however, it tested positive in the mouse lymphoma mutation assay, mouse lymphoma cell cycle test, *in vitro* mouse micronucleus test and in the *in vivo* mouse micronucleus test. The *in vitro* mouse micronucleus test indicated an aneugenic mechanism rather than a clastogenic mechanism (showed by an increase in cells with kinetochore) and a dose of 0.2 μg/ml was negative, indicating a threshold dose

Other studies
-In vitro haemolysis testing in rat and monkey blood
Pazopanib formulated for IV administration (containing Captisol, sodium chloride and phosphate buffer) at concentrations of 1, 3, and 5 mg/mL was tested in EDTA anti-coagulated rat or monkey blood. Following incubation and centrifugation, the haemoglobin concentration of each supernatant was determined. No haemolysis with the vehicle or with pazopanib was observed.

-In vitro haemolysis and plasma protein flocculation testing in human blood
Pazopanib formulated for IV administration (containing Captisol, sodium chloride and phosphate buffer) at concentrations of 1, 3, and 5 mg/mL was tested in EDTA anti-coagulated human blood. Following incubation and centrifugation the haemoglobin concentration of each supernatant was determined. The simulated dosages tested in the flocculation assay were 0, 0.5, 5 and 25 mg/kg of body weight. After mixing with plasma nephelometric turbidity was determined. No haemolysis or plasma protein flocculation with the vehicle or with pazopanib was observed.

- In vitro phototoxicity on Balb/c 3T3 fibroblasts using the neutral red uptake assay

The phototoxic potential of pazopanib was evaluated in Balb/c mouse 3T3 fibroblast cells in the presence of ultraviolet A (UV-A) light. Fibroblast cells were incubated with pazopanib (0.00948 to 30 μg/mL; the highest concentration was limited by precipitation) or chlorpromazine (positive control; 1 to 1000 μg/mL) prior to irradiation (exposure to 4 J/cm^2 UV-A). A second set of plates were kept in the dark to evaluate effects in the absence of UV-A. After irradiation, the plates were incubated for ~20 hours at 37°C in a humidified atmosphere of 5% CO_2 in air. At the end of the incubation period, cytotoxicity was assessed by neutral red uptake.
A concentration-related increase in cytotoxicity was observed following treatment of cells with pazopanib in the absence and presence of UV-A light. The cytotoxicity profiles in the absence and presence of UV-A light were similar and not significantly different from each other. Therefore, pazopanib was not phototoxic in this *in vitro* test system.

Ecotoxicity/environmental risk assessment

- Phase I

$PEC_{surfacewater}$
Based on the maximum daily dose of 800 mg/day, the applicant has calculated $PEC_{surfacewater}$ values using both the default Fpen of 0.01 and a refined Fpen. Using the default Fpen of 0.01, the $PEC_{surfacewater}$ becomes 0.4 μg/L, which is well above the action limit of 0.01 μg/L. When an Fpen based on the prevalence of RCC (3.12×10^{-4}) is used, the $PEC_{surfacewater}$ becomes 0.12 μg/L. Assuming all patients are treated with the prescribed dose for 365 days/year, results in a $PEC_{surfacewater}$ with the same value. When an Fpen based on the estimated yearly consumption (4.46×10^{10} mg/year) and the defined daily dose (DDD, 1250 mg) is used, the $PEC_{surfacewater}$ becomes 0.08 μg/L.

PBT assessment
The applicant has performed an OECD 302C test and OECD 107 test in order to determine the inherent biodegradability and the log Kow for pazopanib, respectively. Pazopanib was determined to be not inherently biodegradable and is thus considered a potential persistent substance. A water sediment study (OECD 308) to determine the effects on sediment organisms should be investigated. Using the currently reported log Kow values the ion-corrected low Dow of pazopanib was determined to be 2.26, 3.33 and 3.92 at pH 5, 7 and 9, respectively, therefore a bioconcentration study (OECD 305) is also warranted.

- Phase II

Based on the $PEC_{surfacewater}$ in the phase I assessment, a phase II assessment is required. The results for the phase II-Tier A assessment for pazopanib are summarized in Table 12:

Table 12: Phase II assessment for pazopanib

Test	Result	PNEC
Activated Sludge Respiration Inhibition Test	EC_{50} = 1,000 mg/L NOEC = 1,000 mg/L	PNECmicro-organisms = 100,000 μg/L
Inhibition of Growth to the Alga *Desmodesmus subspicatus*, OECD 201	EC50 >0.42 mg/L[a] NOEC = 0.42 mg/L[a]	
Acute Toxicity to *Daphnia magna*, OECD 202	EC_{50} (48 hours) > 2.50 mg/L[a] NOEC (48 hours) = 2.50 mg/L[a]	
Reproduction study with *Daphnia magna*, OECD 211	EC_{50} (immobilisation) > 0.50 mg/ L[a] EC_{50} (reproduction) = 0.28 mg/ L[a] LOEC(reproduction) = 0.50 mg/ L[a] NOEC(reproduction) = 0.15 mg/ L[a]	PNECwater = 15 μg/L PNECgroundwater = 15 μg/L
Fish ELS Toxicity Test, *Pimephales promelas*, OECD 210	LOEC > 0.30 mg/L NOEC = 0.30 mg/L	

[a] Based on geometric mean measured concentrations

The $PEC_{groundwater}$ is based on the $PEC_{surfacewater}$. Using the $PEC_{surfacewater}$ of 0.08 μg/L, the $PEC_{groundwater}$ becomes 0.02 μg/L.

$PEC_{surfacewater}/PNEC_{micro\text{-}ogranisms}$ = 0.08 μg/L / 100,000 μg/L = 8.0×10^{-7}. This ratio is lower than the trigger ratio of 0.1.

$PEC_{surfacewater}/PNEC_{water}$ = 0.08 µg/L / 15 µg/L = 5.3 x 10^{-3}. This ratio is lower than the trigger ratio of 1.

$PEC_{groundwater}/PNEC_{groundwater}$ = 0.02 µg/L / 15 µg/L = 1.3 x 10^{-3}. This ratio is lower than the trigger ratio of 1.

In addition, based on the reported Koc value of 2.35, studies for the terrestrial environment are not necessary.

Discussion on the non-clinical aspects

No studies on carcinogenicity were submitted. Carcinogenicity studies were not considered necessary for the current indication, advanced renal cell carcinoma.

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures more than 300-fold lower than the human exposure (based on AUC). Effects included reduced female fertility, increased pre- and post-implantation loss, early resorptions, embryo lethality, decreased foetal body weight and cardiovascular malformation. Decreased corpora lutea, increased cysts and ovarian atrophy were also noted in rodents. In a rat male fertility study, there was no effect on mating or fertility, but decreased testicular and epididymal weights were noted with reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at exposures 0.3 times human exposure based on AUC. This information has been included for information in section 5.3 of the SPC.

Studies with pazopanib in juvenile animals were not conducted. This is accepted since the current application targets an adult population.

A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance in low amounts, was not mutagenic in the Ames assay but genotoxic in the mouse lymphoma assay and in vivo mouse micronucleus assay. Considering the poor life-expectancy for patients with advanced renal cell carcinoma, the presence of a genotoxic impurity is acceptable. The presence of this genotoxic impurity in the drug product has been stated appropriately in section 5.3 of the SPC.

Because $PEC_{surfacewater}$ exceeds the action limit, an aerobic/anaerobic transformation test in aquatic sediment systems (OECD 308) with pazopanib is warranted. The Applicant has committed to provide this information as a follow-up measure.

In addition, as the calculated log Dow is 3.3 a bioconcentration study in fish (OECD 305) determining BCF and also assessing secondary poisoning is necessary. The Applicant will provide this information as a follow-up measure.

2.4 Clinical aspects

Introduction

The anti-tumor activity of pazopanib in RCC was first demonstrated in a first-time in human study VEG10003 that was used as dose finding study. This study led to a phase II study VEG102616 and in a phase III, randomized, double-blind, placebo-controlled study VEG105192.

The clinical pharmacology programme consisted of twenty Phase I studies that have either been conducted or are ongoing to characterize the clinical pharmacology of pazopanib in subjects with cancer including:
- dose ranging pharmacokinetics and pharmacodynamics (VEG10003)
- characterization of absorption, distribution, metabolism and elimination of pazopanib (VEG10004)
- characterization of food effect on pazopanib absorption (VEG10005 Food Effect)
- evaluation of drug-drug interactions (VEG10006, VEG10007, VEG102857 Phase I, VEG105427 Part 1, VEG105424, VEG108925, VEG109599, VEG109607, VEG110190, and VEG109693)
- pharmacokinetics (VEG107200), and the rollover protocol (VEG105430).

In addition, 3 studies in healthy volunteers (MD1103367, MD7110861, and MD7108238) were also completed. Study MD7108240 was conducted in subjects with age-related macular degeneration (AMD) and is still ongoing. Study RES104031 was conducted in subjects with psoriasis using a topical formulation. Of these 20 Phase I studies, several are currently ongoing (VEG105424, VEG108925,

VEG105430, VEG10005 Crushed Tablet, VEG105427 Part 2, VEG105427 Part 3, VEG102857 Phase II, VEG109599, VEG109607, VEG110190, VEG109693 and VEG107200).

The claimed therapeutic indication is:

'Votrient is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC)'

The approved indication is:

'Votrient is indicated for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.'

The recommended dose of pazopnib is 800 mg once daily. Dose modifications should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of pazopanib should not exceed 800 mg.

Between December 2006 and October 2007 the applicant received protocol assistance by the CHMP at three occasions. Major aspects that were addressed regarded the design of the trials.

Protocol assistance December 2006.
In response to the applicant's question whether the control arm of study VEG105192, applying best standard of care and placebo, would be an adequate reference comparator for pazopanib, the CHMP did not recommend initiating a placebo controlled trial. It was envisaged that ethical considerations (availability of other TKi and, eventually, VEGF inhibitor bevacizumab) could make benefit risk assessment problematic.

Since there were at the time of protocol assistance data available supporting the use of sunitinib first- and second line and sorafenib second-line, the CHMP did not support the applicant's proposal for a placebo controlled study, albeit that it was acknowledged that a head to head study with a VEGF TKi was not feasible at the time VEG105192 was performed. In response to the applicant's question whether CHMP could agree with the registration package consisting of VEG105192, the phase II trial VEG102616 and extension trial VEG107769 to be supportive of the indication advanced RCC in the first-line and the second-line population (after failure to cytokines) the CHMP considered this packaged not supportive and an active comparator trial was advised.

Protocol assistance (clarification) February 2007.
The advice regarded the ongoing pivotal study VEG105192.. The study was started prior to European approval of sunitinib and sorafenib, and therefore a placebo controlled trial was pursued by the applicant. In the advice it was stated that CHMP considered VEG105192 not a strong basis for acceptance. It was emphasized that OS data (as secondary endpoint) should be mature and supportive to the PFS data (as proposed primary endpoint), and not detrimental to results from the placebo arm. At that time it was emphasized by CHMP that it was unlikely that the evidence for a positive benefit-risk ratio to support an indication for the treatment of advanced RCC in the first-line and second-line population who have failed cytokines, was obtained from the proposed registration package (pivotal study VEG105192 in combination with the phase II trial VEG102616 and extension trial VEG107769) without the results from comparative trials. The question was however a matter of assessment and outside the remit of protocol assistance.

Protocol assistance October 2007.
Further scientific advice was sought on studies that could fulfil the need for controlled studies on pazopanib with active comparator, as this was advised earlier.

VEG108844 was designed as a phase III open label controlled study of pazopanib vs sunitinib in patients with locally advanced or metastatic RCC. CHMP recommended double blinding. Issues on endpoints, statistical analysis and QoL assessment were also discussed.

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.

Pharmacokinetics

Pazopanib pharmacokinetics has been investigated in 18 clinical pharmacology studies, in either healthy volunteers or patients. In addition, a population pharmacokinetic study report and an interim study report on the ongoing hepatic impairment were submitted.

Pazopanib concentrations were obtained using 3 different HPLC-MS/MS based methods. The first method measured pazopanib in plasma over a standard range of 10 – 2500 ng/mL, and was used for the first 3 studies. The second method used plasma and increased the standard range to 100 – 50000 ng/mL in order to analyze samples from 9 studies which were anticipated to produce higher concentrations. The third method used plasma and increased the sensitivity of the assay giving a standard range of 1 – 500 ng/mL in order to analyze samples from 2 studies which were anticipated to produce lower concentrations. Metabolites of pazopanib were also measured by HPLC-MS/MS.

Pharmacokinetic parameters from plasma concentrations of pazopanib were routinely calculated using non-compartmental techniques. To evaluate the effect of a high- and low-fat meal on the PK of pazopanib, a 90% confidence intervals for the ratio of geometric means for AUC and C_{max} were calculated in drug-drug interaction studies and the food-interaction study.

- Absorption

Healthy volunteers
Limited data were obtained in healthy volunteers. In Study MD1103367, 6 subjects received 100 mg pazopanib once daily for maximally 14 days. The study was ended prematurely due to observed increases in alanine aminotransferase (ALT) of >3 times the upper limit of normal in three subjects who received 100 mg pazopanib once daily. Two additional subjects were withdrawn from the study due to sinus arrest and blood pressure increase. There was no consistent correlation (positive or negative) between high or low systemic exposures and the elevated liver function values: AUC_{0-24h} values in the 3 subjects that experienced ALT elevation ≥3 times the upper limit of normal ranged from 11,0 ng.hr/ml to 112 ng.hr/ml, and C_{max} values ranged from 867 ng/ml to 6.2 µg/ml. The range of AUC_{0-24} values observed on Day 1 in subjects who did not experience ALT elevation ≥3 times the upper limit of normal was 17,2 ng.hr/ml to 138 ng.hr/ml, and C_{max} values on Day 1 ranged from 972 ng/ml to 9.0 µg/ml.

Patients
Single dose absorption data at 800 mg were available from Studies VEG10003 and 10004. In Study VEG10003, single dose plasma samples were collected up to 96 hours post-dose. In this multiple dose, dose escalation study, adult patients with solid tumours received a single oral dose of pazopanib, followed by repeated oral administration for 22 days. Oral doses of 50 mg and 100 mg three times weekly, 50 mg to 2000 mg once daily, and 300 mg and 400 mg twice daily were investigated. Following administration of a single oral dose of 800 mg pazopanib, maximum plasma levels of 19.4 ± 13.4 µg/ml were obtained after median 3.5 (range 1.0 -11.9) hours, and an AUC_{inf} of 653 ± 489 µg.h/ml was obtained. Increases in pazopanib C_{max} and AUC were less than dose proportional. Additional data are available from Study VEG20006 in patients with relapsed or refractory multiple myeloma. These patients received 800 mg pazopanib once daily, and AUC and C_{max} values are comparable with those observed in Study VEG10003.

Bioavailability
Absolute bioavailability of pazopanib was investigated in Study VEG10004. Seven subjects with solid tumour malignancies received a single 5 mg IV pazopanib dose administered over 5 minutes followed by blood sample collection for up to 96 h for the determination of plasma pazopanib concentrations. Subjects then received pazopanib 800 mg orally once daily for the duration of the study starting after collection of the last pharmacokinetic blood sample after IV administration. Blood samples for determination of plasma pazopanib were collected over 8 hours on Day 10 of once daily oral administration (study Day 15). AUC_{0-24h} after day 15 was determined by setting the plasma pazopanib concentration 24 hours after administration equal to the pre-dose value. Pazopanib CL, volume of distribution at steady state (Vss), and the absolute bioavailability (F) were reported only for subjects in whom less than 30% of AUC_{inf} of the 5 mg IV administration was calculated by extrapolation (n=3).

In the three subjects from whom IV AUC_{inf} data were available, absolute bioavailability was 13.5%, 21.4%, and 38.9%, with corresponding clearances (CL) of 0.206, 0.246, and 0.347 l/h (< 5% of glomerular filtration rate and <0.5% of liver blood flow), and steady-state volumes of distribution of 11.1, 9.15, and 13.1 l (<40% of total body water).

A mean of 67% of the administered dose recovered in the faeces as unchanged pazopanib suggests that maximally, approximately 33% of the oral dose was absorbed. This estimate of the percent of an oral pazopanib dose absorbed is consistent with the range of observed absolute bioavailability (13.5% to 38.9%). Given the median absolute bioavailability of 20%, the fraction of the orally bioavailable dose of pazopanib excreted in the urine as pazopanib and metabolites is ~20%.

Influence of food
The effect of food on pazopanib pharmacokinetics was investigated in study VEG10005 in cancer patients. Subjects in the randomized food-effect portion of the study received 2 single 800 mg pazopanib doses in the fasted state and with either a high-fat or low-fat meal. Blood samples for the determination of plasma pazopanib and metabolites were collected over 72 hours after administration of pazopanib.

Administration of pazopanib with food resulted in an approximately 2-fold increase in mean pazopanib C_{max} and AUC values compared to administration under fasted conditions. Median t_{max} for pazopanib was greater after administration with food (6 h) compared to administration in the fasted state (4 h) in both the high-fat and low-fat treatment sequences. The CV% values for mean pazopanib AUC_{0-72h} and C_{max} were similar for the fed and fasted states within the high-fat and low-fat meal groups. Mean AUC_{0-t} and C_{max} of several pazopanib metabolites also increased by approximately 2-fold when pazopanib was administered with a low-fat meal or a high-fat meal compared with administration in the fasted state. Median t_{max} values for all pazopanib metabolites, with the exception of one after administration with a low-fat meal, were greater after administration of pazopanib with a low-fat or high-fat meal compared with administration in the fasted state.

- Distribution

Binding of pazopanib to human plasma protein *in vivo* was greater than 99 % with no concentration dependence over the range of 10-100 μg/ml and to human α1-acid glycoprotein (AAG, >96%). After 5 mg IV administration, pazopanib displayed a volume of distribution of 9.2-13.1 l (<40% of total body water) (VEG10004). *In vitro* studies suggest that pazopanib is a substrate for P-gp and BCRP.

- Elimination

Elimination of pazopanib was investigated in Study VEG10004. Three subjects received a single 400 mg oral radiolabelled pazopanib dose containing approximately 70 μCi of radioactivity on Day 1 followed by blood sample collection over 168 h for the determination of plasma pazopanib and metabolites concentrations, and blood and plasma radioactivity. Urine and faeces were collected over 168 h and total radioactivity, pazopanib, and pazopanib metabolites were measured. Subjects then received pazopanib 800 mg once daily starting on Day 8 for the duration of the study. In the three subjects from whom data were available, recovery of the administered radiolabelled dose was 85 ± 19% through 168 hours post-dose.

Pazopanib was mainly excreted in the faeces, with a faecal recovery of the radiolabelled fraction of 96-98% of the recovered dose (82% of total dose) and a urinary recovery of < 4 % of the administered dose. The major component in faeces was unchanged pazopanib, accounting for a mean of approximately 67% of the administered dose. The mean half-life after a single dose of 800 mg was 30.9 ± 4 hours (VEG10003). Following IV administration of 5 mg pazopanib, pazopanib CL in three patients ranged from 0.21 to 0.35 l/h.

Unchanged pazopanib was the predominant component in plasma, accounting for 85% to 95% of the total radioactivity. The four principle pazopanib metabolites account for 6 % of the exposure in plasma. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a similar potency to that of pazopanib, the others are 10- to 20-fold less active. Therefore, activity of pazopanib is mainly dependent on parent pazopanib exposure.

- Dose proportionality and time dependencies

Pazopanib displays non-linear pharmacokinetics. In the multiple dose, fasted, dose escalation Study VEG10003, adult patients with solid tumours received a single oral dose of pazopanib, followed by repeated oral administration for 22 days. Oral doses of 50 mg to 2000 mg once daily were investigated. After single and repeated dose once daily administration, increases in pazopanib C_{max} and AUC were less than dose proportional. Slope estimates for AUC_{0-24h} and C_{max} on Day 22 were less than 1 and the 90% CIs of the slopes did not contain 1. Systemic exposure to pazopanib appeared to

plateau at doses of 800 mg once daily and higher. Therefore, no further increase in systemic exposure to pazopanib is expected at doses greater than 800 mg once daily.

In the same study, the ratio of means for AUC_{0-24h} on Day 22 (steady-state) and AUC_{inf} after a single dose was calculated for the once daily administration cohorts to determine the time dependence of pazopanib pharmacokinetics upon multiple dose administration. Mean plasma AUC_T values on Day 22 of daily 800 mg pazopanib administration were 743 ± 294 µ.h/ml, which was 1.45 (90% CI 0.75-2.79) greater than mean AUC_{0-24h} values observed after single doses (accumulation ratios). There was no apparent time dependence over the 22-day dosing period within the 50 mg to 2000 mg once daily dose range. The mean accumulation ratios for pazopanib AUC_{0-24h} values over the dose range of 50 mg once daily to 800 mg once daily on Day 22 are consistent with the extent of accumulation expected with once-daily administration of a compound with a $t_{1/2}$ of approximately 30 to 35 hours.

The interindividual pharmacokinetic variability is relatively large, i.e., approximately 40% for AUC and C_{max}.

- Special populations

Renal impairment
Results from population pharmacokinetic modelling (data from subjects with baseline CLCR values ranging from 30.8 ml/min to 150 ml/min) indicated that renal impairment is unlikely to have clinically relevant effect on pazopanib pharmacokinetics. No dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised however in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population.

Hepatic impairment
In subjects with moderate hepatic impairment the median pazopanib C_{max} and AUC(0-6 hr) normalized to a dose of 800 mg once daily were both increased 2-fold compared to those in subjects with normal hepatic function. Safety, tolerability and pharmacokinetic data indicated that the dosage of pazopanib should be reduced to 200 mg once daily in subjects with moderate hepatic impairment. In addition pazopanib is contraindicated in patients with severe hepatic impairment.Data are not available in subjects with mild hepatic impairment.

- Pharmacokinetic interaction studies

Inhibition CYP3A4
Results from Study MD7110861 indicated that co-administration of ocular pazopanib (400 µg) with ketoconazole, a potent inhibitor of CYP3A4 and P-gp, resulted in a 120% increase in AUC_{0-t} (from 501 to 1111 ng/ml) and 50% increase in C_{max}. (from 13.2 to 19.6 ng/ml). The $t_{1/2}$ was increased by 180% in case of ketoconazole co-administration.
Oral absorption contributed to the systemic exposure to pazopanib after ocular administration (based on the similar t_{max} obtained upon ocular and oral administration of approximately 3-4 hours), and according to the applicant pazopanib oral absorption was not dose-dependent at doses of 800 mg and less. Therefore, a similar increase in systemic exposure to pazopanib was expected after oral administration of 800 mg with strong CYP3A4 inhibitors.

In Study VEG10006, pazopanib 800 mg was combined with the moderate, competitive CYP3A4, P-gp and BCRP inhibitor lapatinib 1500 mg. Pazopanib AUC_{0-24h} and C_{max} were increased by 59% (90% CI 1.08-2.34) and C_{max} with 51% (90% CI 1.06-2.16). At a lower 400 mg pazopanib dose mg and 1000 mg lapatinib, no statistical significant effect was present anymore (point estimate (90% CI) for AUC 1.17 (0.96-1.42) and for C_{max} 1.08 (0.84-1.39). This effect may be caused by the moderate inhibition of CYP3A4, P-gp and BCRP by lapatinib

Induction CYP3A4
The effect of CYP3A4 induction on the systemic exposure to pazopanib was investigated in Study VG102857 in patients that received 800 pazopanib once daily, with CYP3A4 inducing anticonvulsants as co-medication. Mean pazopanib AUC_{0-24h} and C_{24} values were reduced by approximately 30% and 50%, respectively, after co-administration of either phenytoin or carbamazepin, as compared to data obtained in Study VEG10003.

Currently a number of drug-drug interaction studies are ongoing.

Effect of pazopanib on other drugs

The possible clinically relevant interaction between pazopanib and various CYP probe drugs was investigated in Study VEG10007. In this study, patients with solid tumours received pazopanib 800 mg once daily for 16 days. After 16 days, a cocktail containing specific probe drugs for CYP1A2 (caffeine 200 mg), 2C9 (warfarin 10 mg), 2C19 (omeprazole 40 mg), 2D6 (dextromethorphan 30 mg) and 3A4 (midazolam 3 mg) were co-administered. Pazopanib pharmacokinetics was mildly affected by co-administration of the cocktail: AUC_{0-24h} and C_{max} were increased approximately by 20% with the cocktail co-administered.

Results from this study indicate that pazopanib 800 mg once daily was a weak inhibitor of CYP3A4 (midazolam, 30-35% increased AUC and C_{max}) and CYP2D6 (dextromethorphan, 33-64% decreased metabolism) and had no clinically relevant effect on the probes for CYP1A2 (caffeine), CYP2C9 (warfarin), or CYP2C19 (omeprazole).

In Study VEG105427, pazopanib 800 mg once daily increased paclitaxel (80 mg/m2, a substrate for CYP2C8, CYP3A4, and P-gp) mean AUC_{inf} by 26% and C_{max} by 31% relative to administration of paclitaxel alone.

- Pharmacokinetics using human biomaterials

No studies have been submitted.

Pharmacodynamics

The pharmacodynamic effect of pazopanib was evaluated by measurements of relationships of sVEGFR2 and pazopanib concentration and by determination of the relationship of pazopanib concentration and blood pressure.

- Mechanism of action

No studies have been submitted.

- Primary and Secondary pharmacology

In study VEG10003 (Phase I in adult cancer patients) pharmacodynamic endpoints measured prior to and during pazopanib administration included circulating biomarkers of angiogenesis (plasma VEGF, d-dimer, vascular cell adhesion molecule 1 [VCAM-1], E-selectin, thrombin, and Factor VIII von Willebrand factor [VWF]), dynamic contrast magnetic resonance imaging (DC-MRI), wound healing, and monitoring blood pressure for a study-specific definition of hypertension. Clinical activity and biological effects associated with VEGF inhibition were observed more frequently in association with a steady-state trough concentration of ≥15 µg/mL which was achieved in 93% of subjects receiving doses of at least 800 mg once daily.

Twenty-one of 63 subjects (33%) in Study VEG10003 experienced at least one drug related hypertension event and 18 events occurred in subjects who received 400 mg to 2000 mg once daily or 400 mg BID pazopanib. A relationship between steady-state trough plasma pazopanib concentrations and the probability of the occurrence of a study-specific definition of hypertension (a greater than or equal to 15 mmHg rise from baseline in mean arterial blood pressure on at least three separate occasions, institution or escalation of anti-hypertensive medications, or both) was described by a logistic regression model. The trough plasma pazopanib concentration at which there was a 50% probability of observing hypertension was 15.3 µg/mL (CV% 25.9).

Study VEG102616 (Phase II in subjects with advanced clear-cell RCC) studied the relationship between the pre-dose plasma pazopanib concentration measured at the week 4 clinic visit and the percent change from baseline in the sVEGFR2 nadir in adult subjects received pazopanib 800 mg administered once daily (see Figure 2). Mean plasma pazopanib trough concentration was greater than the target of 15 µg/mL, suggesting that plasma pazopanib concentrations associated with clinical and biologic activity were achieved in the majority of subjects. Pazopanib decreases sVEGFR2, a marker for VEGF receptor inhibition, in a concentration-dependent fashion.

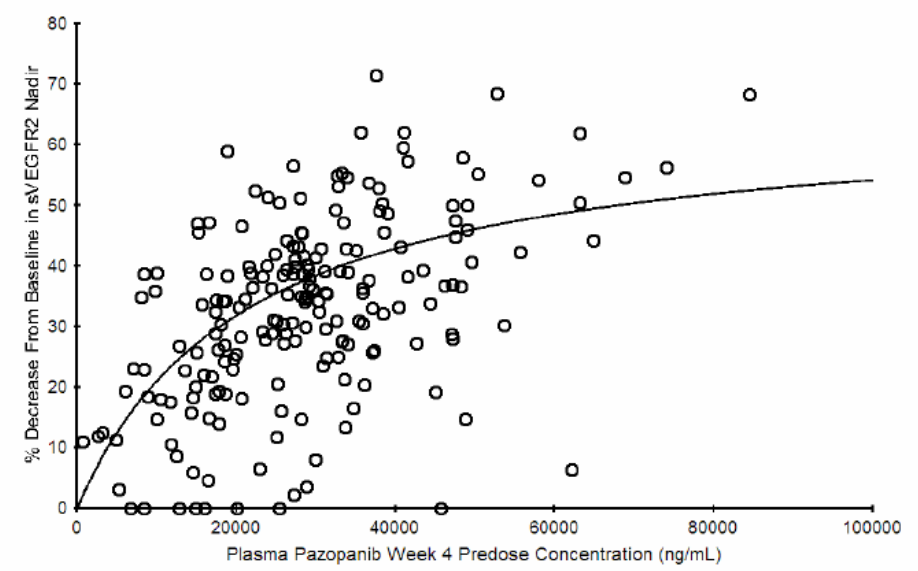


Figure 2. Fit of the Emax Model to the Plasma Pazopanib week 4 pre-dose concentration versus percent of change from baseline in sVEGR2 Nadir (open circles are the observed data and the line is the predicted with the Emax model).

In study VEG104450 (ongoing Phase II in adult female subjects with ovarian epithelial, fallopian tube or primary peritoneal cancer) subjects were treated with pazopanib 800 mg once daily. The primary endpoint was the biochemical response defined as a decrease in cancer antigen-125 (CA-125) of at least 50% from baseline confirmed. Plasma pazopanib concentrations were associated with clinical activity and biologic activity in 86% of subjects from whom data are available. However, a total of 31% of subjects experienced a CA-125 response to pazopanib. These results suggest that factors other than plasma pazopanib concentration likely influence the CA-125 response.

A pharmacokinetic/pharmacodynamic model was developed to describe the relationship between pazopanib plasma concentrations and the QT interval using data from 2 studies. In Study VEG10003, three ECGs (12-lead) were performed at the screening visit, at least 5 minutes apart and after at least a 10 minutes rest. ECGs and blood samples for determination of plasma pazopanib concentrations were obtained pre-dose, and at 1, 2, 4, 8, and 24 hours after pazopanib administration on Day 1 and prior to pazopanib administration on Day 8, 15, and 22. In Study VEG10005, one 12-lead ECG was obtained at the screening visit after at least a ten minute rest. A 12-lead ECG and a blood sample for determination of the plasma pazopanib concentration were obtained at approximately 4 hours after pazopanib administration on the day the subject received pazopanib with food, prior to the second meal that was served 4 hours after pazopanib administration.

Subjects in VEG10003 received single and multiple daily doses of 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg, 1000 mg, 1400 mg, and 2000 mg pazopanib.
Pazopanib dose levels in VEG10003 also included multiple doses of 50 mg three times weekly, 100 mg three times weekly, 300 mg twice daily, and 400 mg twice daily.
Subjects in VEG10005 received a single dose of either 400 mg or 800 mg pazopanib.
A mixed-effects model was used to determine the relationship between plasma pazopanib concentrations and the QT interval.

A plot of the QTcF values versus plasma pazopanib concentrations is displayed in Figure 3. There was no apparent relationship between plasma pazopanib concentrations and the mean QTcF interval within each plasma pazopanib quantile. Furthermore, results of the mixed-effects modeling suggest that there was no relationship between plasma pazopanib concentrations and the QT interval.

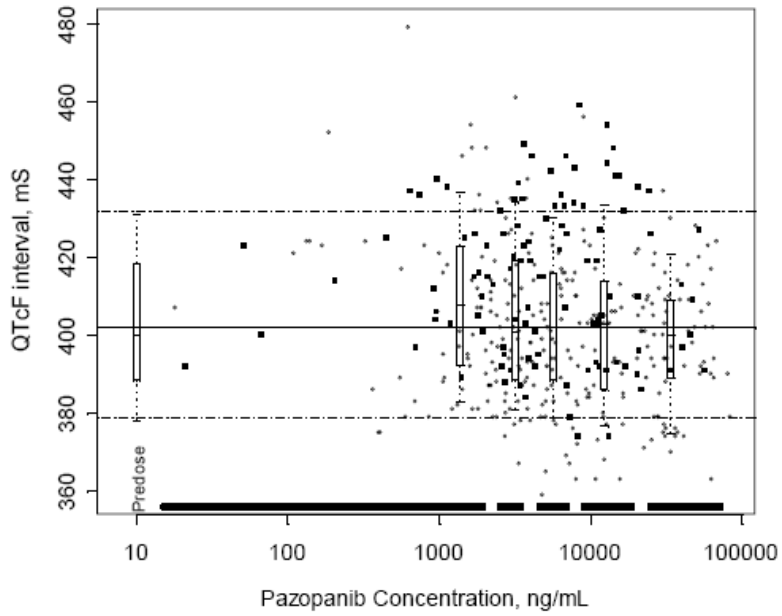


Figure 3. Relationship between plasma pazopanib concentrations and QTcF intervals.

Discussion on clinical pharmacokinetics and pharmacodynamics

The key characteristics of pazopanib pharmacokinetics are summarised below:

• Plasma concentrations of pazopanib peak from 2 to 4 hours following single dose administration.
• Pazopanib is absorbed orally with an estimated absolute oral bioavailability of approximately 20% (range13.5- 38.9%). The relatively low absolute bioavailability is caused by low solubility of the drug.
• Upon oral administration of a single pazopanib 800 mg dose to patients with solid tumours, maximum plasma concentration (C_{max}) of approximately 19 ± 13 µg/ml were obtained after median 3.5 hours (range 1.0-11.9 hours) and an AUC_{∞} of approximately 650 ± 500 µg.h/ml was obtained. Daily dosing results in 1.23- to 4-fold increase in AUC_T. There is no consistent increase in systemic exposure to pazopanib at steady-state when the dose is increased to above 800 mg once daily. These data suggest that absorption is limited by solubility above this dose.
• Exposure to pazopanib is increased approximately 2-fold by administration with a low-fat meal or a high-fat meal. Pazopanib should be administered at least two hours after food or at least one hour before food.
● Pazopanib is a substrate of P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2), which are present in the gut and liver, and may therefore modulate pazopanib bioavailability.
● Administration of a pazopanib 400 mg crushed tablet increased $AUC_{(0-72)}$ by 46 % and C_{max} by approximately 2 fold and decreased t_{max} by approximately 2 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet.

The effect of other medicinal products on pazopanib has been adequately addressed in section 4.5 of the SPC:

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

Pazopanib is a substrate for CYP3A4, P-gp and BCRP. Co-administration of pazopanib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice contains an inhibitor of CYP3A4 and may also increase plasma concentrations of pazopanib.
Administration of 1,500 mg lapatinib (a substrate for and weak inhibitor of CYP3A4 and P-gp and a potent inhibitor of BCRP) with 800 mg pazopanib resulted in an approximately 50 % to 60 % increase

in mean pazopanib $AUC_{(0-24)}$ and C_{max} compared to administration of 800 mg pazopanib alone. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increased exposure to pazopanib.

Concurrent administration of a single dose of pazopanib eye drops (at a low dose of 400 µg (80 µl of 5 mg/ml)) with the strong CYP3A4 inhibitor and P-gp inhibitor, ketoconazole, in healthy volunteers resulted in a 2.2- and 1.5-fold increase in mean $AUC_{(0-t)}$ and C_{max} values, respectively. Inhibition of P-gp and/or BCRP by ketoconazole likely contributed to the increased exposure to pazopanib. At present no dosing recommendations can be made for either potent specific inhibitors of CYP3A4 or ketoconazole.

Co-administration of pazopanib with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations. Co-administration with potent P-gp or BCRP inhibitors may also alter the exposure and distribution of pazopanib, including distribution into the central nervous systems (CNS).

Combination with strong CYP3A4, P-gp or BCRP inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4, P-gp or BCRP is recommended.

CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Co-administration of pazopanib with potent P-gp or BCRP inducers may alter the exposure and distribution of pazopanib, including distribution into the CNS. Selection of an alternate concomitant medication with no or minimal enzyme or transporter induction potential is recommended.

In addition, the effect of pazopanib on other medicinal products has been adequately addressed in section 4.5 of the SPC:

In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human PXR assay. Clinical pharmacology studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30 % in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33 % to 64 % in the ratio of dextrometrophan to dextrophan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 25 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Based on *in vitro* IC_{50} and *in vivo* plasma C_{max} values, pazopanib metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of pazopanib towards BCRP. Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Care should be taken when pazopanib is co-administered with other oral BCRP and P-gp substrates.

In vitro, pazopanib inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g. rosuvastatin).

Administration of pazopanib with a high fat or low fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least two hours after food or at least one hour before food. Appropriate information has been included in sections section 4.2 an 5.2 of the SPC. In addition pazopanib film-coated tablets should be taken whole with water and not broken or crushed.

In addition, the applicant will provide additional information on pharmacology as part of post-authorisation commitments. Agreed follow up measures include: the final study report for study NCI 8063 evaluating the effect of hepatic impairment on pazopanib pharmacokinetics, the final study report for study VEG113971 evaluating the effects of ketoconazole and the effects of increased gastric pH on the pharmacokinetics of orally administered pazopanib, the final study report of the interaction study VEG108925 of pazopanib with the UGT1A1 substrate drug irinotecan, detailed analysis of biomarkers and genetic aberrations with correlations to clinical response to pazopanib or sunitinib in the study report for study VEG108844 comparing pazopanib versus sunitinib, amend the study report for VEG102616 (a Phase II study of pazopanib in locally recurrent or metastatic renal cell carcinoma) to include the Cytokine and Angiogenic Factors (CAF) analysis and amend thestudy report for protocol

VEG102616 (a Phase II study of pazopanib in locally recurrent or metastatic renal cell carcinoma) to include the analysis of HIF1α and HIF2α protein expression in clear cell RCC tissue sections.

Clinical efficacy

The primary evidence to support the clinical efficacy of pazopanib in advanced RCC is provided by the pivotal Phase III study VEG105192. Efficacy data from the Phase II study, VEG102616, and Study VEG107769 have also been submitted.

- Dose response study

The recommended Phase II/III monotherapy dose of pazopanib was determined in Study VEG10003. This was a multi-centre, Phase I, open-label, non-randomized, multiple dose-finding study of pazopanib in adult subjects with solid tumours who were refractory to standard therapy or for whom no standard therapy existed. Safety and tolerability of pazopanib were to be characterized in this dose escalation study by determination of the maximum tolerated dose (MTD) based on dose-limiting toxicity (DLT). Dose-escalation decisions were made after all subjects in the previous cohort completed at least one 22-day treatment cycle and on the basis of the safety profiles observed during the same period. The dose of pazopanib was titrated in cohorts of subjects based upon DLTs within the first treatment cycle.

A MTD was not achieved. The 800 mg once daily dose of pazopanib was selected for evaluation in Phase II/III studies, including the 3 RCC studies, based on the following:
- a manageable safety profile

- increasing the pazopanib dose above 800 mg once daily did not result in a consistent increase in systemic exposure at steady-state, so no further benefit is expected at higher pazopanib doses up to the highest dose evaluated (2000 mg);

- a relationship between steady-state trough plasma pazopanib concentration and the probability of the occurrence of hypertension was observed: the steady-state trough concentration at which a 50% probability of observing hypertension was 15.3 µg/ml. Hypertension has been associated as a pharmacodynamic marker of VEGF inhibition with other small molecule tyrosine kinase inhibitors (TKIs);

- five of the six subjects (83%) that had either a partial response (PR) or stable disease (SD) as their best response, achieved a steady-state trough concentration of ≥15 µg/ml;

- 93% of subjects receiving a dose of 800 mg achieved a target trough concentration of ≥15 µg/mL.

- Changes in DC-MRI consistent with a ≥50% decrease in tumor perfusion (IAUGC60) was observed in 10 of 11 (91%) subjects who received pazopanib at doses of ≥800 mg daily and 300 to 400 mg twice daily (bid).

- Main study

VEG105192
A randomized, double-blind, placebo-controlled, multi-centre Phase III study to evaluate the efficacy and safety of pazopanib compared to placebo in patients with locally advanced and/or metastatic RCC.

METHODS

Study Participants

The study was initially designed to enrol subjects with advanced RCC who had progressed from one prior cytokine-based therapy but was expanded to include treatment-naïve advanced RCC subjects shortly after the first subject was enrolled. Therefore, the overall study population included both treatment-naïve and cytokine-pretreated advanced RCC subjects.

Patients from 80 centers in 23 countries, including Latin-American, Asian, Australian, East and West European and African countries, participated in the study.

Inclusion criteria
1. Signed written informed consent.
2. Diagnosis of clear cell RCC that was predominantly clear cell histology.

3. Locally advanced RCC (defined as disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to Stage IV RCC according to American Joint Committee on Cancer [AJCC] staging).
4. Must have had measurable disease, i.e., presenting with at least one measurable lesion per RECIST. A measurable lesion was defined as a lesion that could be accurately measured in at least one dimension with the longest diameter (LD) ≥20 mm using conventional techniques, or ≥10 mm with spiral computerized tomography (CT) scan.
5. Subjects who received only one prior systemic treatment for locally advanced or metastatic RCC with documented disease progression or documented treatment discontinuation due to unacceptable toxicity. This first-line systemic treatment had to be cytokine-based.
Subjects who received no prior systemic therapy for advanced/metastatic RCC could be enrolled if under any of the following circumstances:

- Subjects who lived in countries or regions where there was no established standard first-line therapy for advanced/metastatic RCC or where there were barriers to the access of established therapies such as sunitinib, sorafenib, IFNα or IL-2.
- Subjects who lived in countries or regions where IL-2 or INF-α had been approved for the treatment of advanced/metastatic RCC, however, these agents were generally not recognized by the local clinical community as a standard treatment for advanced/metastatic RCC, or where the physician and the subject had determined that the available cytokine therapies were not an acceptable therapeutic option.
- Subjects who had recurred following prior adjuvant or neo-adjuvant cytokine therapy for RCC were eligible to participate without receiving a first-line systemic treatment for locally advanced or metastatic RCC. These subjects were stratified as the first-line population.

6. Male or female ≥18 years of age.
A woman was eligible to participate in the study if she was of
a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
b. Childbearing potential, had a negative serum pregnancy test, agreed to use adequate contraception. Oral contraceptives were not reliable due to the potential for drug-drug interactions.
A man with a female partner of childbearing potential was eligible to enter and participate in the study if he was abstinent or used a barrier method of contraception during the study.
7. ECOG performance status (PS) 0 or 1
8. Adequate baseline organ function defined as:

- Hematologic function:
  - Absolute neutrophil count (ANC) ≥1 x 109/L
  - Hemoglobin ≥9 g/dL (5.6 mmol/L)
  - Platelets ≥75 x 109/L
- Hepatic function:
  - Total bilirubin ≤1.5 x upper limit of normal (ULN)
  - Aspartate aminotransferase (AST) and ALT ≤2 x ULN
- Renal function:
  - Calculated creatinine clearance (CrCl) ≥30 mL/min and
  - Urine protein = 0, trace, or +1 determined by dipstick urinalysis, or <1.0 g determined by 24-hour urine protein analysis.

9. At least 4 weeks had elapsed since the last surgery and 2 weeks had elapsed since radiotherapy or the last systemic cytokine therapy.
10. Complete recovery from prior surgery, and/or reduction of all AEs to Grade 1 from prior systemic therapy or radiotherapy.

Exclusion criteria
1. Pregnant or lactating female.
2. History of another malignancy, and not disease free ≥5 years.
3. History or presence of central nervous system (CNS) metastasis or leptomeningeal tumors as documented by CT or MRI scan, analysis of cerebrospinal fluid or neurological exam.
4. Malabsorption syndrome or disease that significantly affected gastrointestinal function, or major resection of the stomach or small bowel that affected the absorption of pazopanib.
5. Unable to swallow and retain orally administered medication.
6. Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to beginning study treatment.
7. History of human immunodeficiency virus infection.
8. Presence of uncontrolled infection.
9. Heart-rate corrected QT interval (QTc) prolongation defined as QTc interval >470 msecs.
10. History of Class III or IV congestive heart failure according to New York Heart Association (NYHA) classification.

11. History of any one of the following cardiac conditions within the past 6 months:
• Cardiac angioplasty or stenting, or
• Myocardial infarction, or
• Unstable angina.
12. History of cerebrovascular accident within the past 6 months.
13. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140mmHg, or diastolic blood pressure (DBP) of ≥90mmHg].
14. History of untreated deep vein thrombosis (DVT) within the past 6 months (e.g. a calf vein thrombosis that is not treated).
Note: Subjects with recent DVT who were treated with therapeutic anti-coagulating agents (excluding therapeutic warfarin) for at least 2 weeks were eligible.
15. Presence of any non-healing wound, fracture, or ulcer, or presence of symptomatic peripheral vascular disease.
16. Evidence of bleeding diathesis or coagulopathy.
17. Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that interfered with subject's safety, obtaining informed consent or compliance to the study.
18. Had taken any prohibited medications that were listed in the study protocol within 14 days of the first dose of investigational product.
19. Prior use of an investigational anti-cancer drug within 4 weeks of start of study.
20. Prior use of an investigational or licensed drug that targeted VEGF or VEGF receptors (e.g., bevacizumab, sunitinib, sorafenib, etc).

Treatments

Subjects received either 800 mg pazopanib daily dosing or matching placebo. Subjects continued on investigational product until disease progression, death, unacceptable toxicity or withdrawal of consent. Eligible subjects who progressed on placebo had the option to receive pazopanib by enrolling into Study VEG107769.

Imaging-based disease assessments were performed for all subjects at baseline, every 6 weeks until Week 24, and every 8 weeks thereafter until progression. Subjects who discontinued investigational product prior to disease progression were to continue disease assessments according to the pre-defined protocol schedule until progression was documented or initiation of another anti-cancer treatment. All subjects were followed for survival.

Objectives

The primary objective of the study was to evaluate and compare the PFS in pazopanib versus placebo-treated subjects. The principal secondary objective was to evaluate and compare the overall survival (OS) in the two treatment arms. Other secondary objectives were to evaluate and compare the two treatment arms for response rat (RR), rate of complete responses (CR) + partial responses (PR) + 6-month stable disease (SD), safety and tolerability. Additional objectives included pharmacokinetics and quality of life assessments.

Outcomes/endpoints

The primary efficacy endpoint was PFS, defined as the interval between the date of randomization and the earliest date of disease progression or death due to any cause. The RECIST criterion for the assessment of progression of solid tumours was used.

The principal secondary endpoint was OS, defined as the time from randomization until death due to any cause.

Other secondary efficacy endpoints were:
- RR (CR+PR). RR was defined as the percentage of subjects who achieved either a confirmed CR or PR per RECIST as their best overall response.
- Rate of CR + PR + 6 months SD
- Duration of response (defined as the time from first documented evidence of CR or PR until the first documentation of disease progression or death due to any cause, whichever was first).
- Time to response (defined as the time from randomization until the first documented evidence of CR or PR (whichever status was recorded first).

Other endpoints included:
Change in health-related quality of life (HRQOL) from baseline at Week 6, 12, 18, 24 and 48, using version 3 of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the EuroQoL-5D (EQ-5D).

A cross-study IDMC was established to monitor safety and make recommendations on the course of the pazopanib RCC studies, based on reviewing of the pre-determined safety and efficacy data sets.

An Independent Imaging Review Committee (IRC) was also established prior to study start to review all imaging for the assessment of subject's disease status. The IRC, which comprised of 6 board-certified radiologists, performed a blinded review of all scans for randomized subjects according to the Imaging Review Charter. Two radiologists independently read each subject's set of scans (double-read), with a third acting as an adjudicator if necessary. The primary analysis of PFS was based on the disease assessments by the IRC as specified in the protocol and Reporting and Analysis Plan (RAP).

Sample size

The sample size calculation for OS was based on 90% power to detect a 50% improvement in median OS with pazopanib treatment compared with placebo. Although the primary endpoint for this study is PFS, the sample size calculation was based on the number of subjects required to detect a treatment effect in the key secondary endpoint of OS. One interim analysis on OS was planned to occur after approximately 70% of the total events and flexible O'Brien-Fleming error spending functions for superiority and futility, this required accrual of 287 death events from approximately 350 enrolled subjects.

Upon amending the protocol via Amendment 3 to include the treatment-naïve subjects, shortly after the first subject was enrolled, the sample size was changed to 350 - 400 subjects to allow a minimum of 150 subjects to be enrolled for each of the treatment-naïve and cytokine pre-treated subgroups, and a minimum of 350 subjects to be enrolled for the entire study. The enrolment for each subgroup was not to exceed 250 subjects with a maximum of 400 subjects to be enrolled for the entire study. This sample size allowed at least 90% power to detect an 80% improvement in median PFS by pazopanib treatment in both the overall study population as well as in each of the treatment-naïve and cytokine-pretreated subgroups. This required at least 127 PFS events observed from each of the subgroups based on the IRC assessment.

The clinical cut-off for the final PFS analysis was subsequently modified to require 90 PFS events in each of the treatment-naïve and cytokine-pretreated subgroups and 160 deaths from the overall study population for interim OS analysis. The new requirement of 90 events in each of the treatment-naïve and cytokine-pretreated subgroups corresponds to ~80% power to detect an improvement of 80% in PFS and 90% power to detect an improvement of 100% in PFS. Reducing the number of required PFS events did not substantially effect the overall sample size requirements for the study because the total number of deaths required for the final OS analysis did not change.

All sample size calculations were performed assuming 2.5% one-sided alpha.

Randomisation
Subjects were randomized in a 2:1 ratio of pazopanib: placebo. Eligible subjects were first stratified according to the following stratification factors: 1) prior systemic therapy: treatment-naïve vs. cytokine-pretreated; 2) baseline ECOG PS 0 vs. 1; and 3) prior nephrectomy status: yes vs. no.

Blinding (masking)
The study was designed as a double-blind trial with an IRC established to centrally evaluate imaging from all study subjects in a blinded fashion, based on RECIST. The central review by the IRC was completed prior to database freeze and unblinding.

Statistical methods

The Intent-to-treat (ITT) population was the primary population used for the analysis of efficacy data. The ITT population comprised all randomized subjects which were analyzed based on the assigned randomized treatment. Sub-populations of interest, including treatment-naïve and cytokine-pretreated subgroups, were also analyzed as pre-specified in the RAP.

The primary analysis of PFS was performed using the data from the IRC review of the imaging scans. Imaging assessments were performed every six weeks prior to Week 24 and every 8 weeks thereafter or as clinically indicated. Subjects were censored, using the previous adequate assessment if the subject had not progressed prior to the clinical cut-off, or if another anti-cancer therapy was initiated prior to progression, or if the subject's PFS event (progression or death) occurred after an extended period of inadequate assessment (PFS event occurred more than 12 weeks after the previous adequate assessment). Subjects without an adequate baseline assessment were censored at randomization.

PFS was summarized using Kaplan-Meier survival curves and compared between treatment arms using a stratified log-rank test. The three stratification factors (baseline ECOG PS, prior nephrectomy status and prior systemic treatment) were to be incorporated according to the analysis plan. Significance tests were conducted for the ITT population and also for the treatment-naïve and cytokine-pretreated subgroups. The Pike estimator of the treatment HR was calculated, together with a 95% CI.

For each treatment group, the Kaplan-Meier estimates for the median PFS, and the first and third quartiles were presented, along with approximate 95% CIs if there were a sufficient number of progressions or deaths. Greenwood's formula was used to calculate the standard error of the estimates from the Kaplan-Meier curve.

Nine pre-specified sensitivity analyses that were performed in the analysis of PFS (see Table 13).

Table 13. Summary of Analyses of PFS – Primary and Sensitivity Analyses (VEG105192)

Analysis	Description	Imaging Assessment
Primary	Primary analysis of PFS	IRC
Sensitivity 1	PFS using actual scan dates to determine dates of censoring and progression	IRC
Sensitivity 2	PFS unadjusted for stratification factors	IRC
Sensitivity 3	PFS using earliest date of progression (including symptomatic progression); Progression date based on the date of the clinical assessment of symptomatic deterioration as applicable	Investigator
Sensitivity 4	PFS using radiological assessments of progression only	Investigator
Sensitivity 5	PFS without censoring for extended loss to follow-up	IRC
Sensitivity 6	PFS with adjustment for earlier investigator assessments of progression	IRC and Investigator
Sensitivity 7	PFS using alternative definition of adequate assessment (regular bone scans for subjects without positive bone scans at baseline are not required)	IRC
Sensitivity 8	PFS by Cox regression analysis (exploratory); Stepwise selection used to choose covariates from stratification factors, and demographic and baseline disease characteristics	IRC
Sensitivity 9	PFS by Cox regression analysis = adjusted for stratification factors	IRC

IRC: independent review committee; PFS: progression-free survival

The same analysis methods as for the primary analysis were used except where specified (sensitivity analysis 2: unadjusted for stratification factors, and sensitivity analyses 8 and 9: Cox regression analysis).

Subgroup analyses of PFS were performed for the pre-specified subgroups of: treatment-naïve, cytokine- pretreated, Memorial Sloane-Kettering Cancer Center (MSKCC) Favourable risk category, MSKCC Intermediate risk category, ECOG PS 0, ECOG PS 1, gender and age (<65 years, ≥65 years), using the data from the IRC assessments. The study was designed to have sufficient power to detect a treatment effect in the treatment-naïve and cytokine-pretreated subgroups. Analysis by race subgroups was planned.

The secondary endpoint OS was analyzed similarly to the primary analysis of PFS. The OS analysis in this report is an interim analysis. One-sided p-values were to be compared to the O'Brien-Fleming error spending boundaries in order to determine superiority or futility. Updated boundaries based on

the exact percentage of information collected for the interim analysis were calculated using East® software. The initial analysis was performed by a Statistical Data Analysis Center and provided to the IDMC. The final analysis will be performed by GSK after 287 total deaths have accrued.

In order to analyze the robustness of the OS results, several sensitivity analyses were performed on the overall ITT population.
Unadjusted Analysis: The unadjusted Pike estimator and standard log-rank p-value were produced, along with the Wilcoxon p-value.
Cox Analysis: OS was also analyzed using a Cox proportional hazards regression analyses. The Cox analysis was performed with and without including the stratification factors as covariates. The summaries of the Cox proportional hazards regression analyses included HRs, 95% CIs, and p-values for the treatment effect and each of the stratification factors.

Subgroup analyses were performed to understand the OS treatment differences in different subgroups (treatment-naïve versus cytokine-pretreated, MSKCC risk categories of favourable and intermediate). In addition, an analysis excluding subjects with post-study therapy was performed. The analysis summary tables included Pike estimators and naïve 95% CI as well as p-values associated with the log-rank test.

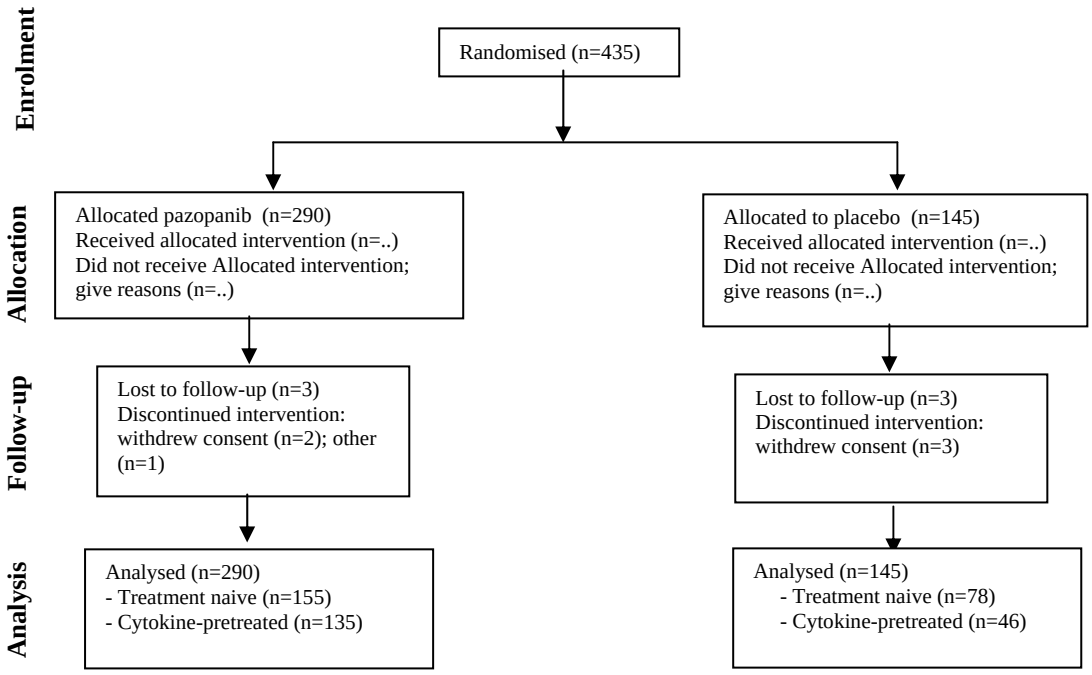
Separate analyses on the response secondary endpoints were performed using the investigator and the IRC data. All response analyses were based on confirmed response. Response was confirmed by two methods: Method A, where bone scans were required for confirmation of CR and PR in subjects with positive baseline bone scans; and Method B, where bone scans were only required for confirmation of CR for subjects with positive baseline bone scans (i.e. not PR or SD).

Response rates and the rates of CR + PR + 6 month SD were compared between treatment arms using a Fisher's exact test. Approximate 95% CIs for the difference were calculated. The response rates (best overall response by Method A) were also summarized separately by each of the stratification factors (ECOG PS 0, ECOG PS 1, prior nephrectomy, no prior nephrectomy, treatment-naïve, and cytokine-pretreated). Duration of response and time to response were summarized descriptively using medians and quartiles.

Health outcomes changes of the mean scores over time were analyzed with a repeated measures analysis of covariance (ANCOVA) using baseline score as covariate. A mixed effects model was used. Analyses were carried out using Proc Mixed of SAS. The final analysis covariance model was to depend on the observed data and ultimately the unstructured covariance matrix was selected.
Summary statistics were provided for 15 domain scores at baseline visit, Week 6, 12, 18, 24 and 48, and for the change from baseline for 15 domain scores. The least squares means and associated standard error (SE) of the changes from baseline are shown for each visit (Week 6, 12, 18, 24 and 48) for both treatment groups. Additionally, the difference between treatment groups along with the 95% CI and p-value were displayed.

Results

Participant flow



Recruitment
Enrollment started from April 18th 2006 to April 24th 2007. May 23rd 2008 was the clinical data cut-off date for this analysis.

Conduct of the study
The study protocol underwent 5 amendments:

- *Protocol Amendment 1* (issued 31 January 2006): The protocol was revised to exclude symptomatic progression as a measure for determining a PD event.

- *Protocol Amendment 2* (issued 22 March 2006): Major revision included reducing clinical visit schedules for disease assessments from every 8 weeks to every 6 weeks for the first 24 weeks; Clinic visit schedule for safety assessments was reduced from every 4 weeks to every 3 weeks within the first 24 weeks.
These two revisions were implemented prior to the start of the study.

- *Protocol Amendment 3* (issued 09 May 2006): Major revisions and rationale included:
1. Expansion of study population to include treatment-naïve advanced RCC subjects.
The initial protocol finalized in November 2005 was to enrol subjects with advanced RCC who had received one prior cytokine-based therapy. Following the approvals of sorafenib and sunitinib for advanced RCC in December 2005 and January 2006, the population of the study was expanded to include subjects with treatment-naïve advanced RCC. When Protocol Amendment 3 was issued, 7 subjects were enrolled into the study.
2. Setting minimum enrolment targets for the overall study population and subgroups of interest, and reducing the number of OS interim analyses from 2 to 1.
Due to the inclusion of treatment-naïve advanced RCC subjects, prior treatment was added as a stratification factor and the protocol was amended to enrol a minimum of 150 subjects for each treatment-naïve and cytokine-pretreated subgroup and a minimum of 350 subjects for the entire study, with the total enrolment target set for 350 to 400. This was to ensure 90% power to assess 80% improvement in median PFS in each of the subgroups as well as in the overall study population. This required a minimum of *127 PD* events to be achieved from each subgroup prior to the final PFS analysis.
3. Allow crossover of subjects in the placebo arm to receive pazopanib treatment as a treatment option through the open label extension study VEG107769.

- *Protocol Amendment 4* (issued 07 August 2006): Revision made to include treatment-naïve subjects in countries where cytokines were approved but were not considered as an effective therapy for advanced RCC by the medical community where the standard treatment was best supportive care.

-Protocol Amendment 5 (issued 23 May 2007): Revision made to update pazopanib safety and efficacy data from other pazopanib studies and to provide detailed instructions for dose modification for liver toxicity. There was a minor revision to the sensitivity analysis.

- *Revision on Clinical Cutoff Timing for the Final PFS Analysis and Rationale:* Prior to unblinding, the timing of the planned final PFS analysis was changed to a time point when at least 90 PFS events had occurred in each subpopulation as determined by independent review. Additionally, a requirement was added that at least 160 out of the 287 planned overall survival events had accrued at the time of this analysis.

Baseline data

Demographic characteristics are summarised in Table 14:

Table 14. Summary of Demographics in Treatment-naïve and Cytokine-pretreated Subgroups (ITT Population)

	Treatment-naïve		Cytokine-pretreated	
Parameters	**Placebo (N=78)**	**Pazopanib (N=155)**	**Placebo (N=67)**	**Pazopanib (N=135)**
Age (yrs)				
Mean (SD)	59.4 (12.40)	59.3 (10.10)	59.9 (9.29)	58.8 (10.03)
Median (range)	62.0 (25 to 81)	59.0 (28 to 82)	59.0 (43 to 77)	58.0 (31 to 85)
Age Group n (%)				
<65 years	43 (55)	104 (67)	42 (63)	92 (68)
≥65 years	35 (45)	51 (33)	25 (37)	43 (32)
≥75 years	7 (9)	7 (5)	4 (6)	7 (5)
Sex n (%)				
Female	20 (26)	49 (32)	16 (24)	43 (32)
Male	58 (74)	106 (68)	51 (76)	92 (68)
Race n (%)				
White	64 (82)	132 (85)	58 (87)	120 (89)
Black	0	1 (<1)	0	0
Asian	14 (18)	21 (14)	9 (13)	15 (11)
Other	0	1 (<1)	0	0

Data Source: VEG105192 Table 6.31, Table 6.32, Table 6.33, Table 6.34

Disease characteristics were generally similar between the treatment-naïve and cytokine-pre-treated subjects. The time since diagnosis of Stage IV disease was longer in the cytokine-pretreated subgroups compared with the treatment-naïve subgroups (see Table 15).

Table 15. Summary of Selected Baseline Disease Characteristics in Treatment-naïve and Cytokine-pretreated Subgroups (ITT Population)

	Treatment-naïve		Cytokine-pretreated	
Parameters	**Placebo (N=78)**	**Pazopanib (N=155)**	**Placebo (N=67)**	**Pazopanib (N=135)**
Stage of disease at initial diagnosis				
I	8 (10)	15 (10)	5 (7)	7 (5)
II	14 (18)	22 (14)	10 (15)	21 (16)
III	24 (31)	49 (32)	22 (33)	44 (33)
IV	32 (41)	67 (43)	29 (43)	60 (44)
Missing	0	2 (1)	1 (1)	3 (2)
Time since initial diagnosis (months)				
Median	8.5	7.9	19.1	26.3
Range	1 to 152	1 to 176	3 to 148	2 to 184
Time since diagnosis of Stage IV Disease (months)				
Median	3.5	3.0	9.5	13.3
Range	0 to 89	0 to 149	2 to 61	1 to 136
Most Frequent Locations of Disease at Baseline[a]				
Lung	55 (71)	114 (74)	51 (76)	100 (74)
Lymph Nodes	48 (62)	89 (57)	38 (57)	68 (50)
Bone	22 (28)	49 (32)	16 (24)	32 (24)
Liver	17 (22)	41 (26)	15 (22)	34 (25)
Kidney	22 (28)	40 (26)	14 (21)	26 (19)
Number of organs involved[a]				
1	10 (13)	23 (15)	10 (15)	30 (22)
2	25 (32)	46 (30)	25 (37)	32 (24)
≥3	43 (55)	86 (55)	32 (48)	73 (54)
ECOG Performance Status				
0	33 (42)	63 (41)	27 (40)	60 (44)
1	45 (58)	92 (59)	40 (60)	75 (56)
MSKCC Risk Category[b]				
Favourable Risk	31 (40)	56 (36)	26 (39)	57 (42)
Intermediate Risk	40 (51)	87 (56)	37 (55)	72 (53)
Poor Risk	5 (6)	6 (4)	0	3 (2)
Unknown[c]	2 (3)	6 (4)	4 (6)	3 (2)

ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloane-Kettering Cancer Center

a. As defined by the Investigator
b. 61 of the assignments in the treatment-naïve subgroup and 47 in the cytokine-pretreated subgroup required the use of total calcium measurements because of missing baseline albumin levels for calculation of corrected calcium.
c. Subjects with an unknown MSKCC risk category were missing results for one or more of the 5 risk criteria.

Numbers analysed

The ITT population was the primary population used for the analysis of efficacy data. There were 233 treatment-naïve subjects (54% of total) and 202 cytokine-pretreated subjects (46% of total) enrolled in the study. The percentages of treatment naïve and cytokine-pretreated subjects between the two arms were balanced due to stratification (see Table 16).

Table 16. Summary of Study Populations (All Subjects) (VEG105192: ITT Population)

	Number (%) of subjects		
	Placebo (N=145)	**Pazopanib (N=290)**	**Total (N=435)**
Intent-to-Treat	145 (100)	290 (100)	435 (100)
Treatment-naïve	78 (54)	155 (53)	233 (54)
Cytokine-pretreated[a]	67 (46)	135 (47)	202 (46)

d. 1 subject was not cytokine-pretreated but had been treated with chemotherapy.

Outcomes and estimation

Primary endpoint (PFS)

In the ITT population a clinically and statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm, with an HR of 0.46 (95% CI, 0.34 to 0.62, p <0.0000001) (Figure 4, Table 17). Median PFS was 9.2 months (95% CI, 7.4, 12.9) in the pazopanib arm compared with 4.2 months (95% CI, 2.8, 4.2) in the placebo arm (Table 17).

Table 17 PFS per IRC Assessment (VEG105192: ITT Population)

	Placebo (N=145)	Pazopanib (N=290)
Subject status, n (%)		
Progressed or Died (event)	98 (68)	148 (51)
Censored, follow-up ended[a]	42 (29)	90 (31)
Censored, follow-up ongoing[b]	5 (3)	52 (18)
Kaplan-Meier Estimates for PFS (months)[c]		
1st Quartile (95% CI)	1.4 (NC, NC)	4.2 (2.8, 5.6)
Median (95% CI)	4.2 (2.8, 4.2)	9.2 (7.4, 12.9)
3rd Quartile (95% CI)	7.4 (5.6, 12.9)	18.4 (16.6, NC)
Adjusted Hazard Ratio[d] (95% CI)	0.46 (0.34, 0.62)	
Stratified Log-Rank p-value[d]	<0.0000001	

NC: not calculable; PFS: progression-free survival
Note: The date of progression or censoring was based on the protocol-defined assessment schedule (not the actual scan dates). A sensitivity analysis using the actual scan date was performed.
a. Subjects were classified as censored with follow-up ended if their progression event occurred after a period of extended inadequate assessment or if they withdrew from the study prior to disease progression.
b. Subjects were classified as censored with follow-up ongoing if the subjects were still on-study and progression-free at their last disease assessment.
c. Quartiles estimated using the Brookmeyer-Crowley method.
d. Hazard ratios were estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test were adjusted for ECOG status and prior systemic treatment for Stage IV RCC at screening.

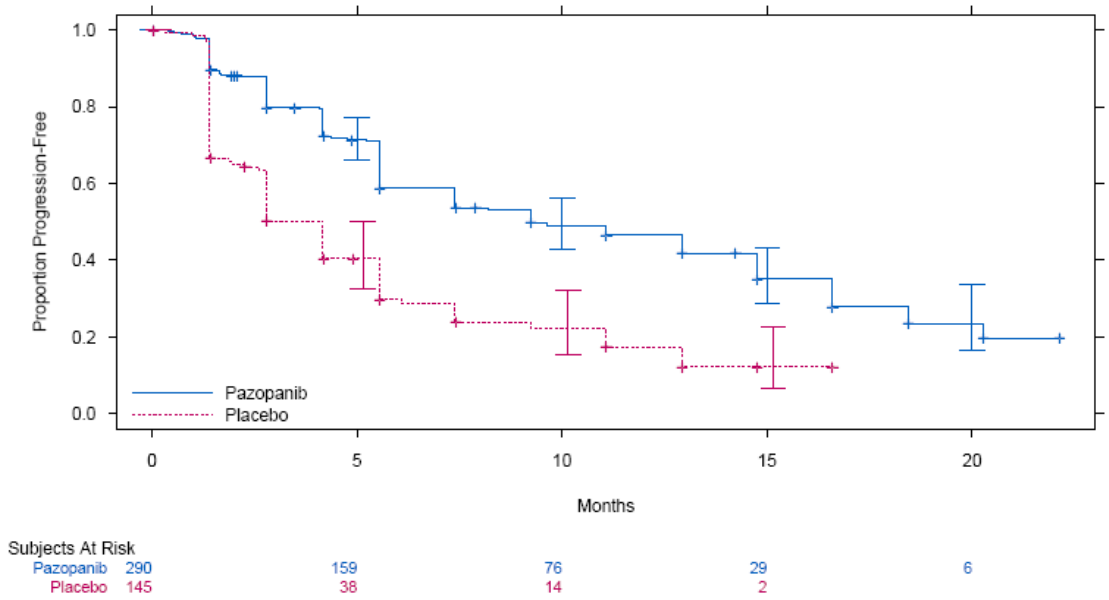


Figure 4. Kaplan-Meier Graph of PFS per IRC Assessment (ITT Population)

By IRC assessment, the percentage of subjects who were censored with follow up ended was balanced between the two treatment arms (31% [90/290] in the pazopanib arm and 29% [42/145] in the placebo arm. The majority of these subjects had ended follow-up because they were assessed as PD by the investigator and had no further scans. Other reasons for subjects having censoring with follow-up ended are provided in footnote 'a' of Table 17.

The treatment effects of pazopanib on PFS were observed in all the subgroups analyzed (age, gender, ECOG PS and MSKCC Risk Category) and they were consistent with the primary result, HRs ranging from 0.40 (95% CI, 0.24, 0.67) in the MSKCC favourable subgroup to 0.52 (95% CI, 0.33, 0.82) in the ≥65 year age group (Figure 5). In all the subgroup analyses, the p-value for the log rank test comparing pazopanib to placebo was less than 0.001.

Secondary endpoints

Overall Survival (OS)
A planned interim analysis of OS was performed with a cut off date of 23 May 2008 when 176 events had occurred (40% of all subjects, or 61% of the events needed for the final analysis). At the time of the cut-off date, 67 subjects (46%) in the placebo arm and 109 subjects (38%) in the pazopanib arm had died (Table 18). Most subjects were still being followed for survival and were censored for these analyses. In addition, 2% of subjects in the placebo arm and 4% of subjects in the pazopanib arm were no longer being followed for survival but were alive when their follow-up ended (the subjects were lost to follow up or had withdrawn consent to remain in the study).

OS appeared to be prolonged in the pazopanib arm compared with the placebo arm (HR 0.73; 95% CI: 0.53, 1.00; 99.16% CI: 0.47, 1.12; one sided p=0.020; Table 18, Figure 5). However, the results did not reach the pre-specified O'Brien-Fleming significance level for the interim analysis (one-sided p≤0.004 for superiority and one sided p >0.201 for futility).

Table 18. Kaplan-Meier Estimates of Interim Analyses on Overall Survival (VEG105192: ITT Population)

	Placebo (N=145)	Pazopanib (N=290)
Number (%) of Subjects		
Died (event)	67 (46)	109 (38)
Censored, follow-up ended	3 (2)	11 (4)
Censored, follow-up ongoing	75 (52)	170 (59)
Estimates for overall survival(months)[a]		
1st Quartile (95% CI)	7.2 (4.7, 9.8)	11.1 (9.4, 13.3)
Median (95% CI)	**18.7 (14.6, 20.1)**	**21.1 (19.3, NC)**
3rd Quartile (95% CI)	NC (20.0, NC)	NC (NC, NC)
Adjusted HR[b]		
Estimate (95% CI) [99.16% CI[c]]	0.73 (0.53, 1.00) [0.47, 1.12]	
Stratified Log-Rank P-Value[b]	0.020	

HR; hazard ratio; NC: not calculable.

- Quartiles estimated using the Brookmeyer-Crowley method
- HRs were estimated using the Pike estimator. A HR <1 indicates a lower risk with pazopanib compared with placebo. The HR and p-value from stratified log-rank test were adjusted for ECOG status and prior systemic treatment for Stage IV RCC at screening.
- Adjusted for interim analysis.

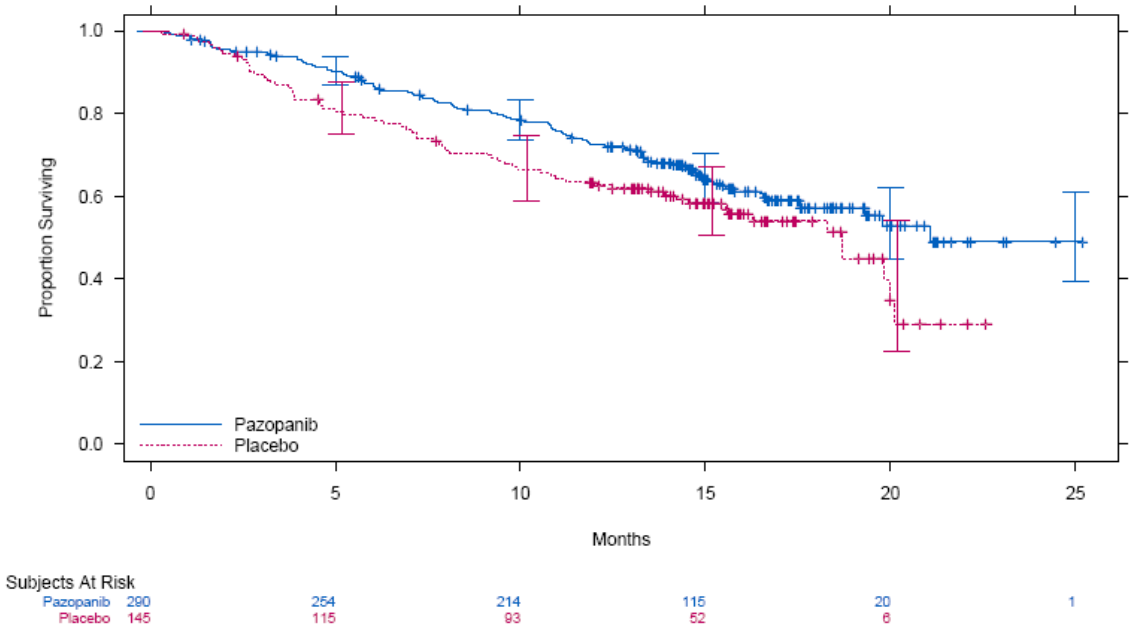


Figure 5. Kaplan Meier Overall Survival Curves (ITT population)

Results for OS were analysed by subsequent anti-cancer therapies received after discontinuation of study treatment. In the placebo arm, 89 (61%) subjects received further anti-cancer therapy post-discontinuation; 70/89 subjects received pazopanib as the subsequent anti-cancer therapy via VEG107769 (see Table 19). A smaller percentage (28%) of subjects in the pazopanib arm compared with the placebo arm received further anti-cancer therapy post-discontinuation.

Table 19. Summary of Anti-cancer Therapy Post Discontinuation of Investigational Product (ITT population)

	Placebo (N=145)	Pazopanib (N=290)
Any anti-cancer therapy, n (%)		
Yes	89 (61)	81 (28)
No	56 (39)	215 (70)
List of anti-cancer therapy[a], n (%)		
Sorafenib	7 (5)	22 (8)
Sunitinib	5 (3)	22 (8)
Interferon	5 (3)	16 (6)
Interleukin-2	1 (1)	2 (1)

Temsirolimus Pazopanib Bevacizumab	1 (1) 70 (48)[b] 0	2 (1) 1 (0.3) 1 (0.3)
Time to start of anti-cancer therapy (days) Median Range	 183.5 47 to 477	 253.0 45 to 654

Note: A subject may have had more than one type of anticancer therapy.
Subjects may have received other anti-cancer therapies, in addition to those listed.
The actual number of placebo-treated subjects treated in VEG107769 was 70. Follow-on pazopanib treatment in VEG107769 was not recorded in the VEG105192 eCRF for 9 subjects.

Response Analyses
Response rates were significantly higher in the pazopanib arm compared with the placebo arm (30% and 3%, respectively, p <0.001). The investigator-evaluated RR was similar: 36% in the pazopanib arm compared with 6% in the placebo arm (p <0.001).

The median duration of response in the pazopanib group was 58.7 weeks (95% CI, 52.1 to 68.1 weeks) as per IRC review and 62.4 weeks (95% CI, 42.0 to 68.6 weeks) as per investigator review. The median time to response with pazopanib treatment was 11.9 weeks.

The RR was analyzed in the treatment-naïve and cytokine-pretreated subgroups by both IRC and investigator assessments in VEG105192. Overall, the RR results in each of the treatment-naïve and cytokine-pretreated subgroups were similar to that of the overall study population and were improved in pazopanib-treated subjects compared with placebo-treated subjects.

Quality of life

EORTC QLQ-C30: Results from a mixed-model repeated measures analysis for change from baseline consistently shows no statistical difference between pazopanib and placebo arms at each assessment time point in global health status/HRQOL. Additionally, the between-group differences are smaller than MID of 5 to 10.

EuroQoL-5D: Results from a mixed-model repeated measures analysis for change from baseline consistently shows no statistical difference between pazopanib and placebo arms at each assessment time point in EQ-5D utility score. Additionally, the between group differences are smaller than MID of 0.08. The within-group differences were also smaller than MID, suggesting that either declines or improvement from baseline were not clinically meaningful in either arm. No differences were observed either using EQ-5D VAS score. Additionally, the between group differences were smaller than MID of 7. The within-group differences were also smaller than MID, suggesting that improvements from baseline were not clinically meaningful in either arm.

Ancillary analyses

A clinically and statistically significant improvement in PFS based on investigator assessments was observed in the pazopanib arm compared with the placebo arm (HR, 0.44; 95% CI, 0.34 to 0.57, p <0.0000001). These results are consistent with those by IRC assessment.

A sensitivity analysis was explored to understand the sensitivity of the results to using a visit-based approach instead of a scan-based approach within the two prior treatment subgroups. Using the scan-based approach the median PFS in the treatment-naïve placebo subgroup is slightly longer at 2.9 months and the median PFS for the cytokine-pretreated placebo subgroup is only 3.2 months (see Table 20. In contrast, the results using these scan date based dates for the pazopanib treated subjects in these subgroups are quite close to the visit-based results; the median for the treatment-naïve subjects is 10.8 months and the median for the cytokine-pretreated subjects is 7.5 months.

Table 20. PFS in Treatment-naïve and Cytokine-pretreated Subgroups (IRC Assessed, ITT Population)

	Treatment-Naïve		**Cytokine-Pretreated**	
	Placebo (N=78)	**Pazopanib (N=155)**	**Placebo (N=67)**	**Pazopanib (N=135)**
Number (%) of Subjects				
Progressed or Died (event)	57 (73)	73 (47)	41 (61)	75 (56)
Censored, follow-up ended	19 (24)	51 (33)	23 (34)	39 (29)

Censored, follow-up ongoing	2 (3)	31 (20)	3 (4)	21 (16)
Unadjusted HR[b] Estimate (95% CI)	0.40 (0.27, 0.60)		0.54 (0.35, 0.84)	
Stratified Log-Rank P-Value[b]	<0.0000001		<0.001	

HR: hazard ratio; NC: Not calculable; PFS: progression-free survival
Quartiles estimated using the Brookmeyer-Crowley method.
The HR is estimated using a Pike estimator. A HR <1 indicates a lower risk with pazopanib compared with placebo.

OS showed a trend to be prolonged in the pazopanib arm compared with the placebo arm in each of the treatment naïve (HR: 0.74; 95% CI, 0.47, 1.15; one-sided p=0.079) and cytokine pretreated subgroups (HR: 0.72; 95% CI: 0.46, 1.14; p=0.067; Table 21).

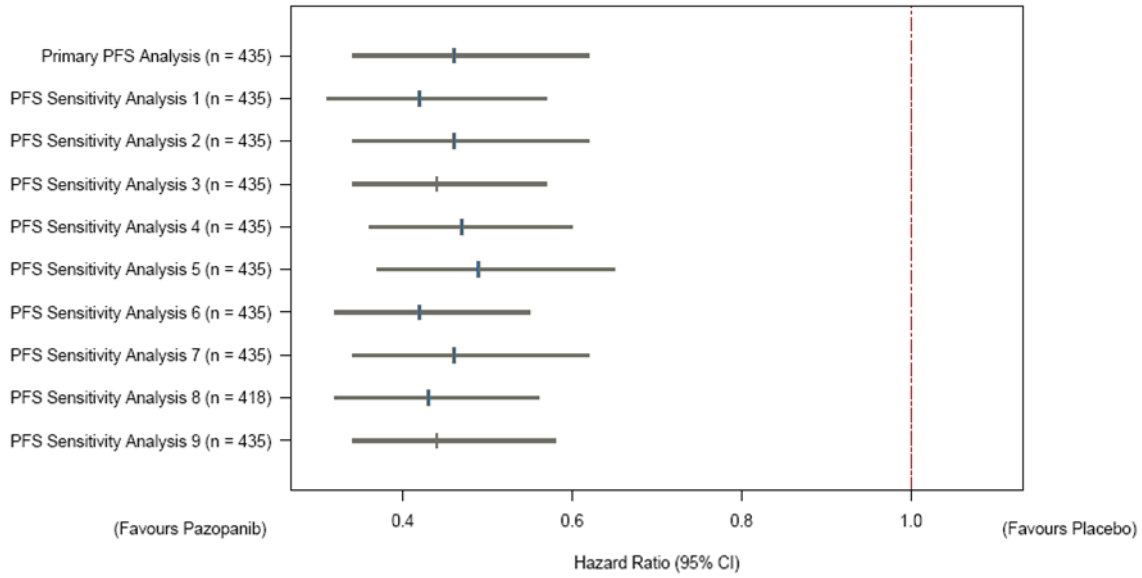
Table 21. Overall Survival Interim Analysis in Treatment-naïve and Cytokine-pretreated Subgroups (ITT Population)

	Treatment-naïve		**Cytokine-pretreated**	
	Placebo (N=78)	**Pazopanib (N=155)**	**Placebo (N=67)**	**Pazopanib (N=135)**
Number (%) of Subjects				
Died (event)	34 (44)	56 (36)	33 (49)	53 (39)
Censored, follow-up ended	1 (1)	9 (6)	2 (3)	2 (1)
Censored, follow-up ongoing	43 (55)	90 (58)	32 (48)	80 (59)
Estimates for overall survival (months)[a]				
1st Quartile (95% CI)	5.0 (3.7, 9.8)	10.9 (7.8, 14.7)	9.1 (6.8, 13.5)	11.7 (9.4, 14.4)
Median (95% CI)	20.0 (10.5, NC)	19.8 (15.8, NC)	18.3 (14.2, 20.1)	NC (17.6, NC)
3rd Quartile (95% CI)	NC (20.0, NC)	NC (19.8, NC)	NC (18.7, NC)	NC (NC, NC)
Adjusted HR[b] Estimate (95% CI)	0.74 (0.47, 1.15)		0.72 (0.46, 1.14)	
Stratified Log-Rank P-Value[b]	0.079		0.067	

Data Source: VEG105192, Table 7.28, Table 7.29.
HR; hazard ratio; NC: not calculable.
a. Quartiles estimated using the Brookmeyer-Crowley method.
b. HRs are estimated using a Pike estimator. A HR <1 indicates a lower risk with pazopanib compared with placebo. HR and P-value from stratified log-rank test are adjusted for ECOG PS.

Sensitivity analyses investigated the effect of utilizing different criteria for assessment of censoring and progression, and analysis by Cox regression. In all cases, the sensitivity analysis confirmed the primary analysis result, indicating a statistically significant improvement in PFS with pazopanib compared with placebo (Figure 6).

Figure 6: Forest Plot of Primary and Sensitivity Analyses of PFS (ITT Population)



Primary: dates based on assessment (visit) dates, adjusted for stratification factors (IRC)
Sensitivity 1: actual scan dates for determining dates of censoring and progression (IRC)
Sensitivity 2: unadjusted for stratification factors (IRC)
Sensitivity 3: using earliest date of progression (including symptomatic progression); progression date based on the date of the clinical assessment of symptomatic deterioration as applicable (investigator).
Sensitivity 4: using radiological assessments of progression only (investigator).
Sensitivity 5: without censoring for extended loss to follow-up (IRC).
Sensitivity 6: with adjustment for early investigator assessments of progression (IRC and investigator).
Sensitivity 7: using alternative definition of adequate assessment (regular bone scans for subjects without positive scans at baseline are not required) (IRC).
Sensitivity 8: Cox regression analysis (exploratory); Stepwise selection used to choose covariates from stratification factors, and demographic and baseline disease characteristics (IRC).
Sensitivity 9: Cox regression analysis; adjusted for stratification factors (IRC).

Covariate analyses were performed for the secondary endpoint OS using the Cox proportional hazards model. The effects of the stratification factors of baseline ECOG PS, prior nephrectomy, and prior systemic therapy were tested. Analysis by ECOG PS was statistically significant (p=0.006), with a longer OS in subjects with PS of 0 compared with 1. Analysis by prior nephrectomy was statistically significant (p=0.004) with a longer OS in subjects who had prior nephrectomy compared with those who had not. There was no significant statistically effect by prior systemic therapy (p=0.931).

The results of a cross-study comparison of pazopanib with sunitinib, sorafenib, bevacizumab + INFα, and temsirolimus are summarised in Tables 22-24

Table 22. Comparison of Efficacy - Pazopanib versus Approved Anti-Angiogenic Agents in Metastatic RCC.

	Control	Analysis	PFS HR (95% CI)	Median PFS of test arm (months)	OS HR (95% CI)	ORR
Pazopanib 1L/2L (N=435)	Placebo	Final PFS Interim OS	0.42 (0.31,0.57)	9.3	0.73 (0.52,1.00)	30%
Pazopanib 1L (N=233)	Placebo	Final PFS Interim OS	0.36 (0.24,0.55)	10.8	0.74 (0.47,1.15)	32%
Sunitinib 1L (N=750)	IFNα	Interim PFS[1] Interim OS	0.42 (0.32,0.54)	10.9	0.65 (0.45,.94)	28%
		Final PFS Final OS	0.54 (0.44,0.66)	11.0	0.82 (0.67,1.00)	39%
Bevacizumab + IFNα 1L AVOREN (N=649)	IFNα	Final PFS Interim OS	0.63 (0.52,0.75)	10.2	0.70 (0.62,1.02)	31%
Bevacizumab + IFNα 1L CALGB 90206 (N=732)	IFNα	Final PFS	0.71 (0.61, 0.83)	8.5	NA	26%
Bevacizumab + IFNα 1L Pooled (N=1381)	IFNα	Final PFS	0.68 (0.60, 0.76)	NA	NA	NA
Pazopanib 2L (N=202)	Placebo	Final PFS Interim OS	0.50 (0.32,0.78)	7.5	0.72 (0.46,1.14)	29%
Sorafenib 2L (N=902)	Placebo	Interim PFS[2] Interim OS	0.44 (0.35,0.55)	5.5	0.72 (0.54, 0.94)	2%
		Final PFS Final OS	0.51 (0.43,0.60)	5.5	0.88 (0.74,1.04)	10%

1. The evaluation of RR and PFS in this analysis is based on 660 subjects.
2. The evaluation of PFS in this analysis is based on 769 subjects.

Table 23. Comparison of PFS results for the control arms of the pivotal studies of pazopanib, sorafenib and bevacizumab

Control		Median PFS of control arm (months)
Pazopanib 1L/2L (N=145)	Placebo	3.0
Pazopanib 1L (N=78)	Placebo	2.9
Sunitinib 1L (N=375)	IFNα	5.0
Bevacizumab + IFNα 1L AVOREN (N=322)	IFNα	5.4
Bevacizumab + IFNα 1L CALGB 90206 (N=363)	IFNα	5.2
Pazopanib 2L (N=67)	Placebo	3.2
Sorafenib 2L(N=451)	Placebo	2.8

Table 24. Indirect HR estimates for Pazopanib relative to approved Agents

	Indirect HR	95% CI
Pazopanib vs IFNα 1L	0.50	(0.31,0.81)
Pazopanib vs Sunitinib 1L	0.93	(0.55,1.56)
Pazopanib vs Bevacizumab 1L	0.74	(0.45,1.21)
Pazopanib vs Sorafenib 2L	0.98	(0.61,1.58)

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

No studies have been submitted.

- Clinical studies in special populations

No studies have been submitted.

- Supportive studies

Supportive Study VEG102616

The supportive study VEG102616 included 225 patients with characteristics similar to the patient population of the pivotal study: patients with advanced RRC, treatment-naïve or patients who had progressed following one prior cytokine treatment. Furthermore, patients who had received prior treatment with bevacizumab were also allowed in this study.

The study was originally designed as a randomized discontinuation study with a 12-week unblinded lead-in phase, after which patients with CR or PR could continue unblinded pazopanib treatment, whereas patients with SD at Week 12 could be randomized to receive 12-week blinded treatment with pazopanib or placebo. A pre-planned interim analyses assessing the Week 12 SD rate for futility, showed a surprisingly high activity of pazopanib: For the first 60 subjects enrolled in the study, the SD rate at Week 12 was 47%. In an ad-hoc analysis, the RR was 32% per investigator assessment and 38% per IRC assessment. Based on these results, the design of the study was revised into an unblinded single-arm study. Following this change, the fact that 28 subjects had received placebo for various periods of time and might have had tumor enlargement during this time, had to be accounted for. Therefore, in the analysis of PFS rather unconventional statistical methods were used including Kalbfleisch-Prentice weighted Kaplan Meier analyses and bootstrap CIs.

The weighted analyses taking into account the 28 patients with SD at 12 weeks and randomized to placebo is a fair compensation when analysing the whole material as a phase II trial of continous pazopanib treatment. These analyses lend support to the pivotal trial regarding the overall results of pazopanib treatment. Moreover, the fact that PFS was much poorer in the 28 patients once they shifted to placebo lends further support to the efficacy of pazopanib.

Disease progression was the most common reason for discontinuation (57%).

In the weighted analysis undertaken to estimate PFS (adjusted for the effect of placebo, see Table 25), the median PFS was 11.9 months per IRC and 9.9 months per investigator assessment. These results are in line with the results of the pivotal study VEG105192 (9,2 (7.4; 12.9) months per IRC assessment.

Tumor response was a primary endpoint in this study: RR per IRC was 35% (95% CI: 28.4% to 40.9%), similar to that reported in the pazopanib arm of VEG105192 (30%). RR per investigator review was also similar (34% [95% CI: 27.6% to 40.0%].

The median duration of response was slightly higher than in the pazopanib arm of VEG105192: 68.0 weeks (95% CI, 53.7 weeks to not calculable) by IRC review and 71.1 weeks (95% CI, 48.4 to 87.7 weeks) by investigator review. The median time to response with pazopanib treatment was – like in study VEG105192 - 12 weeks.

No major differences were observed in the results originating from US-sites contra non-US sites.

In the 55 subjects randomized to either pazopanib or placebo treatment at Week 12, the results indicate that continuous treatment with pazopanib is needed in order to maintain efficacy as patients shifted to placebo displayed a marked drop in the PFS curves.

Figure 7 Subject Disposition (Study VEG102616)

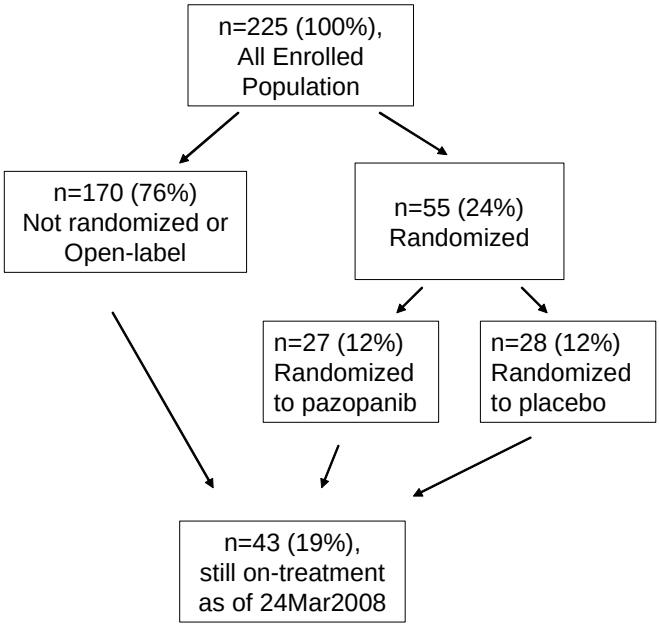


Table 25 PFS (VEG102616: All Enrolled Population)

	IRC	Investigator Assessment
Number of Subjects		
N	225	225
Progressed or Died, n(%)	109 (48)	142 (63)
Censored, Follow-up Endeda, n(%)	89 (40)	40 (18)
Censored, Follow-up Ongoingb, n(%)	27 (12)	43 (19)
Estimate for PFS (including subjects randomized to placebo) (months)c		
Median	10.4	8.5
95% CI	8.3 – 13.6	6.5 – 12.0
Estimate for PFS (adjusted for randomization to placebo) (months)c		
Median	11.9	9.9
95% CI	10.1 – 13.9	6.81 – 13.6

PFS: progression-free survival
a. Subjects were classified as censored, follow-up ended if their progression event occurred after a period of extended inadequate assessment or if they withdrew from the study prior to disease progression. This may have been because of premature withdrawal from the study due to adverse events, withdrawal of consent, etc. In addition, if the IRC did not determine disease progression but the investigator had, follow-up for progression would have stopped, leading to censoring with follow-up ended just for the IRC.
b. Subjects were classified as censored, follow-up ongoing if the subjects were still on-study and progression-free as their last disease assessment.
c. Months were calculated from weeks as displayed in the source data by multiplication by a factor of 0.23.

Supportive Study VEG107769

The supportive study VEG107769 was an unblinded extension study to the pivotal VEG105192 enrolling 71 subjects who had progressed on placebo in the pivotal study. The same enrolment criteria were applied. In addition subjects with an ECOG Performance Status of 2 were allowed inclusion. The primary objective was to assess the safety of pazopanib. Regarding the secondary endpoints, the median PFS was 8.3 months (95% CI: 6.1 to 11.4 months) per Investigator assessment only, the median OS was 16.8 months (16.3, NC) and the RR was 32% (see Table 26). These results are consistent with the results observed in the pivotal study.

Table 26 PFS (VEG107769: All Treated Subjects Population)

	Pazopanib (N=71)
Number (%) of subjects	
Progressed or died (event)	33 (46)
Censored, follow-up ended	9 (13)
Censored, follow-up ongoing	29 (41)
Kaplan-Meier Estimates for PFS (months)a	
1st Quartile (95% CI)	4.1 (2.0, 7.2)
Median (95% CI)	8.3 (6.1, 11.4)
3rd Quartile (95% CI)	12.0 (9.4, 16.1)

PFS: progression-free survival
a. PFS was defined as the time from the start of treatment until the date of disease progression or death due to any cause.

- Discussion on clinical efficacy

Votrient treatment should only be initiated by a physician experienced in the administration of anti-cancer agents. The recommended dose of pazopanib is 800 mg once daily. Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of pazopanib should not exceed 800 mg. Additional information on dosing in special population has been adequately addressed in section 4.2 of the SPC including the following statements:

Pazopanib is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment. Insufficient data are available in patients with mild hepatic impairment to provide a dose adjustment recommendation.

In the RCC studies of pazopanib, overall no clinically significant differences in safety of pazopanib were observed between subjects aged at least 65 years and younger subjects. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites (see section 5.2). Therefore, no dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population.

Pazopanib should be taken without food, at least one hour before or two hours after a meal (see section 5.2). Votrient film-coated tablets should be taken whole with water and not broken or crushed (see section 5.2).

In addition, overdose information has been included in section 4.9 of the SPC. Pazopanib doses up to 2,000 mg have been evaluated in clinical studies without dose-limiting toxicity. There is no specific antidote for overdose with pazopanib and treatment of overdose should consist of general supportive measures.

There is a need to gain more understanding about the efficacy of pazopanib in terms of its effect with respect to other available medicinal products for the same indication. In this regard further evidence is awaited and two specific obligations have been included as part of the conditional approval. The applicant has already initiated a non-inferiority Phase III randomised, controlled clinical study to evaluate the efficacy and safety of pazopanib versus the tyrosine kinase inhibibor sunitinib. In addition the applicant has agreed to perform a pooled analysis of data from study VEG108844 and study VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844) in order to provide robust clinical data to characterise the comparable efficacy and safety of pazopanib versus sunitinib. The combined analysis of the studies will be appropriately powered to demonstrate non-inferiority with a margin of 1.22 and a discussion on the applicability of the efficacy data from VEG113078 to the European population will be provided. The CHMP was of the opinion that a

step wise approach could be undertaken. Therefore should the upper bound of the 95% confidence interval for the Progression Free Survival hazard ratio fall at or below 1.22 in study VEG108844, the second pooled analysis could be considered an unnecessary specific obligation.

In addition, the Applicant has committed to submit final overall survival analyses from both the pivotal study VEG105192 and study VEG108844 comparing pazopanib versus sunitinib as a follow up measure.

Clinical safety

As of the cut-off date of 8 June 2008 for this submission, a combined total of 1645 subjects (including healthy volunteers, subjects with various solid tumors, and subjects with psoriasis or macular degeneration) have been exposed to pazopanib in clinical trials, including 16 monotherapy studies (including the 3 RCC), 6 pazopanib/lapatinib combination studies, 3 studies with healthy volunteers and special populations, 2 studies of psoriasis and macular degeneration, and 6 studies in combination with chemotherapy other than lapatinib.

The clinical database is comprised of the following subject populations:

- 586 subjects with RCC who received at least 1 dose of pazopanib 800 mg as monotherapy in the pivotal study VEG105192 (n=290) and supportive studies VEG102616 (n=225) and VEG107769 (n=71).
- 977 subjects from 11 of the 16 pazopanib monotherapy studies (including the 586 subjects from the 3 RCC studies) who were analyzed as a group for events of interest.
- 1155 subjects with RCC or other cancers who received as least 1 dose of pazopanib 800 mg (which includes the 586 subjects from the 3 RCC studies).
- 56 subjects from Phase I studies in healthy volunteers and elderly subjects who received at least 1 dose of pazopanib (ranged from 0.4 mg to 100 mg).
- 10 subjects with psoriasis (topical preparation of 0.1 to 1% pazopanib ointment; Phase I Study RES104031) and 15 subjects with age-related macular degeneration (AMD) (eye drop formulation of 2-5 mg/ml; Study MD7108240) who received at least 1 dose of pazopanib.

The safety population for VEG105192 comprised all subjects who received at least 1 dose of investigational product (for this study safety and ITT populations were identical for both pazopanib and placebo treatment groups). For the integrated analyses across RCC or monotherapy studies, the all-treated population comprised all subjects who received at least 1 dose of pazopanib.

Safety data from the 2 supportive RCC studies, VEG102616 and VEG107769 are based on clinical cut-off dates of 24 March 2008 and 23 May 2008, respectively. For the pivotal study VEG105192, the clinical cut-off date of 23 May 2008 was applied. Serious adverse event (SAE) data per the respective clinical cut-off dates as well as through the cut-off date of 8 June 2008 has been reported.

- Patient exposure

Overall, the median duration of exposure was approximately 7.4 months (including dose interruptions) for subjects receiving pazopanib in the RCC studies VEG105192, VEG102616, and VEG107769 (Table 24). Study VEG102616 was the first study of the three to be initiated and had a median exposure of approximately 8.4 months. Study VEG107769 was the last study to start and had a correspondingly shorter median exposure of 5.7 months as of the clinical cut-off date. Study VEG105192 had a median exposure of 7.4 months for the pazopanib arm.

For the 3 primary RCC studies, 24% of subjects were exposed to pazopanib for >6 months to 12 months and 32% were exposed for longer than 12 months (exposure including dose interruptions). Values calculated excluding dose interruptions were similar and are also displayed in Table 27.

Table 27 Summary of Exposure (Pazopanib-treated Subjects) in RCC Studies

	Subjects Receiving Pazopanib (N=586)
Duration of treatment (including dose interruptions) [a]	
Median (range), months	7.39 (0.07-27.60)
<3 months, n (%)	148 (25)
3-6 months, n (%	112 (19)
>6-12 months, n (%)	141 (24)
>12-18 months, n (%)	108 (18)
>18 months, n (%)	77 (13)
Duration of treatment (excluding dose interruptions)[a]	
Median (range), months	7.23 (0.07-30.03)
<3 months, n (%)	153 (26)
3-6 months, n (%)	110 (19)
>6-12 months, n (%)	142 (24)
>12-18 months, n (%)	113 (19)
>18 months, n (%)	68 (12)

a. Subject 62 participated in the VEG105192 and the VEG107769 studies (as Subject 117 in the latter study) and is counted twice in the exposure calculations.

- Adverse events

The most important serious adverse reactions were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation and pulmonary, gastrointestinal and cerebral haemorrhage, all adverse reactions being reported in < 1 % of treated patients (see Table 28).

Fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischemic stroke.

The most common adverse reactions (experienced by at least 10 % of the patients) of any grade included: diarrhoea, hair colour change, hypertension, nausea, fatigue, anorexia, vomiting, dysgeusia, elevated alanine aminotransferase and elevated aspartate aminotransferase.

Table 28. Treatment-related adverse reactions reported in RCC studies (n=586)

System Organ Class	Adverse Reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic disorders	Thrombocytopenia	25 (4 %)	3 (< 1 %)	3 (< 1 %)
	Neutropenia	17 (3 %)	4 (< 1 %)	2 (< 1 %)
	Leukopenia	14 (2 %)	1 (< 1 %)	0
Endocrine disorders	Hypothyroidism	23 (4 %)	0	0
Metabolism and nutrition disorders	Decreased appetite[e]	122 (21 %)	6 (1 %)	0
	Hypophosphataemia	4 (< 1 %)	2 (< 1 %)	0
	Hypomagnesaemia	3 (< 1 %)	0	0
Nervous system disorders	Dysgeusia[c]	92 (16 %)	0	0
	Headache	41 (7 %)	0	0
	Dizziness	19 (3 %)	0	1 (< 1 %)
	Lethargy	12 (2 %)	1 (< 1 %)	0
	Paraesthesia	12 (2 %)	2 (< 1 %)	0
	Peripheral sensory neuropathy	5 (< 1 %)	0	0
	Hypoaesthesia	4 (< 1 %)	0	0
	Transient ischaemic attack	3 (< 1 %)	2 (< 1 %)	0
	Cerebrovascular accident	1 (< 1 %)	0	1 (< 1 %)
	Ischaemic stroke	1 (< 1 %)	0	0

Eye disorders	Eyelash discolouration	3 (< 1 %)	0	0
Cardiac disorders	Bradycardia	3 (< 1 %)	0	0
	Cardiac dysfunction	4 (< 1 %)	1 (< 1 %)	1 (< 1 %)
	Myocardial infarction	2 (< 1 %)	0	2 (< 1 %)
	Myocardial ischaemia	1 (< 1 %)	1 (< 1 %)	0
Vascular disorders	Hypertension	225 (38 %)	34 (6%)	0
	Hot flush	11 (2 %)	0	0
	Flushing	5 (< 1 %)	0	0
	Haemorrhage	1 (< 1 %)	0	0
	Hypertensive crisis	1 (< 1 %)	0	1 (< 1 %)
Respiratory, thoracic and mediastinal disorders	Epistaxis	16 (3 %)	0	0
	Dysphonia	15 (3 %)	0	0
	Pulmonary embolism	4 (< 1 %)	1 (< 1 %)	3 (< 1 %)
	Haemoptysis	3 (< 1 %)	0	0
	Pulmonary haemorrhage	1 (< 1 %)	0	0
Gastrointestinal disorders	Diarrhoea	286 (49 %)	19 (3 %)	2 (< 1 %)
	Nausea	161 (27 %)	3 (< 1 %)	0
	Vomiting	89 (15 %)	7 (1 %)	1 (< 1 %)
	Abdominal pain[a]	60 (10 %)	8 (1 %)	0
	Dyspepsia	24 (4 %)	2 (< 1 %)	0
	Stomatitis	24 (4 %)	0	0
	Flatulence	20 (3 %)	0	0
	Abdominal distension	15 (3 %)	0	0
	Mouth ulceration	4 (< 1 %)	1 (< 1 %)	0
	Frequent bowel movements	3 (< 1 %)	0	0
	Gastrointestinal haemorrhage	3 (< 1 %)	1 (< 1 %)	0
	Rectal haemorrhage	3 (< 1 %)	1 (< 1 %)	0
	Large intestine perforation	2 (< 1 %)	1 (< 1 %)	0
	Mouth haemorrhage	2 (< 1 %)	0	0
	Enterocutaneous fistula	1 (< 1 %)	0	0
	Haematemesis	1 (< 1 %)	0	0
	Haematochezia	1 (< 1 %)	0	0
	Haemorrhoidal haemorrhage	1 (< 1 %)	0	0
	Ileal perforation	1 (< 1 %)	0	1 (< 1 %)
	Melaena	1 (< 1 %)	0	0
	Oesophageal haemorrhage	1 (< 1 %)	0	1 (< 1 %)
	Pancreatitis	1 (< 1 %)	0	0
	Peritonitis	1 (< 1 %)	0	0
	Retroperitoneal haemorrhage	1 (< 1 %)	0	0
	Upper gastrointestinal haemorrhage	1 (< 1 %)	0	0
Hepatobiliary disorders	Hepatic function abnormal	20 (3 %)	6 (1 %)	0
	Hyperbilirubinaemia	18 (3 %)	2 (< 1 %)	1 (< 1 %)
	Hepatotoxicity	5 (< 1 %)	3 (< 1 %)	0
	Jaundice	2 (< 1 %)	1 (< 1 %)	0
	Hepatic failure	1 (< 1 %)	0	1 (< 1 %)
	Hepatitis	1 (< 1 %)	1 (< 1 %)	0
Skin and subcutaneous disorders	Hair colour change	231 (39 %)	1 (< 1 %)	0
	Rash	52 (9 %)	3 (< 1 %)	0
	Alopecia	50 (9 %)	0	0

	Palmar-plantar erythrodysaesthesia syndrome	43 (7 %)	7 (1 %)	0
	Skin hypopigmentation	25 (4 %)	0	0
	Erythema	15 (3 %)	0	0
	Pruritus	13 (2 %)	0	0
	Skin depigmentation	13 (2 %)	0	0
	Dry skin	12 (2 %)	0	0
	Hyperhidrosis	9 (2 %)	0	0
	Photosensitivity reaction	7 (1 %)	0	0
	Skin exfoliation	7 (1 %)	0	0
	Rash vesicular	3 (< 1 %)	0	0
	Pruritus generalised	2 (< 1 %)	1 (< 1 %)	0
	Rash papular	2 (< 1 %)	0	0
	Plantar erythema	1 (< 1 %)	0	0
	Rash erythematous	1 (< 1 %)	0	0
	Rash generalised	1 (< 1 %)	0	0
	Rash macular	1 (< 1 %)	0	0
	Rash pruritic	1 (< 1 %)	0	0
Musculoskeletal and connective tissue disorders	Myalgia	15 (3 %)	2 (< 1 %)	0
	Muscle spasms	12 (2 %)	0	0
Renal and urinary disorders	Proteinuria	40 (7 %)	5 (< 1 %)	0
	Haemorrhage urinary tract	1 (< 1 %)	0	0
Reproductive system and breast disorders	Menorrhagia	1 (< 1 %)	0	0
	Metrorrhagia	1 (< 1 %)	0	0
	Vaginal haemorrhage	1 (< 1 %)	0	0
General disorders and administration site conditions	Fatigue	139 (24 %)	16 (3 %)	0
	Asthenia	41 (7 %)	8 (1 %)	0
	Mucosal inflammation	27 (5 %)	2 (< 1 %)	0
	Oedema[b]	19 (3 %)	0	0
	Chest pain	14 (2 %)	2 (< 1 %)	0
	Mucous membrane disorder	1 (< 1 %)	0	0
Investigations	Alanine aminotransferase increased	83 (14%)	28 (5 %)	4 (< 1 %)
	Aspartate aminotransferase increased	72 (12%)	17 (3 %)	3 (< 1 %)
	Weight decreased	38 (6 %)	2 (< 1 %)	0
	Blood creatinine increased	13 (2 %)	2 (< 1 %)	0
	Blood bilirubin increased	11 (2 %)	1 (< 1 %)	1 (< 1 %)
	White blood cell count decreased[d]	10 (2 %)	1 (< 1 %)	0
	Lipase increased	9 (2 %)	4 (< 1 %)	1 (< 1 %)
	Blood pressure increased	6 (1 %)	0	0
	Blood thyroid stimulating hormone increased	6 (1 %)	0	0
	Gamma-glutamyltransferase increased	6 (1 %)	1 (< 1 %)	1 (< 1 %)
	Hepatic enzyme increased	6 (1 %)	2 (< 1 %)	0
	Aspartate aminotransferase	5 (< 1 %)	2 (< 1 %)	0
	Blood urea increased	5 (< 1 %)	1 (< 1 %)	0
	Electrocardiogram QT prolonged	5(< 1 %)	1 (< 1 %)	0
	Blood amylase increased	4 (< 1 %)	0	0

	Blood glucose decreased	4 (< 1 %)	0	0
	Alanine aminotransferase	3 (< 1 %)	2 (< 1 %)	0
	Transaminase increased	3 (< 1 %)	1 (< 1 %)	0
	Blood pressure diastolic increased	2 (< 1 %)	0	0
	Thyroid function test abnormal	2 (< 1 %)	0	0
	Blood pressure systolic increased	1 (< 1 %)	0	0
	Liver function test abnormal	1 (< 1 %)	0	0

- Serious adverse event/deaths/other significant events

In the pivotal study VEG105192 serious adverse events (SAE) were reported for 24% of subjects in the pazopanib arm and 19% of subjects in the placebo arm (including fatal and non-fatal events). Diarrhea was the most frequent SAE in the pazopanib arm according to preferred term (n=6 [2.1%]). All other SAEs were reported for <2% in the pazopanib arm. More cases of SAEs of liver abnormalities, arterial/thrombotic events and hemorrhagic events were reported in the pazopanib arm compared with the placebo arm.

Thirty-four (12%) subjects in the pazopanib arm and 3 (2%) subjects in the placebo arm had SAEs, which to the investigator's opinion, were treatment-related. Treatment-related SAEs reported in 2 or more subjects in the pazopanib arm were diarrhea (2%), anemia (1%), hepatic function abnormal (≤1%), hepatotoxicity (1%), hypertension (<1%), and vomiting (<1%).

SAEs that lead to permanent discontinuation of investigational product were reported for 44 (15%) subjects in the pazopanib arm and 8 (6%) subjects in the placebo arm.

Overall in the RCC studies, the incidence of SAEs (including fatal and non-fatal events) was 27% for subjects receiving pazopanib. The most common SAE according to preferred term was diarrhea (9 subjects [2%]) as also observed in Study VEG105192. The pattern of SAEs observed for the RCC studies was similar to the most common events reported in VEG105192.

Across RCC studies, there were 76 (13%) subjects in the pazopanib group who had SAEs, which in the investigator's opinion, were treatment-related. This incidence is similar to the 12% rate of related SAEs observed in Study VEG105192. The SAEs reported by >1 subject, which were considered by the investigator to be treatment-related, were as follows with the percent incidence in parentheses: diarrhea (1%), vomiting (<1%), gastrointestinal hemorrhage (<1%), large intestine perforation (<1%), hepatotoxicity (<1%), hepatic function abnormal (<1%), jaundice (<1%), atrial fibrillation (<1%), myocardial infarction (<1%), ALT increased (<1%), AST increased (<1%), anemia (<1%), leukopenia (<1%), thrombocytopenia (<1%), pulmonary embolism (<1%), hypertension (<1%), and hyponatremia (<1%). A similar pattern of related SAEs was observed for Study VEG105192.

Deaths

As of the clinical cut-off date of 23 May 2008 for study VEG105192, a total of 176 subjects died during the study (67 in placebo arm, 109 in pazopanib arm). The primary cause of death in both treatment groups was cancer progression. Deaths due to disease progression were not to be reported as SAEs.

In this study the incidence of fatal SAEs was similar in the pazopanib group (4%) and the placebo group (3%), although, the causes of fatal events were not similar (see Table 29). Fatal SAEs were considered by the investigator to be related to investigational product for 4 of 9 subjects in the pazopanib arm and for none of 3 subjects in the placebo arm. The events considered treatment-related included abnormal hepatic function and rectal hemorrhage, abnormal hepatic function, peritonitis and ischemic stroke.

Table 29. Fatal Serious Adverse Events (Safety Population) in Study VEG105192

MedDRA preferred term	Number (%) of subjects	
	Placebo (n=145)	Pazopanib (n=290)
Any Fatal SAE	4 (3)	12 (4)
Preferred term		
Hemoptysis	0	2 (<1)
Hepatic function abnormal[a]	0	2 (<1)
Bronchopneumonia	0	1 (<1)
Cardiac failure	0	1 (<1)
Dyspnea	0	1 (<1)
Gastric hemorrhage	0	1 (<1)
Gastric cancer	0	1 (<1)
Ischemic stroke	0	1 (<1)
Myocardial ischemia	0	1 (<1)
Peritonitis	0	1 (<1)
Rectal hemorrhage[a]	0	1 (<1)
Acute pulmonary edema	1 (<1)	0
Asthenia	1 (<1)	0
Lower respiratory tract infection	1 (<1)	0
Sudden death	1 (<1)	0

a. Subject 160 died due to rectal bleeding with concurrent hyperbilirubinemia and AST/ALT elevation. The Investigator classified both rectal hemorrhage and hepatic function abnormal as Grade 5 events for this subject.

Overall for the RCC studies, the incidence of fatal SAEs was 3% for pazopanib-treated subjects as of the clinical cut-off date. Seven patients died due to SAEs that were considered related to pazopanib treatment by the investigators.

Events of Special Interest

Hypertension
In the pivotal study, subjects in the pazopanib arm had a 40% incidence of AEs of hypertension or worsening of hypertension compared with 10% in the placebo-group. Dose reductions because of AEs of hypertension were required in 21 pazopanib treated subjects versus 2 subjects in the placebo arm. Nevertheless, severe hypertension was rare in the pazopanib arm. The treatment-related hypertension therefore seems manageable and it's a well-known class-effect of VEGF-inhibitors.

QTc prolongations
In the pivotal study 3% of subjects in the pazopanib arm versus 2 % in the placebo arm had a post-baseline QTc value shift from < 480 msec at baseline to QTc values of 480-499 msec post-baseline. 3 pazopanib treated subjects developped a post-baseline QTc value of >500 msec. Only 1 subject had a manifest SAE of QT prolongation. However, one case of "Cardiac arrest" was reported in the pazopanib arm in study VEG105192. Across all RCC studies, 10 out of 558 subjects developed QTc prolongations > 500 msec (1.8%) and 1 case of "Sudden death" was observed in the group of pazopanib-treated subjects across RCC studies. Tables 30 and 31 summarise the results on QTc prolongations in study VEG105192 and across RCC studies, respectively.

Table 30 Summary of Maximum Shift Post-Baseline in Bazett's QTc from Baseline (Safety Population) in Study VEG105192

Treatment	Baseline Value (msec)	Number (%) of subjects				
		Post-Baseline (msec)				
		<450	450-479	480-499	≥500	Total
Placebo (n=145)						
	<450	115 (81)	16 (11)	0	0	131 (92)
	450-479	4 (3)	4 (3)	3 (2)	0	11 (8)
	Total	119 (84)	20 (14)	3 (2)	0	142 (100)
Pazopanib (n=290)						
	<450	207 (75)	33 (12)	5 (2)	1 (<1)	246 (89)
	450-479	14 (5)	9 (3)	4 (1)	1 (<1)	28 (10)
	480-499	1 (<1)	0	0	1 (<1)	2 (<1)
	Missing	1 (<1)	0	0	0	1 (<1)
	Total	223 (81)	42 (15)	9 (3)	3 (1)	277 (100)

Data Source: Study VEG105192 Table 8.57

Table 31 Summary of Maximum Shift Post-Baseline in Bazett's QTc from Baseline (Pazopanib-treated Subjects) in RCC Studies

Baseline Value (msec)	Pazopanib N=586, n (%)					
	Post-Baseline (msec)					
	<450	450-479	480-499	500-549	≥550	Total
Post-baseline n=558						
<450	442 (79)	55 (10)	7 (1)	5 (<1)	2 (<1)	511 (92)
450-479	21 (4)	14 (3)	5 (<1)	2 (<1)	0	42 (8)
480-499	1 (<1)	0	0	1 (<1)	0	2 (<1)
500-549	0	0	0	0	0	0
≥550	0	0	0	0	0	0
Missing	2 (<1)	1 (<1)	0	0	0	3 (<1)
Total	466 (84)	70 (13)	12 (2)	8 (1)	2 (<1)	558 (100)

Data Source: Integrated SCS Table 8.47

Cardiovascular events

Treatment with pazopanib was associated with an increased risk of vascular events, specifically arterial thromboembolic events: In the pivotal trial 10% in the pazopanib arm and 6% in the placebo arm experienced at least 1 cardiac and/or vascular AE. The exposure-adjusted incidence rates for all cardiac and vascular events were similar between the 2 arms: 11.99 [CI 7.55, 16.43] per 100 patient-years in the pazopanib arm compared with 10.22 [CI, 3.14, 17.30] in the placebo arm. In addition the exposure-adjusted incidence rate for Grade 5 events was higher in the placebo arm (1.28 vs. 2.55 per 100 patient-years). The exposure-adjusted incidence rates of non-vascular cardiac events and venous thromboembolic events were also similar between the 2 arms. In contrast, the exposure-adjusted incidence rate of arterial thromboembolic events was higher in the pazopanib arm compared to the placebo arm (3.85 [CI 1.33, 6.37] versus 0 ([CI could not be estimated] per 100 patient-years).

The overall rates of cardiac and vascular events were similar across RCC and monotherapy studies.

The applicant submitted updated information on cardiac safety following a report of congestive heart failure (CHF) received from a sarcoma trial that described positive dechallenge and rechallenge data, suggesting a causal association with pazopanib. This incident triggered a review of cardiac failure and related terms was carried out using the GSK Worldwide Safety Database Database (OCEANS). Twenty-one reports from pazopanib clinical trials were retrieved from the OCEANS database. In four reports, including the report describing the positive dechallenge and rechallenge, a causal association with pazopanib could not be excluded.

Hemorrhagic events

As for other inhibitors of angiogenesis, an increased incidence of hemorrhagic events was observed in pazopanib-treated patients: In the pivotal study the exposure-adjusted incidence rate of hemorrhagic events was 15.85 (CI 10.74, 20.96) per 100 patient-years in the pazopanib arm compared to 8.94 (CI 2.32, 15.56) in the placebo arm. The exposure-adjusted incidence rates of Grade 3, Grade 4 and

Grade 5 hemorrhagic events in the pazopanib arm were 1.28, 0.43 and 1.71 in the pazopanib arm compared with 0 in the placebo arm. The most common hemorrhagic events in the pazopanib arm were hematuria (n= 11, 4%), epistaxis (n= 5, 2%), hemoptysis (n= 5, 2%) and rectal hemorrhage (n= 4, 1%). 9 subjects in the pazopanib arm experienced serious hemorrhagic events (versus 2 in the placebo arm), out of which 3 events were considered possibly related to the study drug (retroperitoneal bleeding, hematuria and bleeding esophageal varices.

Across RCC studies and monotherapy studies a similar pattern was found. The nature of the hemorrhagic events was mainly dependent on the location of the primary tumour and associated metastases. Serious and potentially fatal hemorrhagic events were rare.

Thyroid function abnormalities
Changes in thyroid parameters, mainly increases in TSH, are a well-known adverse event and "class effect" that has been adequately addressed in the SmPC. In the pivotal study 32% of pazopanib treated patients experienced a TSH increase. Manifest hypothyroidism was only confirmed in 4% of patients.

Bowel Perforations and enteral fistulae
GI perforations or fistulae are rare but serious and potentially fatal adverse events of all inhibitors of angiogenesis. In study VEG105192, 1 subject in the pazopanib arm experienced a fatal SAE of gastrointestinal perforation and peritonitis which was considered related to investigational product. Two other subjects in the pazopanib arm had enteral fistulas: 1 subject had a Grade 1 anal fistula AE which was not considered related to investigational product and another subject experienced an enterocutaneous fistula of unknown grade, which was reported as an SAE and was considered related to investigational product. Neither subject was discontinued from investigational product treatment.

In the RCC population, 5 subjects (0.9%) suffered SAEs related to GI perforations or fistulae. The 5 events were described as follows: ileal perforation (n=1, [VEG102616]), large intestine perforation (n=2; [VEG102616]), peritonitis secondary to intestinal perforation (n=1, [VEG105192]), and enterocutaneous fistula (n=1, [VEG105192]). Two of these events (large intestine perforation, and peritonitis secondary to intestinal perforation) were fatal. One event of large intestinal perforation was associated with diverticulitis. Three events of perforation were related to underlying tumor.

Proteinuria
Proteinuria is a well-known AE related to VEGF inhibitors. The incidences of AEs of proteinuria were similar between Study VEG105192 (9%) and the combined RCC study populations (8%). Most cases of proteinuria were mild in severity, but discontinuations of pazopanib have been seen due to proteinuria. The applicant has provided recommendation for subjects who develop grade 4 proteinuria (nephrotic syndrome) (discontinuation). Proteinuria is included as an identified risk in the Risk Management Plan.

- Laboratory findings

Hematologic Assessments
In study V*EG105192* the worst case hematologic toxicity grade shift from baseline is displayed in Table 32. Most toxicity grade shifts were to Grade 1 or 2 in both groups. The incidences of leukopenia, neutropenia, and thrombocytopenia with any grade increase were 37%, 34% and 32%, respectively in the pazopanib arm, which were higher than in the placebo arm (6%, 6% and 5%, respectively). The incidences of grade increases in other hematologic parameters were similar in the pazopanib and placebo arms.

Post-baseline increases to Grade 3 in any hematologic parameter were uncommon in both treatment arms, occurring between <1% to 4% in the pazopanib arm. An increase to Grade 4 hematological toxicity was rare.

Table 32. Summary of Worst-case Hematologic Toxicity Grade Shift from Baseline (Safety Population) in Study VEG105192

Hematologic Toxicity	Number (%) of subjects							
	Placebo (n=145)				Pazopanib (n=290)			
	N	Any gradea	Grade 3	Grade 4	N	Any gradea	Grade 3	Grade 4
Leukopenia	144	9 (6)	0	0	280	103 (37)	0	0

Neutropenia	144	9 (6)	0	0	280	94 (34)	3 (1)	1 (<1)
Thrombocytopenia	144	7 (5)	0	1 (<1)	280	89 (32)	2 (<1)	1 (<1)
Lymphocytopenia	144	34 (24)	2 (1)	0	280	86 (31)	11 (4)	1 (<1)
Increased PTT	140	34 (24)	1 (<1)	0	271	72 (27)	4 (1)	0
Anemia	144	44 (31)	2 (1)	1 (<1)	280	62 (22)	5 (2)	2 (<1)
INR	128	25 (20)	2 (2)	0	246	42 (17)	4 (2)	0

Abbreviations: PTT= Partial thromboplastin time; INR= International Normalized ratio.
a. Any grade increase from baseline. Subjects with missing baseline grade were assumed to have baseline grade of 0.

For the RCC studies, most hematology abnormalities were of Grade 1-2 severity and Grade 4 toxicities were uncommon. The incidences of leukopenia, neutropenia, thrombocytopenia, lymphocytopenia, and anemia in the RCC subjects were similar to those observed in the pazopanib arm of Study VEG105192.

Chemistry Assessments
In Study VEG105192 the most common increases in any toxicity grade for clinical chemistry in the pazopanib arm which were higher than the incidences in the placebo arm were ALT, AST, and total bilirubin elevation, which occurred in 53%, 53% and 36% subjects, respectively; these rates were higher than the respective incidences in the placebo arm (22%, 19%, and 10%) (Table 33).

Other clinical chemistry parameters with a higher incidence in any grade shift in the pazopanib arm compared with the placebo arm included low phosphate (34% versus 11%), hypoglycemia (17% versus 3%), hypokalemia (9% versus 2%), and hypomagnesemia (26% versus 14%).

Overall, the majority of the toxicity grade shifts in clinical chemistry were to Grade 1 or Grade 2 in both arms. ALT and AST elevation and hypophosphatemia were the most common clinical chemistry parameters with increases to Grade 3 (10%, 7% and 4%, respectively) in the pazopanib arm where the rates were higher than in the placebo arm (1%, <1% and 0%, respectively). A toxicity grade shift of clinical chemistry parameters to Grade 4 was uncommon (2% or less for any individual lab test).

Table 33. Summary of Worst-Case Toxicity Grade Shift for Clinical Chemistry Parameters from Baseline (Safety Population) in Study VEG105192

Clinical Chemistry Parameter	Number (%) of subjects							
	Placebo (n=145)				Pazopanib (n=290)			
	N	Any gradea	Grade 3	Grade 4	N	Any gradea	Grade 3	Grade 4
ALT increase	144	32 (22)	2 (1)	0	289	152 (53)	30 (10)	5 (2)
AST increase	144	27 (19)	1 (<1)	0	288	152 (53)	21 (7)	2 (<1)
Hyperglycemia	144	47 (33)	2 (1)	0	280	115 (41)	2 (<1)	0
Total Bilirubin increase	144	15 (10)	2 (1)	1 (<1)	280	102 (36)	7 (3)	2 (<1)
Hyponatremia	144	35 (24)	6 (4)	0	280	86 (31)	11 (4)	4 (1)
Hypophosphatemia	141	16 (11)	0	0	276	95 (34)	11 (4)	0
Hypocalcemia	137	35 (26)	2 (1)	1 (<1)	272	91 (33)	4 (1)	4 (1)
Hyperkalemia	144	33 (23)	7 (5)	0	280	76 (27)	12 (4)	1 (<1)
Alkaline phosphatase	144	50 (35)	3 (2)	0	280	75 (27)	4 (1)	1 (<1)
Creatinine increase	144	36 (25)	1 (<1)	0	280	73 (26)	0	2 (<1)
Hypomagnesemia	141	20 (14)	0	0	276	72 (26)	2 (<1)	4 (1)
Hypoglycemia	144	4 (3)	0	0	280	47 (17)	0	1 (<1)
Hypermagnesemia	141	13 (9)	3 (2)	0	276	31 (11)	9 (3)	0
Hypernatremia	144	11 (8)	0	0	280	30 (11)	2 (<1)	0
Hypercalcemia	137	25 (18)	2 (1)	0	272	29 (11)	0	4 (1)
Hypokalemia	144	3 (2)	0	0	280	24 (9)	3 (1)	2 (<1)

a. Any grade increase from baseline.
Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase.

For Study VEG105192, routine urinalysis was performed at baseline and every clinical visit using dipstick for urine protein, red blood cells and glucose. There were no significant changes in urine red blood cells and glucose levels from baseline in both arms. There was an apparent increase in the urine protein level from baseline in the pazopanib arm compared with the placebo arm.

Overall for the RCC studies, most clinical chemistry abnormalities were of Grade 0-2 severity. Similar to Study VEG105192, Grade 4 events for any of the analytes were infrequent (<1%). The incidence of chemistry laboratory abnormalities in RCC subjects was similar to the rates observed in the pazopanib arm of VEG105192.

- Safety in special populations

In clinical trials with pazopanib for the treatment of RCC, 196 subjects (33%) were aged ≥65 years, and 34 subjects (6%) were aged >75 years. No overall differences in the safety of pazopanib treatment were observed between these subjects and younger subjects. No differences in the safety profile, as assessed by AEs, SAEs, and hepatic enzyme laboratory abnormalities were noted based on gender. No safety concerns appear to be correlated with race.

- Safety related to drug-drug interactions and other interactions

Studies evaluating the safety of pazopanib in the presence of other chemotherapy agents were conducted. Studies VEG10006 and VEG102857 were conducted to evaluate the drug-drug interactions of pazopanib with lapatinib and Study VEG105427 was conducted to evaluate the drug-drug interactions of pazopanib with paclitaxel (data not shown).

- Discontinuation due to adverse events

For Study VEG105192, AEs leading to permanent discontinuation of investigational product were reported for 44 (15%) subjects in the pazopanib arm and 8 (6%) subjects in the placebo arm, respectively. In the pazopanib arm, AEs associated with liver function/enzyme abnormalities (including increased ALT, AST, hepatotoxicity, increased hepatic enzyme and hyperbilirubinemia) led to discontinuation of investigational product for 11 (3.8%) subjects. Dose modification rules in the original protocol included guidelines to discontinue study drug for recurrent AST or ALT Grade ≥2 following 1 dose reduction. There were no specific criteria for bilirubin elevations. These were the rules in effect when most subjects were discontinued for transaminase elevations. The stopping rules were subsequently modified in Amendment 5 of the protocol (after all subjects had been enrolled) to include stopping for any AST/ALT >8xULN or for AST/ALT >3x ULN in the presence of hypersensitivity symptoms or concomitant bilirubin elevation to ≥2xULN.

In the pazopanib arm, diarrhea led to discontinuation of investigational product for 6 (2%) subjects. For 3 of the 44 subjects in the pazopanib arm with AEs leading to discontinuation, the investigator indicated that the reason for discontinuation was 'other' since the investigator considered that disease progression also contributed to discontinuation.

Across RCC studies, 86 (15%) pazopanib-treated subjects experienced AEs leading to discontinuation or withdrawal from study. The most common AE leading to discontinuation was ALT increased (10 subjects, 2%). The next most common AEs leading to discontinuation or withdrawal were diarrhea, AST increased, and asthenia. AEs associated with liver function/enzyme abnormalities led to discontinuation of investigational product for 23 (3.9%) subjects. This is a similar pattern as observed for Study VEG105192. Comparison of treatment-naïve subjects with subjects reporting at least 1 prior systemic therapy revealed no trend for differences in the incidence of AEs leading to investigational product discontinuation.

In the pivotal study more subjects in the pazopanib arm compared to the placebo arm had AEs that led to dose reductions (24% versus 3%). The most common AEs that led to dose reductions were hypertension and diarrhea. There were also more AEs leading to dose interruptions in the pazopanib arm (33%) versus 9% in the placebo arm. The most common events that led to dose interruptions were also transaminase liver enzyme elevations, diarrhea and hypertension.

- Post marketing experience

No studies have been submitted.

- Discussion on clinical safety

Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. The safety and pharmacokinetics of pazopanib have not been fully established in patients with pre-existing hepatic

impairment, therefore administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. In addition, in clinical studies with pazopanib, increase in serum transaminases (ALT, AST) and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin.

Monitor serum liver tests should be performed before initiation of treatment with pazopanib and at least once every 4 weeks for the first 4 months of treatment, and as clinically indicated. In addition periodic monitoring should then continue after this time period. Patients with isolated transaminase elevations ≤ 8 X upper limit of normal (ULN) may be continued on pazopanib with weekly monitoring of liver function until transaminases return to Grade 1 or baseline. Patients with transaminases of > 8 X ULN should have pazopanib interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks (see section 4.2). Following reintroduction of pazopanib, if transaminase elevations > 3 X ULN recur, then pazopanib should be discontinued. If transaminase elevations > 3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, bilirubin fractionation should be performed. If direct (conjugated) bilirubin is > 35 % of total bilirubin, pazopanib should be discontinued.

To address hepatic safety concerns a contraindication (section 4.3) and warnings (section 4.4) have been included in the SPC.

Blood pressure should be well controlled prior to initiating pazopanib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. Hypertension occurs early in the course of treatment (88 % occurring in first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the pazopanib dose may be reduced. Temporary suspension is recommended in patients if hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction. Pazopanib treatment may be resumed once hypertension is appropriately controlled. Warnings have been included in section 4.4 of the SPC.

In clinical studies with pazopanib, events of QT prolongation and Torsade de Pointes have occurred. Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrythmics or other medicinal products that may prolong QT interval and those with relevant pre-existing cardiac disease. When using pazopanib, base line and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within normal range is recommended and appropriate warnings have been included in section 4.4 of the SPC.

Myocardial infarction, ischemic stroke, and transient ischemic attack have been observed in clinical studies with pazopanib. Therefore, pazopanib should be used with caution in patients who are at increased risk for any of these events. A treatment decision should be made based upon the assessment of individual patient's benefit/risk. Warnings have been included in section 4.4 of the SPC.

In clinical studies with pazopanib haemorrhagic events have been reported. Pazopanib is not recommended in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal (GI) haemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of haemorrhage. Warnings have been included in section 4.4 of the SPC.

Events of GI perforation or fistula have also occurred in clinical studies with pazopanib. Pazopanib should therefore be used with caution in patients at risk for GI perforation or fistula. No formal studies on the effect of pazopanib on wound healing have been conducted however. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgement of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence. The safety and pharmacokinetics of pazopanib in patients with moderate to severe heart failure has not been studied. Warnings addressing these risks have been included in section 4.4 of the SPC.

In clinical studies with pazopanib, events of hypothyroidism have occurred. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of pazopanib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on pazopanib treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice. In addition, proteinuria has been reported. Baseline and periodic urinanalysis during treatment is recommended and patients should be monitored for worsening proteinuria. Pazopanib

should be discontinued if the patient develops Grade 4 proteinuria. Warnings for hypothyroidism and proteinuria have been included in section 4.4 of the SPC.

No studies on the effects on the ability to drive and use machines have been performed. A detrimental effect on such activities cannot be predicted from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of pazopanib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired or weak as stated in section 4.7 of the SPC.

Pazopanib should not be used in patients with hypersensitivity to the active substance or to any of the excipients and a contraindication has been included in section 4.3 of the SPC.

Warnings have been included in section 4.4 of the SPC providing special warning on interactions. Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib. In addition selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BCRP should be considered. Concomitant treatment with inducers of CYP3A4 should also be avoided due to risk of decreased exposure to pazopanib. Concomitant administration of pazopanib with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan) should be undertaken with caution since pazopanib is an inhibitor of UGT1A1. Finally, grapefruit juice should be avoided during treatment with pazopanib.

As stated in section 5.3 of the SPC, there are no adequate data from the use of pazopanib in pregnant women and the potential risk for humans is unknown. Pazopanib should not be used during pregnancy unless the clinical condition of the women requires treatment. If pazopanib is used during pregnancy, or if the patient becomes pregnant while receiving pazopanib, the potential hazard to the foetus should be explained to the patient. Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with pazopanib. In addition, the safe use of pazopanib during lactation has not been established. It is not known whether pazopanib is excreted in human milk and a risk to the suckling child cannot be excluded. Breast feeding should be discontinued during treatment with pazopanib.

In addition, the applicant will provide additional information on the safety of pazopanib as part of post-authorisation commitments. Agreed follow up measures include: the final study report for study VEG113971 (an open-label study in cancer patients to evaluate the effects of ketoconazole and the effects of increased gastric pH on the pharmacokinetics of orally administered pazopanib), the full protocol for post marketing hepatic monitoring (WEUKSTV4601) addressing the time period for accrual of pazopanib patients in PHARMO RLS and determining the comparability of data from this system with data collected outside the EU, and the full protocol for post marketing monitoring of cardiovascular outcomes (WEUKSTV4602) including analysis of the potential increased risk that could be detected after 4 years of monitoring and whether, in addition to comparing incidence rates with other VEGF inhibitors, a comparison to those from pazopanib clinical trials would provide meaningful data.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hepatic dysfunction	Routine proactive pharmacovigilance activities Utilising oncology-specific electronic medical record epidemiological databases, to monitor the rates of liver chemistry abnormalities in pazopanib users.	ALT increased, AST increased, blood bilirubin increased, hyperbilirubinaemia, and hepatic function abnormal are included as adverse events in SmPC Section 4.8 (Undesirable Effects). SmPC Section 4.4 (Special Warnings and Precautions for Use) will include guidance on the frequency of periodic monitoring of LFTs when isolated transaminase elevations occur, and when transaminase and bilirubin elevations are observed concurrently. Increase in enzymes produced by the liver is included as adverse event in the package leaflet.
Pulmonary haemorrhage	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will caution that pazopanib is not recommended in patients who had a history of haemoptysis in the past six months, and recommend that pazopanib be used with caution in patients with a significant risk of haemorrhage.
GI bleeding	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will caution that pazopanib is not recommended in patients who had a history of clinically significant GI bleeding in the past six months, and recommend that pazopanib be used with caution in

		patients with a significant risk of haemorrhage.
Cerebral haemorrhage	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will caution that pazopanib is not recommended in patients who had a history of cerebral haemorrhage in the past six months, and recommend that pazopanib be used with caution in patients with a significant risk of haemorrhage.
GI perforation and fistula	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will recommend that pazopanib should be used with caution in patients at risk for GI perforation or fistula.
Cardiac arrhythmias	Routine pharmacovigilance	No specific risk minimisation activities are proposed. Please see below regarding QT effects, including torsade de pointes.
Cardiac ischaemia	Routine pharmacovigilance Utilising epidemiological healthcare insurance claims databases to monitor cardiac ischaemic events (MI, angina).	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will recommend that pazopanib should be used with caution in patients at risk for cardiac ischaemic events such as MI.
Cerebrovascular ischaemic events	Routine pharmacovigilance Utilising epidemiological healthcare insurance claims databases to monitor cerebrovascular ischaemic events (CVA, TIA).	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will recommend that pazopanib should be used

		with caution in patients at risk for cerebrovascular ischaemic events such as ischaemic stroke and TIA.
Venous thromboembolic events	Routine pharmacovigilance	No specific risk minimisation activities are proposed.
Hypertension	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will caution that BP should be well controlled prior to initiating pazopanib, and provide guidance on pazopanib treatment when hypertension is present despite anti-hypertensive therapy.
Hypothyroidism	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will recommend monitoring of thyroid function tests at baseline and periodically.
Diarrhoea	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Fatigue/Asthenia	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Hypoglycaemia	Routine pharmacovigilance	Blood glucose increased is included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are

		proposed.
Impaired Healing	Routine pharmacovigilance	SmPC Section 4.4 (Special Warnings and Precautions for Use) will recommend treatment with pazopanib be stopped 7 days prior to scheduled surgery, and that resumption of treatment should be based on clinical judgement of adequate wound healing. No additional risk minimisation activities are proposed.
Proteinuria	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will recommend baseline and periodic urinalyses during pazopanib treatment, and treatment discontinuation if Grade 4 proteinuria develops. No additional risk minimisation activities are proposed.
Thrombocytopenia	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Leukopenia and Neutropenia	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Cardiac dysfunction	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No specific risk minimisation activities are proposed.
Inhibition of p-gp and BCRP	Routine pharmacovigilance	The effects attributed to inhibition of p-gp and BCRP

by co-administered drugs		when lapatinib was co-administered with pazopanib will be included in SmPC Section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) and package leaflet.
Interaction with substrates of cytochrome P450	Routine pharmacovigilance	The effects of pazopanib on cytochrome P450 substrates will be included in SmPC Section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) and package leaflet.
Interaction of pazopanib with inhibitors of CYP3A4	Routine pharmacovigilance	The effects of CYP3A4 inhibitors on pazopanib, and a recommendation to either avoid the use of strong CYP3A4 inhibitors or use a concomitant medication with no or minimal potential to inhibit CYP3A4, will be included in SmPC Sections 4.2 (Posology and Method of Administration) and 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will include the recommendation to avoid the use of strong CYP3A4 inhibitors, and cross-reference SmPC Sections 4.2 and 4.5.
Food effect	Routine pharmacovigilance	The effect of either a high fat or low fat meal on pazopanib will be described in SmPC Section 4.5 (Interaction with Medicinal Products and Other Forms of Interaction). The recommendation to take pazopanib without food, at least one hour before or two hours after a meal, will be included in SmPC Section 4.2 (Posology and Method of Administration) and package leaflet.
Concomitant treatment with inducers of CYP3A4	Routine pharmacovigilance	The recommendation to avoid concomitant treatment with inducers of CYP3A4 due to risk of decreased exposure to pazopanib will be included in SmPC Section 4.4. (Special Warnings and Precautions for

		Use). A statement that CYP3A4 inducers may decrease pazopanib plasma concentrations, and a recommendation to use a concomitant medication with no or minimal enzyme induction potential, will be included in SmPC Section 4.5 (Interactions with Medicinal Products and Other Forms of Interaction).
Interactions with substrates of p-gp and BCRP	Routine pharmacovigilance	A statement that in vitro studies suggested pazopanib is a substrate for p-gp and BCRP will be included in SmPC Section 5.2 (Pharmacokinetic Properties).
Interactions related to inhibition of OATP1B1 by pazopanib	Routine pharmacovigilance	Statements that in vitro studies showed pazopanib inhibits OATP1B1, and that it cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g. rosuvastatin) will be included in SmPC Section 4.5 (Interactions with Medicinal Products and Other Forms of Interaction).
Reproductive effects	Routine pharmacovigilance	SmPC Section 4.4 (Special Warnings and Precautions for Use) will caution that if pazopanib is used during pregnancy, or if the patient becomes pregnant whilst using pazopanib, the potential harm to the foetus should be explained to the patient. Similarly, the package leaflet will recommend that a patient who is pregnant or considering pregnancy should talk with her doctor about the risks and potential benefits of taking pazopanib during pregnancy. SmPC Section 4.6 (Pregnancy and Lactation) and the package leaflet will indicate that women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant whilst taking pazopanib. Additionally, these will

		indicate that as the safe use of pazopanib during lactation has not been established, and as it is not known if pazopanib is excreted in human milk, breast feeding should be discontinued during pazopanib treatment. SmPC Section 5.3 (Preclinical Safety Data) will include foetal teratogenic effects observed during preclinical studies with pazopanib.
Potential for carcinogenicity	Routine pharmacovigilance Two-year carcinogenicity studies in rats and mice will be conducted in the future to determine a potential for carcinogenicity.	SmPC Section 5.3 (Preclinical Safety Data) will indicate that although definitive carcinogenicity studies with pazopanib have not been performed, proliferative lesions in the liver were observed during preclinical studies in mice.
Adult Off-Label Use	Routine pharmacovigilance	SmPC Section 4.1 (Therapeutic Indications) will indicate that pazopanib is indicated for the treatment of advanced RCC. Additionally, SmPC Section 4.2 (Posology and Method of Administration) will state that treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.
Paediatric Off-Label Use	Routine pharmacovigilance	SmPC Section 4.2 (Posology and Method of Administration) will indicate that pazopanib is not recommended for use in children and adolescents under 18 years of age due to insufficient data on safety and efficacy.
Use in patients with hepatic dysfunction	Routine pharmacovigilance Ongoing NCI study 8063 will establish recommendations for use in patients with mild to severe hepatic dysfunction.	SmPC Section 4.2 (Posology and Method of Administration) will include a statement that the safety and pharmacokinetics of pazopanib in patients with hepatic impairment have not been fully established, and cross-reference SmPC Section 4.4 (Special Warnings and Precautions for Use). It will also indicate that insufficient data are available to provide a dose adjustment

		recommendation for patients with mild hepatic impairment, and include the recommended dose of 200 mg pazopanib daily for patients with moderate hepatic impairment. SmPC Section 4.3. (Contraindications) will indicate that pazopanib is not recommended for patients with severe hepatic impairment. SmPC Section 4.4 (Special Warnings and Precautions for Use) will caution about the use of pazopanib in patients with pre-existing hepatic impairment.
QT effects, including torsade de pointes	Routine pharmacovigilance Utilising epidemiological healthcare insurance claims databases to monitor events of torsade de pointes. Study VEG111485 will establish if pazopanib has an effect on cardiac conduction.	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) will recommend that pazopanib should be used with caution in patients who have a history of QT interval prolongation, are taking antiarrhythmics or other medications that may prolong QT interval, or have a relevant pre-existing cardiac disease. Additionally, there will be a recommendation that baseline and periodic monitoring of ECGs and electrolytes should be performed when using pazopanib.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The preclinical safety profile of pazopanib was assessed in mice, rats, rabbits and monkeys. In repeat dose studies in rodents, effects in a variety of tissues (bone, teeth, nail beds, reproductive organs,

haematological tissues, kidney and pancreas) appear related to the pharmacology of VEGFR inhibition and/or disruption of VEGF signalling pathways with most effects occurring at plasma exposure levels below those observed in the clinic. Other observed effects include body weight loss, diarrhoea and/or morbidity that were either secondary to local gastrointestinal effects caused by high local mucosal medicinal product exposure (monkeys) or pharmacologic effects (rodents). Proliferative hepatic lesions (eosinophilic foci and adenoma) were seen in female mice at exposures 2.5 times human exposure based on AUC.

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures more than 300-fold lower than the human exposure (based on AUC). Effects included reduced female fertility, increased pre- and post-implantation loss, early resorptions, embryo lethality, decreased foetal body weight and cardiovascular malformation. Decreased corpora lutea, increased cysts and ovarian atrophy have also been noted in rodents. In a rat male fertility study, there was no effect on mating or fertility, but decreased testicular and epididymal weights were noted with reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at exposures 0.3 times human exposure based on AUC.

Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat in vivo micronucleus). A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance in low amounts, was not mutagenic in the Ames assay but genotoxic in the mouse lymphoma assay and in vivo mouse micronucleus assay.

Carcinogenicity studies with pazopanib have not been performed.

Efficacy

The efficacy of pazopanib in RCC was evaluated in a Phase III, randomized, double-blind, placebo-controlled multi-centre study. A total of 435 patients with advanced RCC who had not received prior systemic treatment or who had only received prior cytokine treatment for advanced disease were randomized to receive pazopanib 800 mg once daily or placebo. There are no comprehensive data on the benefits in patients who have previously received systemic treatments other than with cytokines. The benefits of pazopanib were shown in terms of a statistically significant increased PFS as primary endpoint (median PFS 9.2 vs. 4.2 months, hazard ratio HR=0.46, 95% CI 0.34-0.62; p<0.0000001). In addition secondary endpoints showed an increased overall response rate of 30% in the pazopanib arm (95% CI, 25.1 to 35.6) vs. 3% in the placebo arm (95% CI, 0.5 to6.4) 95% CI; p <0.001) and a duration of response of 58.7 weeks in the pazopanib arm (95% CI, 52.1 to 68.1 weeks). The median time to response with pazopanib treatment was 11.9 weeks. The analysis of PFS and response was based on disease assessment by independent radiological review in the entire study population.

From the total of 435 patients in this study, 233 patients were treatment naïve and 202 patients who had received one prior IL-2 or INFα-based therapy. The median PFS in the treatment-naïve subgroup is slightly longer at 11.1 months compared to the median PFS for the cytokine-pretreated subgroup that is 7.4 months (hazard ratio for the naïve subgroup HR=0.4 95%CI (0.27,0.6) vs. hazard ratio for the cytokine-pretreated subgroup HR=0.4 95%CI (0.35,0.84).

At the time of the analysis for the primary endpoint, the overall survival data were not sufficiently mature, however a trend has been shown in terms of improved overall survival in the pazopanib arm compared with the placebo arm (HR 0.73; 95% CI: 0.53, 1.00; 99.16% CI: 0.47, 1.12; p=0.020).

No statistical differences were observed between treatment groups for Global Quality of Life using EORTC QLQ-C30 and EuroQoL EQ-5D.

Safety

A total of 1645 subjects have been exposed to pazopanib in clinical trials, including 16 monotherapy studies, 12 studies in combination with chemotherapy, 3 studies with healthy volunteers and special populations and 2 studies of psoriasis and macular degeneration.

Pooled data from 586 subjects the pivotal RCC study (VEG105192, n=290), extension study (VEG107769, n=71) and the supportive Phase II study (VEG102616, n=225) was evaluated in the overall evaluation of safety and tolerability of pazopanib (total n=586) in subjects with RCC. Overall, the median duration of exposure was approximately 7.4 months (including dose interruptions).

The most common adverse reactions of any grade included diarrhoea (49%), hair colour change (39), hypertension (38%), nausea (27%), fatigue (24%), anorexia (21%), vomiting (15%), dysgeusia (16%), elevated alanine aminotransferase and elevated aspartate aminotransferase (14% and 12% respectively) and abdominal pain (10%). Based on indirect comparisons, there are some events that appear to occur with a higher frequency for the approved agents (rash, mucositis, hand and foot syndrome (HFS)) while others occur with a higher frequency with pazopanib (high grade ALT elevations, all-grade hypertension and hair discoloration).

The most important serious adverse reactions were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation and pulmonary, gastrointestinal and cerebral haemorrhage, all adverse reactions being reported in < 1 % of treated patients.

Four fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischemic stroke.

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

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

Pazopanib has been shown to be an effective drug for patients with advanced renal cell carcinoma, both naïve and cytokine-pretreated. The difference in median PFS of about 5 months compared to placebo was found statistically significant and it is considered clinically relevant.

The choice of placebo as comparator in the pivotal trial was an initial concern supported by two centralised scientific advices (initial and clarification) given by the CHMP recommending the conduction of a study with an active comparator. Although cytokine-based therapy (IFN-α, IL-2) was generally accepted as the treatment of choice at the time this trial was initiated, the CHMP acknowledged that cytokine-based therapy was not considered the standard of care in many countries due to its limited efficacy and excessive toxicity. At the time of submission of this application however, several new therapies were available for patients with advanced RCC (including the anti-VEGF antibody bevacizumab, tyrosine kinase inhibitors such as sorafenib and sunitinib, and mTOR inhibitors such as temsirolimus and everolimus). Therefore, the CHMP was of the opinion that even though in the specific case of pazopanib it has been shown that the product is effective, an active comparator with other TKI inhibitors was necessary in order to rule out that the use of pazopanib would mean a loss of opportunity for the patients. Analysis of historical data including a qualitative comparison and discussion of biases has been provided by the applicant, however the data itself were not considered to provide conclusive evidence.

The safety profile of pazopanib was overall similar to other marketed TKIs and inhibitors of angiogenesis and a consistent pattern was demonstrated across all RCC studies. Most of the toxicities are manageable including diarrhoea, hair colour change, hypertension, nausea, fatigue, anorexia, vomiting, dysgeusia, elevated alanine aminotransferase and elevated aspartate aminotransferase and abdominal pain as the most frequent, but serious and potentially fatal SAEs can occur (transient ischaemic attack, ischaemic stroke, myocardial ischaemia, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation and pulmonary, gastrointestinal and cerebral haemorrhage). Fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischemic stroke. In conclusion, no new safety concerns have been identified, however of particular importance is the fact that pazopanib inhibits the same targets as other TKIs with a different potency and selectivity leading to differences in the safety profiles.

As per CHMP request, an oncology Scientific Advisory Group (SAG) meeting was convened on 8 January 2010 to discuss the benefits/risks of pazopanib from a clinical perspective and whether it was possible to rule out with reasonable certainty that pazopanib could be associated with the risk of a clinically relevant loss in terms of efficacy or safety compared to currently approved agents in this indication. The SAG provided advice on the following questions raised by the Committee:

1. Please discuss from a clinical perspective the benefit and risk of pazopanib in advanced RCC on the basis of the Rapporteurs' reports and the data presented by the applicant (pivotal study VEG105192).

The SAG unanimously agreed that from a clinical perspective the benefits particularly in terms of PFS as observed from the main results of the pivotal Phase III Study VEG105192 compared favorably against the toxicity, which was considered as generally manageable and overall acceptable compared to the benefits.
It is important to note that the data presented refer to patients who have had no or only cytokine-based treatment for advanced RCC. There are no comprehensive data on the benefits and risks of pazopanib in patients who have previously received systemic treatments other than with cytokines. In the absence of relevant data, no benefit-risk assessment for pazopanib can be made for patients pretreated with other systemic treatments (including TKI inhibitors, mTOR inhibitors or a combination of cytokines and anti-VEGF).

2. Please discuss how appropriate choice of therapy can be made in clinical practice in the light of the current data about efficacy and safety of pazopanib and the currently approved agents. Is further information needed in order to make an appropriate choice of therapy?
Currently, there are no direct comparative data to allow an accurate estimation of the differences between available treatments for first-line treatment of advanced RCC. In the absence of direct comparative data, indirect comparisons based in particular on the individual safety profiles can guide the clinical choice among different agents that have shown a high activity in this setting. Based on indirect comparisons, there are some events that occur with a higher frequency for the approved agents (rash, mucositis, HFS) while others occur with a higher frequency with pazopanib (high grade ALT elevations, all-grade hypertension and hair discoloration). There may be other factors such as route of administration and other preferences that will play a role.
Although this should not be a prerequisite for approval, it is important that comparative studies are conducted, and that these are adequately powered to detect small differences (in either direction) in terms of efficacy, and that they allow a thorough exploration of any important differences in terms of toxicity. It should be assessed if the ongoing comparative study of pazopanib versus sunitinib fulfills these requirements. Although this was not extensively presented, a non-inferiority design and a delta of >2 months difference in median PFS may not be the ideal design to detect small treatment differences. The statistical considerations, including power, sample size and design of this study should be carefully assessed.

3. Please discuss the relevance and acceptability of the applicant's inter-trial comparison for the assessment of the benefit and risk of pazopanib in advanced RCC as compared to other TKIs.

The inter-trial comparisons presented are relevant and useful to put the data into a clinical and historical perspective. However, it is impossible to draw any firm conclusions because the historical comparison includes studies with different populations, prognosis, etc.

4. With the available information about pazopanib and the currently approved agents, is it possible to rule out with reasonable certainty a risk of clinically relevant loss in terms of efficacy or safety when using pazopanib in the claimed indication compared to currently approved agents in this indication? What is the strength of evidence for the conclusions? What would be the magnitude of such loss?

The SAG agreed that a major loss in efficacy (e.g., several months of difference in median PFS or OS) or safety appears unlikely to be associated to pazopanib compared to other available treatment options. The basis of evidence for this assumption is the clear benefit of pazopanib and acceptable toxicity as observed in a well-conducted randomised controlled trial against placebo, as well as indirect comparisons and expert clinical judgement. However, the available data do not allow drawing any firm conclusions. An adequately powered study should be conducted post-approval to formally assess any differences in efficacy and allow a thorough exploration of important differences in toxicity (see also answer to Question 2). According to some members, the clinical documentation was not considered to be comprehensive in the absence of an active-controlled study, and argued that this study was considered essential to confirm the benefit-risk balance and should be conducted as part of a specific obligation in a conditional marketing authorisation.

The CHMP considered the data submitted by the applicant and the argumentation put forward by the applicant and the SAG experts. The CHMP considered that the benefit-risk balance for pazopanib was

positive. There is a need however to obtain further data of the efficacy and safety in the context of an adequate active comparator to allow an accurate estimation of the differences between available treatments. The CHMP acknowledged that the pivotal trial was at a very advanced stage at the time when other TKI therapies were approved and that the trial was started at a time when useful comparators were not available. Thus, the CHMP proposed a conditional marketing authorisation, after having consulted the applicant. The CHMP considered that pazopanib is an orphan medicinal product which aims at the treatment of a life-threatening disease, and therefore falls within the scope of Regulation (EC) No 507/2006.
In connection with the review of the orphan designation criteria by the Committee on Orphan Medicinal Products (COMP) at its meeting of 7-8 April 2010, the Applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products on 7 April 2010.
As a consequence, the CHMP considered at its April CHMP meeting that Votrient still falls within the scope of Regulation (EC) No 507/2006, i.e. under Article 2(1) – medicinal product which aims at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases and issued a revised opinion recommending the granting of conditional Marketing authorisation.

In addition the CHMP considered that pazopanib fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

a) Efficacy in terms of PFS prolongation has been demonstrated in a pivotal Phase III, randomized, double-blind, placebo-controlled multi-centre study conducted in advanced renal cell carcinoma patients. Overall, a delay of the median time to progression of about 5 months was observed. A favourable effect of pazopanib was also observed in terms of secondary endpoints including overall response rate and duration of response. Treatment with pazopanib was associated with manageable toxicity including diarrhoea, hair colour change, hypertension, nausea, fatigue, anorexia, vomiting, dysgeusia, elevated alanine aminotransferase and elevated aspartate aminotransferase and abdominal pain. These concerns do not constitute blocking issues for an anti-cancer compound in this indication. Therefore, the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

b) There is a need to gain more understanding about the benefit-risk profile of pazopanib in the context of other available medicinal products for the same indication. In this regard the applicant has already initiated a non-inferiority Phase III randomised, controlled clinical study to evaluate the efficacy and safety of pazopanib versus the tyrosine kinase inhibibor sunitinib. The applicant has agreed to perform a pooled analysis of data from study VEG108844 and study VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844) in order to provide robust clinical data to compare the efficacy and safety of pazopanib versus sunitinib. The studies will be appropriately powered to demonstrate non-inferiority with a margin of 1.22 and a discussion on the applicability of the efficacy data from VEG113078 to the European population will provided. Thus, it is likely that the applicant will be in a position to provide the comprehensive clinical data.

c) Despite other agents that have shown relevant clinical efficacy in this setting, such as different regimens of cytokines, combination treatment with interferon alfa-2a and the anti-VEGF antibody bevacizumab, tyrosine kinase inhibitors such as sorafenib and sunitinib, and mTOR inhibitors such as temsirolimus and everolimus, there remains a large unmet medical need in the treatment of this condition because the disease eventually progresses in most patients and available treatments are associated with clinically important adverse drug reactions. Thus, different agents through different safety and efficacy profiles may offer major therapeutic advantages to those affected in terms of clinical efficacy, safety or other aspects such as patient preference. Pazopanib has been associated with high tumour response rate and important improvement in terms of PFS in treatment naïve patients with advanced RCC and in patients with advanced RCC who were refractory to prior cytokine therapy based on a randomized controlled trial. The safety profile has been well-characterized and is considered manageable. Based on indirect comparisons, there are some events that appear to occur with a higher frequency for the approved agents (rash, mucositis, HFS) while others occur with a higher frequency with pazopanib (high grade ALT elevations, all-grade hypertension and hair discoloration). Furthermore, compared to other agents that have shown activity in advanced RCC, pazopanib has a distinct pharmacodynamic profile in terms of potency in inhibiting the main receptor tyrosine kinases involved in angiogenesis. The different pharmacodynamic profile may explain the potential differences observed in the indirect comparisons presented, although this would have to be confirmed in adequately powered randomized controlled trials. The addition of a safe treatment option that is associated with clear clinical benefits and with a distinct pharmacodynamic profile is considered

to offer major advantage in the context of the therapies for this disease. Therefore the CHMP considers that unmet medical needs will be fulfilled for the treatment of advanced RCC.

d) In view of the favourable benefit-risk profile, the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Votrient is not similar to Nexavar (sorafenib), Torisel (temsirolimus) and Afinitor (everolimus) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by a majority decision that the risk-benefit balance of Votrient in the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease was favourable and therefore recommended the granting of the conditional marketing authorisation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Votrient not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Nexavar (sorafenib), Torisel (temsirolimus) and Afinitor (everolimus) for the same therapeutic indication.