**Australian Government**

Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report
# for
# Pazopanib hydrochloride

**Proprietary Product Name: Votrient**

**Submission No: PM-2009-01084-4**

**Sponsor: GlaxoSmithKline Australia Pty Ltd**

*September 2010*

# Contents

# I.    Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | New Chemical Entity |
| *Decision:* | Approved |
| *Date of Decision:* | 22 June 2010 |
| *Active ingredient(s):* | Pazopanib hydrochloride |
| *Product Name(s):* | Votrient |
| *Sponsor's Name and Address:* | GlaxoSmithKline Australia Pty Ltd<br>PO Box 168, Boronia VIC 3155 |
| *Dose form(s):* | Film Coated Tablets |
| *Strength(s):* | 200 and 400 mg |
| *Container(s):* | Bottle packs |
| *Pack size(s):* | 14, 28 and 84 tablets |
| *Approved Therapeutic use:* | Treatment of advanced and/or metastatic renal cell carcinoma (RCC). |
| *Route(s) of administration:* | Oral (PO) |
| *Dosage:* | 800 mg/day |
| *ARTG number(s):* | 161 281 and 161 282 |

## Product Background

Pazopanib is a tyrosine kinase inhibitor (TKI) which acts upon several receptors including vascular endothelial growth factor receptor (VEGF-R). Approval is being sought for use in renal cell carcinoma (RCC). In recent years, the Australian Drug Evaluation Committee (now known as the Advisory Committee of Prescription Medicines, ACPM) has considered and recommended approval of several new agents for the treatment of this disease. The list includes two other TKIs which inhibit VEGF-R (sunitinib and sorafenib). Due to the rarity of advanced or metastatic RCC, pazopanib has been designated as an Orphan Drug in Australia.

The hypothesis that tumour development is dependent on angiogenesis has been based on the observation that tumours require and recruit their own blood supply as they grow beyond microscopic size. This has sparked a new era in anticancer drug development. Since then, multiple pro-angiogenic growth factors, including VEGF, PDGF, fibroblast growth factor (FGF), transforming growth factor- , and tumour necrosis factor-  have been identified. A number of novel therapeutic agents targeting the various components of the angiogenesis pathway have been developed and continue to be tested in human clinical trials. The strategies pursued with these agents include inhibition of the growth factors and/or their receptors with the resulting inhibition of neovascularisation, disruption of existing tumour vasculature, and inhibition of pro-angiogenic growth factor release. Pazopanib, discovered and developed by GlaxoSmithKline (GSK), as 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). Pazopanib tablets are under development by GSK for the treatment of a broad range of tumour types and pazopanib eye drops are under development for treatment of age-related macular degeneration (AMD).

RCC is a disease characterised by the frequent loss of the von Hippel-Lindau (VHL) tumour suppressor gene. The protein product of this gene is critical for the regulation of hypoxia inducible factor (HIF) HIF-1 , a transcription factor for VEGF and PDGF genes. The up-regulation of these genes in RCC leads to tumour angiogenesis. Pazopanib inhibits VEGFR and PDGFR, which are critical for the pathways that stimulate angiogenesis. The anti-tumour activity of pazopanib in RCC was first demonstrated in the 'first-time in human' study, VEG10003. This study led to its evaluation in VEG102616 (a Phase II study) and in VEG105192 (a Phase III, randomised, double-blind, placebo-controlled study).

### Regulatory Status

On 24 March 2009 Votrient was granted Orphan Drug status by the TGA.

A similar application to the current Australian submission was approved in the USA on the 19 October 2009. A positive Committee for Medicinal Products for Human Use (CHMP) opinion was granted on 18 February 2010 and it is currently awaiting a European Commission decision. Similar applications are under evaluation in Canada, New Zealand and Switzerland.

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

## II.   Quality Findings

### Drug Substance (active ingredient)

Pazopanib is a synthetic sulfonamide. Pazopanib is achiral and has no isomers. The pKa values are 2.1, 6.4 and 10.2. Pazopanib hydrochloride is crystalline solid; multiple crystalline forms are known.

**Figure 1.** Chemical structure of pazopanib hydrochloride.
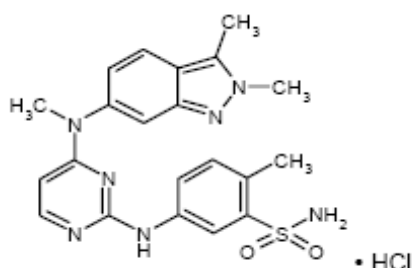


$$C_{21}H_{23}N_7O_2S.HCl \qquad\qquad MW\ 437.53\ (base)$$

Pazopanib includes a substituted *meta*-aminobenzenesulfonamide ring, which differs from the *para*-arrangement in 'sulfonamide' drugs such as sulfanilamide and sulfamethoxazole.

Pazopanib hydrochloride is very slightly soluble at pH 1 (0.65 mg/mL in 0.1 M HCl) and practically insoluble above pH 4 (0.00005 mg/mL in pH 7.0 phosphate buffer).

The drug substance is synthetic. Impurity levels are fairly low. A number of genotoxic or potentially genotoxic impurities are controlled during the synthesis.

### Drug Product

*'Votrient'* 200 and 400 mg, immediate release, film-coated tablets are proposed (earlier *'Patorma'* was proposed as the trade name). The tablets have a modified capsule-shape. The two strengths are different sizes and different colours and have distinct code markings. Tablets are not scored. Bottle packs of 30 and 60 tablets (200 mg), or 30 and 90 tablets are proposed.

Tablets are labelled with the equivalent mass of pazopanib base. Tablets are made by wet granulation using conventional excipients. The two strengths have directly scaled tablet cores.

Early clinical trials used 50, 100 and 500 mg tablets strengths with formulations closely related to those proposed for registration (studies VEG10003, VEG10007, VEG10006, VEG102616 and VEG20006). Other clinical trials used 200 and 400 mg tablet formulations which are identical to the proposed commercial formulations except for shape, film coat colour and debossing.

### 'Real Time Release'

Unusually, the sponsor proposes that future batches of *Votrient* tablets will be made and released without any direct batch testing (for example, of identification, impurities or dissolution). The sponsor has introduced controls during the manufacturing process which are claimed, in combination with validation studies, to ensure batch quality. The quality evaluator does not consider that the manufacturing and stability experience are yet sufficient to completely eliminate routine batch testing. As there are specifications available which could be applied routinely, a decision on this does not need to delay the Advisory Committee of Prescription Medicines (ACPM) considerations.

### Bioavailability

Pazopanib hydrochloride is reported to have high intestinal permeability and is thus classified as a 'Biopharmaceutics Classification Scheme Class 2' compound, that is, low solubility / high permeability. Such drugs are likely to have bioavailability which is solubility or dissolution rate limited.

Pazopanib is the biologically active species. It is metabolised primarily by cytochrome P450 (CYP) isozyme CYP3A4. Excretion is predominantly faecal. Absorption is non-linear (lower at higher doses). There are significant individual differences in exposure; for example six individual profiles at steady state (800 mg / day) are shown below (Figure 2).

**Figure 2.** Individual plasma pazopanib concentration-time plots. Cycle 1 Day 15, 800 mg/day (Part B).
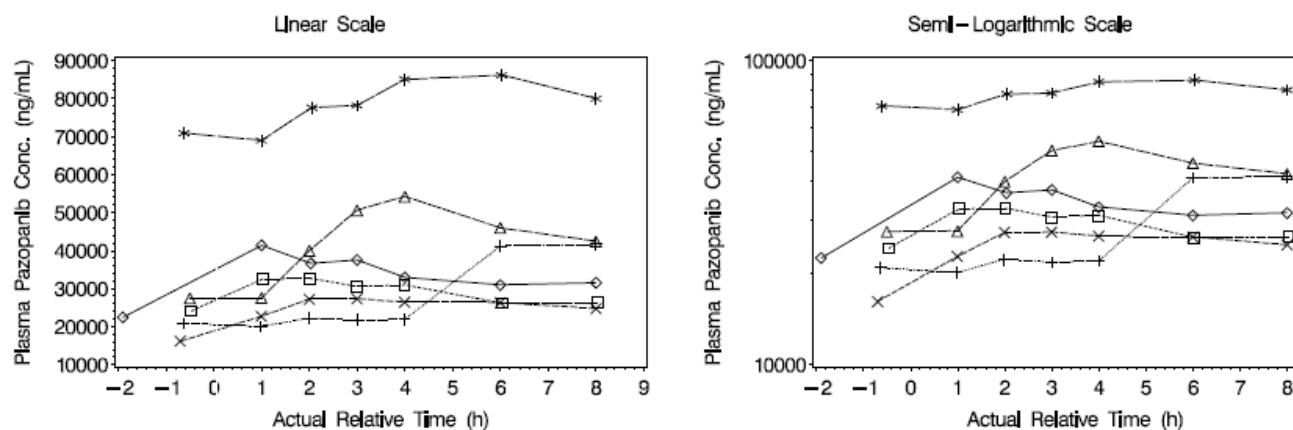


Two pharmacokinetic reports were reviewed.

**Study RM2008/00850/00** characterised absorption, distribution, metabolism and elimination of pazopanib following intravenous (IV) and PO (oral) doses in subjects with solid tumours. The study thus includes determination of the absolute bioavailability. Part A of Study RM2008/00850/00 examined the fate of radiolabelled pazopanib taken as an oral solution (formulation unclear) in three patients. The faecal recovery of radioactivity was 93, 92 and 61%. Data showed that pazopanib is not extensively metabolised and that first-pass metabolism is minor after oral administration. Renal excretion is low.

Part B of the study compared the bioavailability of 200 and 400 mg tablets and a 5 mg, 5 minute intravenous infusion in 7 patients undergoing cancer treatment. The intravenous solution had drug (2 or 5 mg/mL) dissolved by adding the complexing agent β-cyclodextrin sulfobutylether (70 mg/mL). Plasma pazopanib concentrations were measured in blood samples collected over 96 h. Full pharmacokinetic characterisation was unfortunately limited by a fairly high quantification limit in the high performance liquid chromatography/mass spectrometry (HPLC-MS/MS) assay.

The observed absolute bioavailability of oral pazopanib was 14 %, 21 % and 39 % in the 3 subjects from whom full analysis was possible. Thus oral absorption of pazopanib was incomplete; the majority of the oral dose recovered unchanged in faeces is probably unabsorbed drug.

**Study RM2007/00706/00** was a study of the effect of food on bioavailability in patients. The study was a comparison of the effects of a low-fat meal or a high-fat meal versus fasting on tablet bioavailability (800 mg dose) in a 2 treatment crossover design (evaluable n=13 for low fat; n=11 for high fat). (In other sections of the study, pazopanib was also given as crushed tablets and as a suspension.)

Blood samples were collected over 72 hours and analysed for pazopanib by HPLC/MS/MS. Both meals dramatically increased mean bioavailability, well outside bioequivalence ranges; both for a **low** fat meal (C; Figure 3):

**Figure 3.** Median plasma pazopanib concentration-time plots for subjects in randomised food effect low fat/fasted or fasted/low fat sequence.



A = 800 mg/Fasted
C = 800 mg/Low Fat
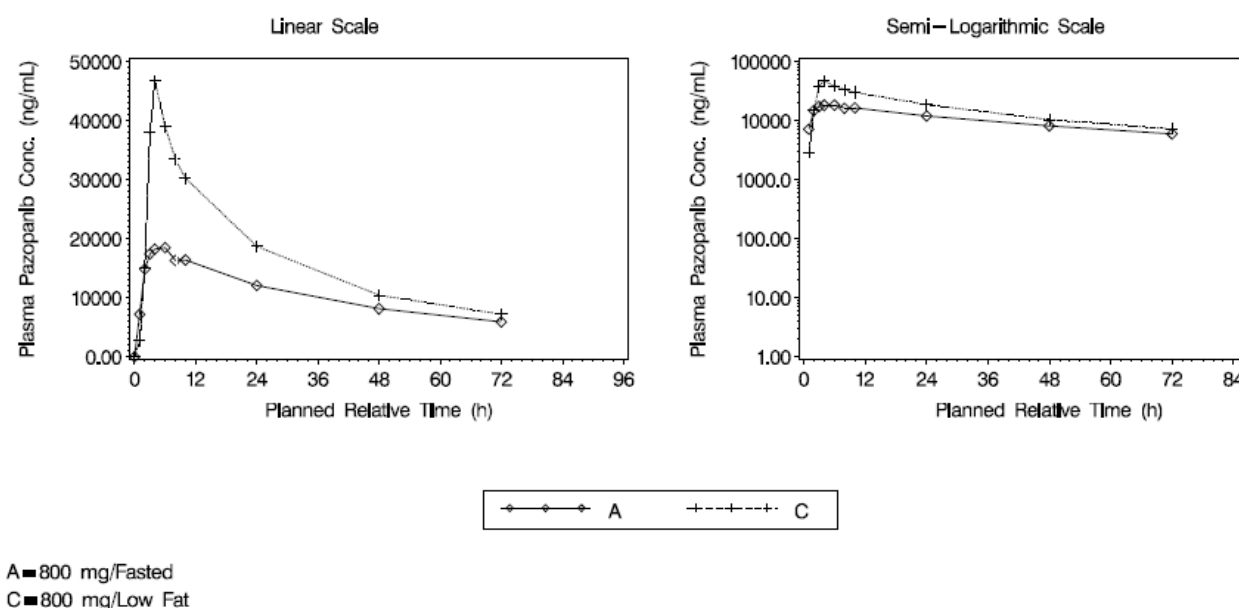
and for a **high** fat meal (B; Figure 4):

**Figure 4.** Median plasma pazopanib concentration-time plots for subjects in randomised food effect high fat/fasted or fasted/high fat sequence.
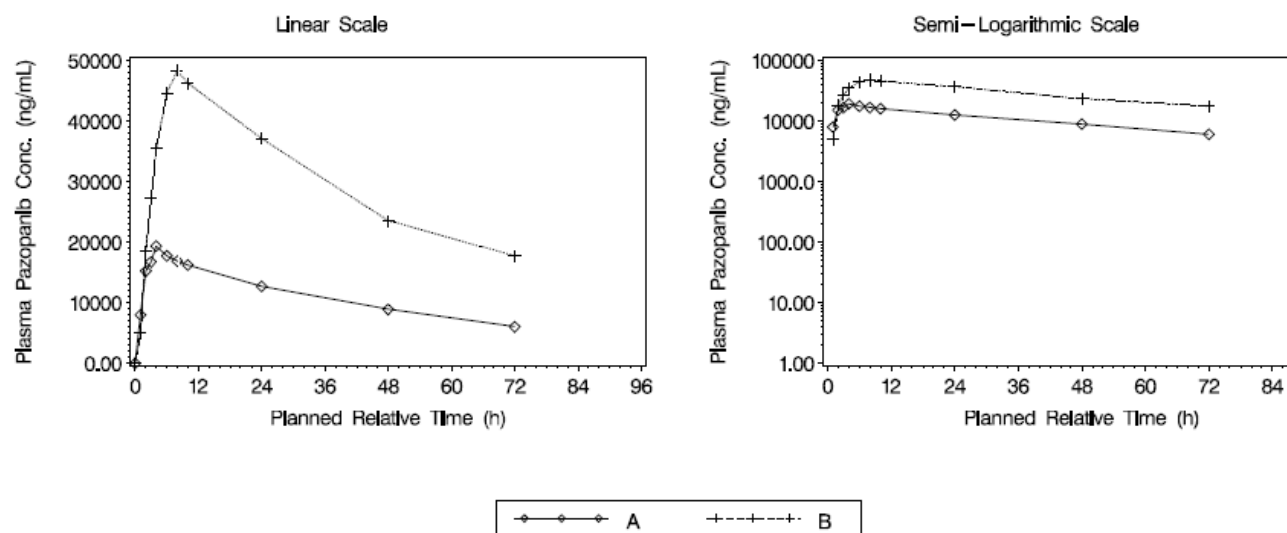


A = 800 mg/Fasted
B = 800 mg/High Fat

**Table 1.** Comparison of plasma pazopanib PK parameters for assessment of food-effect.

| Parameter | N | Meal | Geometric Least Squares Mean Ratio | 90% CI |
|---|---|---|---|---|
| AUC(0-t) | 11 | High-fat | 2.34 | (1.64, 3.35) |
| | 11 | Low-fat | 1.92 | (1.24, 2.98) |
| Cmax | 12 | High-fat | 2.08 | (1.51, 2.87) |
| | 12 | Low-fat | 2.10 | (1.51, 2.91) |

**Table 2.** Summary of non-paramteric analysis of Pazopanib $t_{max}$ (time to maximum plasma concentration).

| Parameter | Comparison of Interest (Test/Reference) | Number of Comparison Pairs | Estimated Median Difference (hr) | 90% CI |
|---|---|---|---|---|
| Tmax | B : A | 12 | 3.00 | (0.02, 6.00) |
| | C : A | 12 | 0.06 | ( -1.00, 1.22) |

Data Source: Table 11.35
A = Pazopanib 800 mg/fasted, B = Pazopanib 800 mg/High-Fat Meal
C = Pazopanib 800 mg/Low-Fat Meal

Thus administration of a single dose of 800 mg pazopanib tablet doses with food in cancer patients increased the bioavailability (relative to fasting) approximately two-fold. This is apparently due to increases in absorption (not clearance).The draft PI recommends that the tablets should be taken at least 1 hour **before** or 2 hours **after** a meal. The bioavailability evaluator suggested that the reasons for this recommendation should be given in both the PI and the Consumer Medication Information (CMI).

The bioequivalence of the 200 and 400 mg tablets has not been investigated. Equivalence is plausible given that the tablet cores are directly scaled.

## Quality Summary and Conclusions

Some aspects of the quality control data have been queried with the sponsor. The proposed 'real time release' is considered premature; this is a quality control issue which can be dealt with via conditions of registration if necessary.

Registration is recommended with respect to chemistry and biopharmaceutics aspects, subject to finalisation of the above issues and the Pharmaceutical Subcommittee's advice.

# III. Nonclinical Findings

## Introduction

The sponsor has conducted mostly adequate studies on the pharmacodynamics, pharmacokinetics and toxicity of pazopanib, in accordance with the relevant guidelines. All pivotal nonclinical safety studies were conducted using the micronised monohydrochloride salt of pazopanib, which is the form proposed for use in humans, but some preliminary studies used the parent compound and the dihydrochloride salt of pazopanib. It was noted in the sponsor's "Nonclinical Overview" that *in vitro* and in biological matrices, salt forms of pazopanib dissociate to the parent compound. Generally the doses and concentrations were expressed in terms of the parent compound.

Most toxicity studies were performed according to Good Laboratory Practice (GLP) conditions, and non-GLP studies were generally adequately documented. The toxicity studies comprised an acute IV study in the rat and repeat PO dose studies up to 13 weeks in the mouse, 26 weeks in the rat, 4 days in the dog and 52 weeks in the cynomolgus monkey. The genetic toxicity of pazopanib has been investigated in a battery of *in vitro* and *in vivo* assays. Reproductive toxicity studies included male and female fertility, early embryonic development and embryofetal toxicity (with dose range-finding studies) in the rat and a dose range finding study in the rabbit, all following oral administration. In addition, studies to assess haemolytic/protein flocculation potential of pazopanib and phototoxicity *in vitro* were submitted. Repeat ocular dose studies were conducted in the rabbit and dog for durations of 4 and 26 weeks, respectively, but these (along with topical local tolerance studies) were not relevant to the proposed indication and therefore were not evaluated.

## Pharmacology

### Primary pharmacodynamics

Angiogenesis is initiated by proangiogenic factors including VEGF and PDGF, which act by binding to TK receptors on endothelial and other stromal cells[1]. VEGFR-2 is the primary TK receptor mediating downstream events such as vascular permeability, endothelial cell proliferation, invasion, migration and survival[2]. Ligand binding induces dimerisation of VEGFR-2 leading to receptor autophosphorylation and activation of downstream signalling including the Raf-MEK-Erk and the PI3K-AKT pathways resulting in mitogenic and pro-survival signals [3]. VEGF is expressed by various tumour and host cells and is up-regulated in

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[1] for example: Cao Y and Liu Q (2007). Therapeutic targets of multiple angiogenic factors for the treatment of cancer and metastasis. *Advances in Cancer Research,* 97:203-24.

[2] Dvorak HF (2002). Vascular permeability factor/vascular endothelial growth factor: A critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *Journal of Clinical Oncology,* 20:4368-80.

[3] Wu L-W, Mayo LD, Dunbar JD, Kessler KM, Baerwald MR, Jaffe EA et al (2000). Utilization of distinct signaling pathways by receptors for vascular endothelial cell growth factor and other mitogens in the induction of endothelial cell proliferation. *The Journal of Biological Chemistry,* 275:5096-103.

the tumour microenvironment[4], and inhibition of PDGFR signalling appeared to augment the anti-tumour and anti-angiogenic effects of VEGFR inhibitors by destabilizing pericytes[5]. Both VEGF (via VEGFR-3) and PDGF have also been implicated in lymphangiogenesis. Thus, compounds that inhibit the intrinsic tyrosine kinase activity of VEGFRs are expected to block the biological activity of the receptors. Therefore, in the event that inhibition of both VEGFR and PDGFR signaling in endothelial cells and pericytes as well as both the vascular and lymphatic endothelial compartments could be achieved, multi-targeted TKIs such as pazopanib are presumed to be effective in inhibiting cancer progression via several mechanisms (as noted in the sponsor's "Pharmacology Written Summary"): (a) regression of existing tumour microvasculature; (b) normalization of existing microvasculature; (c) inhibition of formation of new microvasculature; (d) inhibition of lymphangiogenesis and, therefore, tumour metastasis. The assessment of the nonclinical pharmacology studies therefore is focused on the evidence for inhibition of VEGFR and PDGFR signaling, as well as for potential antitumour activity in animal models *in vivo*.

In *in vitro* cell free assays, pazopanib inhibited the kinase activity of VEGFR-1, -2 and -3 (50% inhibitory concentration, $IC_{50}$, 10-50 nM), PDGFR-$\alpha$ and -$\beta$ and c-kit ($IC_{50}$ <100 nM) and FGFR-1 and -3 and c-fms ($IC_{50}$ <150 nM). Pazopanib inhibited the cellular autophosphorylation of VEGFR-2, c-Kit and PDGFR-$\beta$ receptors with estimated $IC_{50}$ values of 8, 3 and 3 nM, respectively, in human umbilical vein endothelial cells (HUVEC), NCI-H526 (human small cell lung carcinoma) and human foreskin fibroblast (HFF) cells, respectively. Pazopanib and imatinib inhibited wildtype c-Kit activation in cells with $IC_{50}$ values of 3 nM and 230 nM, respectively. Pazopanib selectively inhibited proliferation of HUVEC stimulated with VEGF ($IC_{50}$ = 21 nM) compared to basic fibroblast growth factor (bFGF) stimulated proliferation ($IC_{50}$ = 721 nM). However, the potencies of pazopanib against Flt-3 receptor activation (autophosphorylation) in RS4;11 cells and cell proliferation in MV4-11 cells were considerably lower than with sorafenib and sunitinib ($IC_{50}$ = $\geq$1 $\mu$M compared with 1-5 nM nM for both sorafenib and sunitinib). Pazopanib also had considerably lower potency towards inhibition of human bone marrow progenitor cells that had been stimulated by Flt-3, than both sunitinib and sorafenib. Therefore pazopanib was shown to inhibit VEGFR-2, c-Kit and PDGFR-$\beta$ cellular activity, but had relatively lower potency against the Flt-3 receptor.

A metabolite of pazopanib, GSK1268997, exhibited comparative VEGF-induced anti-proliferative activity in HUVEC to pazopanib, whereas 3 other metabolites showed at least 10-fold lower activity. Another similarity with the pazopanib parent was that GSK1268997 also exhibited >20-fold selectivity for VEGF stimulated proliferation than for bFGF stimulated proliferation of HUVEC.

Overall these data showed that pazopanib had inhibitory activity against VEGF (including VEGF-2 and 3, which are considered to have a significant role in the inhibition of angiogenesis and lymphagenesis, respectively) *in vitro* both in cell-free and (human endothelial) cellular media, at clinically relevant concentrations. Renal cell carcinoma cells were not specifically investigated in these *in vitro* studies.

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[4] Berse B, Brown LF, Van De Water L, Dvorak HF and Senger DR (1992). Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. *Molecular Biology of the Cell,* 3:211-20.

[5] Bergers G, Song S, Meyer-Morse N, Bergsland E and Hanahan D (2003). Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. *Journal of Clinical Investigation,*111:1287-95.

In *in vivo* studies, pre-treatment of mice with pazopanib (up to 100 mg/kg) inhibited VEGF-induced phosphorylation of VEGFR-2 in the lung tissue in a dose- and time-dependent manner. Also, oral administration of pazopanib ($\geq$30 mg/kg) inhibited bFGF- and VEGF-induced angiogenesis in Matrigel plug and corneal micropocket models of angiogenesis in mice.

Pazopanib inhibited growth of 4/5 human renal cell tumours (CAKI-2, ACHN, A498 and 786-O, but not CAKI-1) in xenograft models in mice. The CAKI-2 model was the most sensitive to pazopanib where 99% tumour growth inhibition was seen in mice dosed at 100 mg/kg/day for 24 days. In contrast, no significant inhibition of tumour growth was seen with the same treatment regimen following implantation of CAKI-1 cells (or with 786-O cells with pazopanib alone in a combination study over 21 days). Repeat oral administration of pazopanib (100 mg/kg/day) for 21 days to mice bearing HT29 (colon) and HN5 (head and neck) human tumour xenografts resulted in 66% to 90% inhibition of tumour growth. A375P (melanoma) and PC3 (prostate) human xenografts were less sensitive to treatment with pazopanib. Other xenograft studies indicated that repeated oral administration of pazopanib had some inhibitory activity against various other tumour cell lines (including Colo-205, HN5, BT474 and NCI-H322). Also, repeated doses of pazopanib at 10, 30 or 100 mg/kg (for 35 days) increased survival dose-dependently and decreased ascites (at 28 days) and tumour volume (at 22 days) as measured in mice with intraperitoneal (IP) or subcutaneous (SC) OVCAR-3 (ovarian) xenograft, and also resulted in increased CA-125 levels in plasma, ascites and tumour lysate. The generally effective dose (100 mg/kg/day) was associated with toxicity findings in mice following treatment for a longer period (13 weeks; see under "Toxicity", below) than in the xenograft studies. Also, at this dose the area under the concentration versus time curve (AUC)-based exposure was greater (1-2-fold) than the exposure in humans at the recommended clinical dose, and the maximum plasma concentration ($C_{max}$) was 2-3-fold greater. However, activity towards some (non-renal carcinoma) cell lines was also detected at lower doses (10 mg/kg/day) in the xenograft studies.

Drug combination studies using renal carcinoma cells were only conducted in CAKI-1 and 786-O xenograft models. No effect was seen in these studies relative to GSK690693 alone. In combination studies in other xenograft models, increased tumour growth inhibition (TGI) was seen against SKOV3 cells with pazopanib and GSK690693 in combination compared to either agent alone. Other combinations with pazopanib resulted in no or modest increases in TGI compared to either agent alone.

In Clinical Study VEG102616, fit of the Emax Model[6] to the plasma pazopanib Week 4 predose (trough) concentration versus % change from baseline in soluble VEGFR-2 nadir (the lowest point) resulted in the relationship shown in the graph below (Figure 5; open circles are the observed data and the line is the data predicted with the Emax model). The 50% effective concentration ($EC_{50}$) for the decrease in plasma soluble VEGFR-2 was 21.3 µg/mL (coefficient of variation, CV, 24.5%). As noted under "*Pharmacokinetics*" (below) according to the sponsor's "Summary of Clinical Pharmacology", a plasma pazopanib trough concentration of approximately 15 µg/mL (34 µM) was associated with clinical activity (partial response or stable disease) and biologic effects (in study VEG10003; Report RM2006/00501/00). While these data are subject to verification by the clinical evaluator, they suggest that the findings described above were generally within a clinically relevant range.

According to the sponsor's "Clinical Overview", the effect of pazopanib monohydrochloride on angiogenesis was less marked in comparison to pazopanib dihydrochloride.

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[6] The Emax model is a nonlinear model frequently used for dose–response analyses.

**Figure 5**.
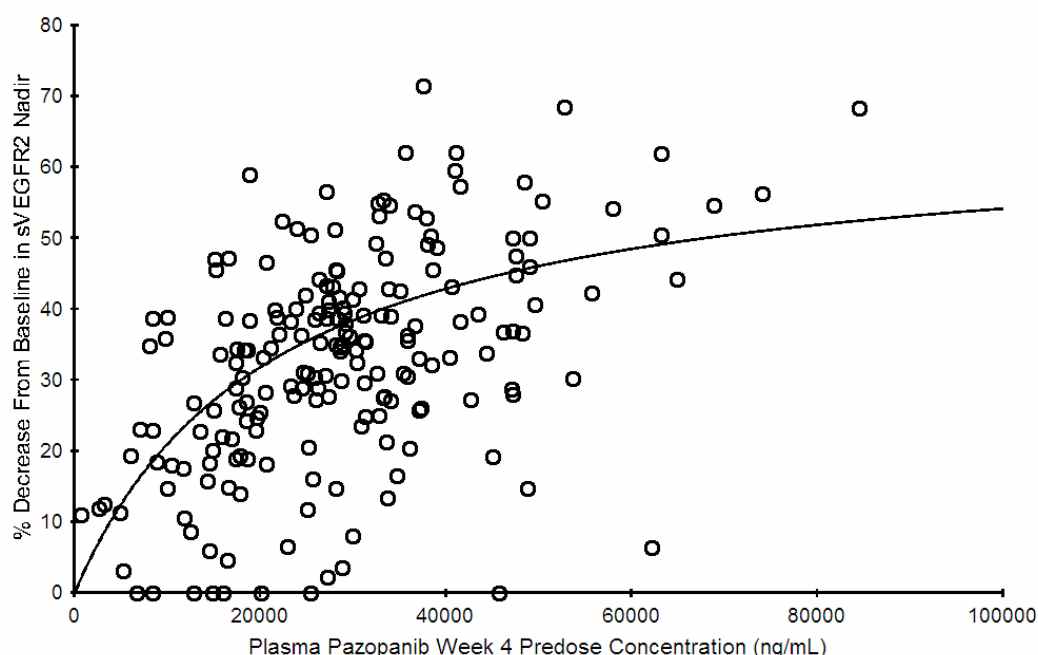


**Secondary pharmacodynamics and safety pharmacology**

Radioligand binding assays with pazopanib (10 μM) showed significant binding activity (>50% inhibition of radioligand binding) at the following targets: adenosine $A_3$, adrenoceptors $\alpha_2$ and $\beta_1$, histamine $H_2$, muscarinic $M_1$, and serotonin 5-hydroxytryptamine (5-HT)$_{1A}$, 5-HT$_{5A}$ and 5-HT$_7$. In addition to receptor binding assays indicating a potential for pazopanib to bind to β-adrenoreceptors, pazopanib (30 μM) increased the contractile force of rat isolated atria, but without affecting the atrial rate. In contrast, pre-incubation with pazopanib (30 μM) reduced the maximum contractile force response to isoproterenol (1 to 10 nM), indicating that pazopanib can exhibit a non-β-adrenoreceptor-mediated inotropic effect. However, in a non-GLP safety pharmacology study in rats, there was no detectable effect on β-adrenergic control of the cardiovascular system following IV treatment with up to 10 mg/kg pazopanib.

The above finding contrasted with a slight decrease in heart rate (without concomitant changes in arterial pressures) in conscious male cynomolgus monkeys after a single IV dose of 3.75 mg/kg pazopanib (~3 fold the area under the concentration versus time curve , AUC,-based exposure in humans following a single dose). Elevated blood pressure was not observed in the animal models, despite hypertension having been noted in some human patients taking pazopanib and with other compounds in this class. Pazopanib slightly but statistically significantly inhibited hERG channel repolarisation up to the limits of solubility (~19% at 4.14 μM), but had no effect on cardiac repolarisation in dog Purkinje fibers (up to 80 nM) and did not affect QTc interval in monkeys following repeated daily dosing with pazopanib for up to 52 weeks (at up to 500 mg/kg/day).

Overall, there were no clinically relevant findings in safety pharmacology studies which investigated the effects of pazopanib on the cardiovascular, respiratory and central nervous systems in appropriate animal models. However, in clinical studies with pazopanib, QT prolongation was identified in <2% of patients and torsade de pointes was observed in <1% of patients who received pazopanib monotherapy. According to the sponsor's "Nonclinical Overview", a study to evaluate the effects of pazopanib on the QT interval in patients with cancer was planned for initiation in early 2009.

In terms of pharmacodynamic interactions, the pre-treatment of mice bearing HT29 or NCI-H460 xenograft tumours with pazopanib (100 mg/kg twice a day, bid, oral for 7 days) or bevacizumab (10 mg/kg bid intraperitoneal on Days 1, 3 and 6) had no effect on the delivery of chemotherapeutic agents (5-fluorouracil, irinotecan, paclitaxel and carboplatin) to the tumours.

## Pharmacokinetics

The pharmacokinetic parameters of pazopanib have been determined in the rat, dog and monkey. The oral bioavailability of pazopanib was 61.4% in fasted and 72% in unfasted rats (10 mg/kg), 47% in fasted beagle dogs (1 mg/kg) and 49-53% in cynomolgus monkeys (5 mg/kg). In a clinical study, the bioavailabilities in 3 subjects with cancer were 14%, 21%, and 39% (Clinical Study Report RM2008/00850/00).

Clearance was low but comparable in rats, dogs and cynomolgus monkeys (1.4-2.1 mL/min/kg). Volume of distribution, Vd, was also low, 267-297 mL/kg, in dogs and cynomolgus monkeys, but a little greater in rats (478-582 mL/kg). These values were comparable with pazopanib plasma clearance (0.206 to 0.347 L/h; values similar to mL/min/kg assuming 60 kg body weight, BW) and volume of distribution at steady-state (9.1-13.1 L or 153-219 mL/kg that is, <40% of total body water) in humans. Clearance was considerably faster (18.3 mL/min/kg) and Vd was low (1.1 mL/kg) in minipigs, but this species was not used in the relevant toxicity studies. The pazopanib half-life, $t_{\frac{1}{2}}$, after IV administration in humans was ~30 h (Clinical Study Report RM2008/00850/00), which is much longer than the $t_{\frac{1}{2}}$ values observed in animal species. A ~2-fold increase in pazopanib exposure was observed after administration of pazopanib with food in subjects with cancer (Clinical Study Report RM2007/00706/00). Exposure data in a 4-day non-GLP repeat dose study in dogs were not dose-dependent within the range of doses used (50 and 150 mg/kg/day). There was too much variability in the data from animal species concerning the effect of fasted versus fed state on absorption for any conclusions to be drawn. Less than dose-proportional exposure was observed in mice, rats and dogs as well as humans. In humans, the proposed clinical dose resulted in exposures close to the plateau level.

Pazopanib displayed high plasma binding (>98.8%) in mouse, rat, dog, monkey and human plasma. Binding to human serum albumin and α-1-acid glycoprotein were >96%. Human serum albumin could bind phenylbutazone but not palmitate or warfarin simultaneously with pazopanib. Association of pazopanib-related material with blood cells was low following *in vivo* administration of radiolabelled pazopanib to rats and cynomolgus monkeys.

Following radioactive carbon ($^{14}$C)-pazopanib monohydrochloride administration (single 10 mg/kg PO dose to pigmented Long-Evans rats), radioactivity was widely distributed throughout the body, including the central nervous system (CNS). Most tissues exhibited their highest radioactivity concentrations at 2 h post dose; however, in males, these were generally lower than the concentrations in the blood. The highest levels of radioactivity in males were observed in the gastrointestinal (GI) tract, liver, lung, adrenal, kidney, eye, brown adipose, heart, urinary bladder and meninges, and in females in meninges, liver, adrenal medulla, lung and aorta. Concentrations of radioactivity in the CNS (except meninges and pituitary in males) were low and were not quantifiable beyond 8 h post-dose. While concentrations of radioactivity were not quantifiable in most tissues by 3 days post-dose, concentrations of radioactivity were still associated with pigment-containing tissues (eye, skin and meninges) at 35 days post-dose, having declined slowly over the monitored time period. As noted in the sponsor's "Pharmacokinetics Written Summary", this suggested a selective association of pazopanib-related material with melanin containing tissues.

Following oral administration of $^{14}$C-pazopanib, the principal radiolabelled component in the plasma was unchanged pazopanib in humans as well as in all animal species used in the nonclinical studies. In humans, four circulating metabolites were detected: Two mono-oxygenation products (GSK1268992 and GSK1268997) and 2 demethylation products (GSK1071306 and GW700201). Each accounted for <10% of the parent drug concentration in plasma at all time points, therefore these metabolites were considered minor. Overall, the profile of circulating metabolites was qualitatively similar between humans and animal species, and no unique circulating metabolites were observed in humans. Qualitatively, all the metabolites detected in humans were also detected in one or more of the animal species used in the toxicity studies (albeit not necessarily in the same matrix), with the exception of M34, which appeared to be detectable in human urine only. The oxidative metabolism of pazopanib in human liver microsomes was mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

In human liver microsomes, pazopanib inhibited the activity of CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1, with $IC_{50}$ values ranging from 7.9 µM (2C9) to 18 µM (2D6), but not CYP2A6 ($IC_{50}$ >100 µM). CYP3A4 induction was also shown in the human pregnane X receptor reporter assay. In cultured human hepatocytes, 1 and 10 µM pazopanib showed potential for inducing both the gene expression and catalytic activity, respectively, of CYP3A4 and CYP2B6. However, there was no significant effects on CYP1A, CYP2B, CYP3A or CYP4A activities following repeat oral dosing in rats (up to 300 mg/kg/day) or monkeys (up to 500 mg/kg/day) for 4 weeks.

*In vitro* studies demonstrated that pazopanib was a substrate for the human P-glycoprotein (P-gp) and murine breast cancer resistance protein (BCRP)-1 transporters, suggesting potential effects on its pharmacokinetics by inhibitors of P-gp and/or BCRP. At concentrations up to 30 µM pazopanib did not inhibit human P-gp or BCRP *in vitro*. The pazopanib metabolites GSK1268992 and GSK1268997 at concentrations up to 100 µM also did not inhibit human P-gp. However, they were both shown to inhibit human BCRP with an $IC_{50}$ of 10 µM. *In vitro*, pazopanib was also an inhibitor of human UDP-glucuronosyltransferases 1A1 (UGT1A1; $IC_{50}$ 1.2 µM) and human organic anion transporting polypeptide (OATP1B1) ($IC_{50}$ 0.79 µM).

According to the sponsor's "Summary of Clinical Pharmacology", a plasma pazopanib trough concentration of approximately 15 µg/mL (34 µM) was associated with clinical activity (partial response or stable disease) and biologic effects (in study VEG10003 (Report RM2006/00501/00). This minimum target concentration is approximately 2- to 4-fold greater than the *in vitro* $IC_{50}$ values for inhibition of CYP enzymes, 28-fold greater than the *in vitro* $IC_{50}$ value for UGT1A1 inhibition, and 43-fold greater than the *in vitro* $IC_{50}$ for inhibition of OATP1B1. Moreover, the maximum plasma concentration, $C_{max}$, following repeated doses at 800 mg/day was 40 µg/mL, and as noted in the sponsor's "Primary Pharmacodynamics" report, the $EC_{50}$ for the decrease in plasma soluble VEGFR-2 was 21.3 µg/mL. Therefore, pazopanib has the potential to affect the pharmacokinetics of medications that are substrates for CYP enzymes (1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1), UGT1A1, and OATP1B1 in humans at clinically relevant concentrations.

In rats, ~57% of the dose was excreted in the faeces and 16% in the urine. In cynomolgus monkeys, the excretion was greater in the faeces (86%) and lower in the urine (2.5%). In humans, pazopanib was predominately excreted as unchanged parent in faeces (67% of dose administered cf <4% in the urine). The excretion pattern was considered qualitatively similar to humans in cynomolgus monkeys, but a greater proportion of the dose was excreted in the urine in rats.

**Relative exposure**

Doses of pazopanib administered in the repeated-dose toxicity studies ranged from 3 to 1000 mg/kg daily in studies 4 weeks or longer in mice, rats and cynomolgus monkeys. The AUC data used to calculate the exposure ratios in the table below were based on the repeat dose pharmacokinetic data for these species. The data in humans were from Clinical Study VEG10003, which was a Phase 1, open label, multiple dose study in adult subjects with solid tumours who were refractory to standard therapy or for whom no standard therapy existed. All exposures presented in the table below (Table 3) were detected after PO doses.

**Table 3.** Relative exposures.

| Species, Study duration | Doses (mg/kg/day) | Sex | Systemic exposure^ | | Exposure ratio* | |
| | | | $C_{max}$ (µg/mL) | $AUC_{0-24 h}$ (µg.h/mL) | $C_{max}$ | $AUC_{0-24 h}$ |
|---|---|---|---|---|---|---|
| Mouse, 14 days | 200, 1000, 2000 | M | 158.8, 121.4, 127.3 | 1493, 2041, 2067 | 4.0, 3.0, 3.2 | 2.3, 3.1, 3.2 |
| | | F | 171.5, 155.1, 131.9, | 1728, 2453, 2603 | 4.3, 3.9, 3.3 | 2.7, 3.8, 4.0 |
| Mouse, 13 weeks | 100, 300, 1000 | M | 102, 97.9, 80.7 | 818, 1044, 932 | 2.5, 2.4, 2.0 | 1.3, 1.6, 1.4 |
| | | F | 132, 134, 114 | 1434, 1463, 1607 | 3.3, 3.3, 2.8 | 2.2, 2.3, 2.5 |
| Rat, 4 weeks | 3, 10, **30**, 100, 300 | M | 9.6, 21.7, **29.9,** 26.3, 38.8 | 54.9, 116, **221**, 174, 258 | 0.2, 0.5, **0.7**, 0.7, 1.0 | 0.1, 0.2, **0.3**, 0.3, 0.4 |
| | | F | 10.4, 28.7, **51.0**, 38.6, 56.0 | 83.0, 232, **365**, 257, 472 | 0.3, 0.7, **1.3**, 1.0, 1.4 | 0.1, 0.3, **0.6**, 0.4, 0.7, |
| Rat, 26 weeks | 3, 30, 300 | M | 8.6, 44.6, 67.5* | 76.6, 374, 830* | 0.2, 1.1, 1.7 | 0.1, 0.6, 1.3 |
| | | F | 10.5, 60.9, 94.1* | 100, 544, 887* | 0.3, 1.5, 2.3 | 0.1, 0.8, 1.4 |
| Rabbit, pregnant | 10, 30, 100 | F | - | 1.7, 7.6, 24.7 | - | 0.003, 0.01, 0.04 |
| Monkey, 4 weeks | 5, 50, **500** | M | 11.7, 20.6, **40.9** | 46.6, 120, **296** | 0.3, 0.5, 1.0 | 0.1, 0.2, 0.4 |
| | | F | 12.1, 19.6, **30.6** | 36.0, 99.5, **335** | 0.3, 0.5, **0.8** | 0.1, 0.1, **0.5** |
| Monkey, 52 weeks | 5, **50**, 500 | M | 13.3, **31.8**, 44.5 | 46.0, **235**, 252 | 0.3, 0.8, 1.1 | 0.1, 0.3, 0.4 |
| | | F | 12.8, **44.0**, 57.2 | 36.3, **289**, 670 | 0.3, **1.1**, 1.4 | 0.1, **0.4**, 1.0 |
| Human, 22 days | 16 | M+F | 40.0 | 648.4 | - | - |

Plasma AUC animal:human exposure ratios are based on the clinical $AUC_{0-24h}$ of 648.4 µg.h/mL from Clinical Study no. VEG10003; NOAELs are bolded; ^At end of treatment; *week 13

Exposure to plasma metabolites were also assessed in humans and the animal species. The data are presented in the table below.

**Table 4.** Metabolite exposures after repeated oral doses.

| Study | Dose pazopanib (mg/kg/day) | Analyte | $AUC_{0-t}$ (μg.h/mL) Day 7[@] | Extrapolated $AUC_{0-t}$ (μg.h/mL)[$] | Exposure ratios Day 7[@] | Extrapolated exposure ratios[$] |
|---|---|---|---|---|---|---|
| **Mouse** (CD-1) | | | | | | |
| 07DMM038 Report no. CD2007/00494/01 | <u>100</u>, 1000 | Pazopanib | 987 | 9870 | NA | NA |
| | | GSK1268992 | 7.4 | 74 | 0.13 | 1.3 |
| | | GSK1268997 | 61.7 | 617 | 2.0 | 20 |
| | | GSK1071306 | 15.6 | 156 | 1.1 | 11 |
| | | GSK700201 | 3.3 | 33 | 0.37 | 3.7 |
| **Rat** (SD) | | | | | | |
| 07DMM022 Report no. CD2007/00493/01 | <u>**30**</u>, 300 | Pazopanib | 317 | 3170 | NA | NA |
| | | GSK1268992 | 2.14 | 214 | 0.04 | 0.4 |
| | | GSK1268997 | 16.3 | 163 | 0.54 | 5.4 |
| | | GSK1071306 | 1.55 | 155 | 0.11 | 1.1 |
| | | GSK700201 | 2.65 | 265 | 0.30 | 3.0 |
| **Cynomolgus monkey** | | | | | | |
| 06DMM150 Report no. RD2001/01538/01 | <u>**50**</u>, 500 | Pazopanib | 95.3 | 953 | NA | NA |
| | | GSK1268992 | 3.6 | 36 | 0.06 | 0.6 |
| | | GSK1268997 | 16.7 | 167 | 0.55 | 5.5 |
| | | GSK1071306 | 9.24 | 924 | 0.66 | 6.6 |
| | | GSK700201 | 1.35 | 135 | 0.15 | 1.5 |
| **Human** | | | | | | |
| Single dose: VEG1005 Report no. RM2007/00706/00 Repeated doses: VEG1007 Report no. RM2008/00266/00 | **16**[#] | Pazopanib | 1040 | | | |
| | | GSK1268992 | 58.8 | | | |
| | | GSK1268997 | 30.3 | | NA | |
| | | GSK1071306 | 13.9 | | | |
| | | GSK700201 | 8.94 | | | |

Actual AUC data from the dose underlined; [$]Extrapolated AUC and exposure ratios are values calculated from the actual AUC data obtained in the studies indicated at 7 days and extrapolated to the highest dose used in pivotal toxicological studies in that species, assuming linear kinetics; [@]Day 16 in humans; [^]16 h after the last dose; [#]800 mg/day, based on 50 kg person; GSK1268992, GSK1268997 and GSK1071306 were also referred to as M24, M26 and M27, respectively; NA=Not Applicable.

In the cynomolgus monkeys, AUC based exposures to these metabolites observed in human plasma were lower at the no adverse effect level (NOAEL) dose (50 mg/kg/day) than in humans. However, extrapolated data indicated exposures to these metabolites greater than in humans at the highest doses of pazopanib used in the pivotal studies used in these species (1000, 300 and 500 mg/kg/day in mice, rats and cynomolgus monkeys, respectively), with the exception of GSK128992, the exposure to which in cynomolgus monkeys and rats was ~60% and 40%, respectively, of that seen in humans. Moreover, while there was evidence for potential for accumulation of these metabolites in both humans and cynomolgus monkeys, there was a longer period of exposure in cynomolgus monkeys in the toxicity study (12 months), compared with 16 days to measurement of the metabolite in humans. Furthermore, all the metabolites appear to be minor metabolites (AUC less than 10% of the AUC of the parent in each case) and only GSK128997 possessed comparable pharmacological activity (VEGF-induced anti-proliferative activity in HUVEC) to that of pazopanib. Overall, it is considered that the risk of significant

toxicity arising from these plasma metabolites is considered to be low relative to the parent compound.

## Toxicology

### *Acute toxicity*

Acute toxicity studies comprised an IV study in rats and a PO study in dogs. Studies to investigate the acute toxicity of pazopanib did not meet the requirements set out in the EU directive for single-dose toxicity[7]. The PO study in dogs was minimally documented, and was not conducted under GLP conditions (no controls, only single animals per dose, no details of the animals and so on), and therefore was not considered to have contributed towards investigations into the acute toxicity of pazopanib. In the study in rats, only a single route of administration (IV, not proposed clinically) was used. Necropsies, recommended in the ICH Guidelines for all animals, were performed on rats, but after only 1 day of observation. Although no toxicity was observed, since only two doses were used in the study in rats (only up to 5.4 mg/kg, resulting in AUC-based exposures considerably lower than in the repeat dose studies in this species), the study design precluded any significant conclusions from being made from the study.

In a rat micronucleus study, doses of up to 2000 mg/kg were given PO on 2 consecutive days without adverse clinical signs (~3-fold the exposure in humans at the recommended dose).

### *Repeat dose toxicity*

Studies of up to 13 weeks duration were conducted in mice, 26 weeks in rats and 52 weeks in cynomolgus monkeys, all involving oral administration. Following preliminary studies in dogs, they were not considered a suitable species, on pharmacokinetic grounds, for investigating the toxicity of pazopanib. The duration of the pivotal studies, the species used (mice, rats and cynomolgus monkeys), group sizes and the use of both sexes were consistent with ICH guidelines. The dose levels selected in the pivotal rat and monkey studies were limited by toxicity. In rats, at the maximum dose (300 mg/kg/day; ~equivalent to the exposure in humans at the recommended dose based on AUC), dosing was terminated after 14 weeks (males) and 20 weeks (females) due to severe body weight (BW) loss, moribundity and mortality. Significant BW loss was also seen at 500 mg/kg/day (at or below the exposure in humans at the recommended dose, based on AUC) in cynomolgus monkeys in the 52 week study, and dosing was suspended after 34 weeks.

Major toxic effects were evident in the teeth, bone and bone marrow, nails, gastrointestinal system, kidney, liver and male and female reproductive systems. Most of these changes are considered to be consistent with the primary pharmacological actions of pazopanib.

Adverse effects on teeth in rats and mice were characterised by excessive growth and brittleness of the incisors, which were accompanied by one or more microscopic findings of periodontal oedema, ameloblastic atrophy/necrosis, enamel degeneration, dental pulp necrosis, dentine thinning and/or degeneration and (in mice) irregular/thickened predentine. Teeth changes were noted in rats given doses ≥30 mg/kg/day (~0.3- fold the AUC-based exposure at the recommended clinical dose) following the 6 weeks recovery period after 4 weeks of dosing and from week 6 of dosing in the 13 and 26 weeks studies, and in mice in the 13 week study at all doses (that is, at ≥100 mg/kg/day; 1-2 –fold the AUC-based exposure at the recommended clinical dose). Body weight loss was seen in rats along with the changes in the teeth and therefore was likely to be associated with an inability to eat their hard, pelleted food, particularly

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[7] pages 3-8 of Rules 1998 (3B)-3Bs1a. *Single dose toxicity*. Directive 75/318/EEC. 1987. See tga.gov.au.

since body weight recovered when powdered diet was offered in subsequent 13 week and 26 week toxicity studies in mice and rats. Mild increases in white blood cell counts (WBC) and serum cholesterol at ≥30 mg/kg/day in rats were suggested (in the sponsor's "Nonclinical Overview" report) also likely to be related to inflammation associated with the dental changes or to altered food consumption. All teeth changes observed after 4 weeks of dosing reversed during an extended recovery period (10 weeks) with the exception of dentine degeneration. Similar rodent effects on teeth have been noted with other marketed products in this class. Since adult rat incisors are growing continuously, incisor growth is a potential target secondary to vascular disruption due to a VEGFR-2 inhibitory activity of pazopanib. No effects on dentition were observed in adult monkeys, a species with similar dental biology to that of adult humans, that is, in which, unlike in rodents, continual growth of incisor teeth does not occur. However, no studies have been conducted in juvenile non-rodent species to fully assess the relevance of this observation on rodent dentition to potential effects on juvenile human dentition development.

There were mild treatment-related changes in haematologic parameters seen after 26 weeks in rats which included a decrease in total red blood cells and haematocrit with increased mean corpuscle volume (MCV) and mean corpuscle hemoglobin (MCH), but without reductions in total haemoglobin. Mice given pazopanib for 13 weeks also had slight decreases in total red blood cell (RBC) number with increased MCV and MCH, but had increased haematocrit and haemoglobin. Bone marrow hypocellularity was seen in rats given pazopanib (≥30 mg/kg/day for 3 months or longer, 300 mg/kg/day for 4 weeks). This may have contributed to the mechanism of altered RBC parameters, but since VEGF signalling is known to play a role in haematopoiesis[8] other VEGF-related pharmacologic effects on haematopoiesis may also have been involved. Decreases in RBC parameters have been noted in rodents with other marketed compounds in this class. Increased incidences of haemosiderosis were noted in the spleen of mice given ≥100 mg/kg/day and this may have been secondary to the observed peripheral blood changes. Splenic responses were not noted in rats. No haematological effects were seen in cynomolgus monkeys.

In rats, bone effects were seen microscopically as hypertrophy of the epiphyseal growth plate (physis) in sternum and/or femur or stifle and hypocellularity of metaphyseal bone marrow at ≥100 mg/kg/day (~0.4 –fold the exposure in humans at the recommended dose based on AUC), after 4 weeks. Additional findings after 13 or 26 weeks included trabecular atrophy and periosteal chondroid change of the femur at ≥30 mg/kg/day. In mice, findings in the sternum and femur noted after 13 weeks included cartilage thickening or degeneration at doses ≥100 mg/kg/day, and partial fusion or osteoarthrosis of the stifle joints were seen at 1000 mg/kg/day (1-2.5 –fold the exposure in humans at the recommended dose based on AUC). Both bone and bone marrow effects in mice and rats were attributed to pharmacological inhibition of VEGFR-2 as VEGF has been shown to be involved in cartilage remodelling, ossification and angiogenesis during endochondrial bone formation[9]. Bone changes were not observed in monkeys given pazopanib. It was suggested in the sponsor's "Nonclinical Overview" report that the difference could be explained by the greater protein binding of pazopanib. The sponsor's "Nonclinical Overview" report also noted that unlike rodents, primate epiphyseal growth plates have minimal or no postpubertal growth, suggesting that VEGFR-2-mediated bone effects occur

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[8] Gerber HP, Ferrara N (2003). The role of VEGF in normal and neoplastic hematopoiesis. *J Mol Med* 81:20–31.

[9] Gerber HP, Vu TH, Ryan AM, Kowalski J, Werb Z & Ferrara N (1999). VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nat Med.* 5:623-628.

in actively growing bones and therefore may not pose an increased risk to adult human patients with closed physes.

Changes seen in the nails/nailbed of rats and mice included an increased incidence of broken, overgrown or absent nails. It was suggested in the sponsor's "Nonclinical Overview" report that given the bone changes in distal epiphyses of digits, these lesions may be associated with phalanx deformities related to VEGF inhibitory activity. Similar changes have been noted with other molecules targeting the VEGF pathway. In the 26-week study in rats, microscopic examination showed dyskeratosis, considered a VEGFR-2-related effect, at ≥30 mg/kg/day (~0.3 times the exposure in humans at the recommended dose based on AUC).

Gastrointestinal effects were seen particularly in cynomolgus monkeys (and at necropsy without clinical manifestation in mice and rats) given high doses of pazopanib for greater than 4 weeks. Cynomolgus monkeys given 500 mg/kg/day (approximately equivalent to the exposure in humans at the recommended dose based on AUC) in the 52 week study had severe gastrointestinal effects (deteriorating clinical condition secondary to recurrent loose/watery faeces, inappetence, decreased activity and weight loss) resulting either in suspension of dosing or early termination. Microscopic examination revealed accumulation of crystalline material, identified as pazopanib, within macrophages and multinucleated giant cells in the lamina propria of duodenum and jejunum, and within mesenteric lymph node macrophages of some monkeys. Similar material, mostly associated with macrophages in small intestinal villi and mesenteric lymph nodes, was also seen in mice given 1000 mg/kg/day for 13 weeks and rats given 300 mg/kg/day for 26 weeks. However, these changes were considered unlikely to be responsible for decreased body weight in the rodent studies given the marked dentition effects which lead to reduced food consumption. It was suggested in the sponsor's "Nonclinical Overview" report that the gastrointestinal findings were secondary to administering large oral doses (~31 times a dose of 800 mg/day to humans, on a mg/kg basis) of a drug with poor solubility at neutral pH, resulting in local precipitation and subsequent local effects in some animals, and hence did not indicate an increased risk of gastrointestinal findings in patients. According to the sponsor's "Clinical Overview" report, diarrhoea has been noted clinically in human patients, but the extent to which the pathogenesis may have been related to local drug precipitation was not discussed.

Renal effects in rats after 26 weeks of dosing included (at ≥3 mg/kg/day; 0.3 –fold the exposure in humans at the recommended dose based on AUC) increases in globulin, decreases in albumin:globulin ratio and increased urinary protein excretion and (at ≥30 mg/kg/day) protein/creatinine ratio, as well as increased serum phosphorous. These effects correlated microscopically with an exacerbation of (possibly age-related, as suggested in the sponsor's "Nonclinical Overview" report) chronic progressive nephropathy. Basophilic tubules and other kidney changes suggesting nephropathy were seen after 13 weeks in mice at 1000 mg/kg/day. It has been reported that neutralization of circulating VEGF by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria in mice[10], and (reversible) proteinuria was noted in some patients given pazopanib (see sponsor's "Clinical Overview" report). VEGF is believed to play a role in maintaining function of glomerular podocytes and renal vasculature[11], and therefore renal changes appear associated with the pharmacologic activity of this class of drugs.

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[10] Sugimoto H, Hamano Y, Charytan D, Cosgrove D, Kieran M & Sudhakar A (2003). Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. *The Journal of Biological Chemistry,* 278:12605-12608.

[11] Hara A, Wada T, Furuichi K et al (2006). Blockade of VEGF accelerates proteinuria, via decrease in nephrin expression in rat crescentic glomerulonephritis. *Kid Intl*, 69: 1986-1995.

Although proteinuria and histologic renal lesions were not noted in monkeys, this may be due in part to marked differences in urinary excretion between monkeys (~3% of the dose) and rats (16% of the dose).

Hepatic effects included increased incidences of eosinophilic foci (in 2 mice) and an adenoma in female mice given 1000 mg/kg/day (~2.5 times the AUC based exposure at the recommended clinical dose) for 13 weeks. According to the sponsor's study report, these latter two findings were not detected amongst background data from nine recently conducted 13-week studies in CD-1 mice at the laboratory at which the study was conducted and were therefore, despite their low incidences, considered related to treatment. Liver enzyme activities were elevated in male mice receiving 300 mg/kg/day and in male and female mice given 1000 mg/kg/day. Increases in liver function parameters (aspartate aminotransferase, AST, and alanine aminotransferase, ALT, and/or bile acids) also occurred in individual rats given ≥300 mg/kg/day for 4 weeks, and alkaline phosphatase (ALP) and ALT were elevated after 26 weeks at ≥3 mg/kg/day. However, none of the changes in rats were associated with microscopic findings in the liver. No histologic evidence of hepatic toxicity was observed in monkeys receiving up to 500 mg/kg of pazopanib for up to 52 weeks but 2 monkeys given 500 mg/kg had moderately increased total bilirubin. According to the sponsor's "Clinical Overview" report, changes in liver enzymes have been noted in patients administered pazopanib, and are consistent with probable drug-induced liver enzyme elevations and therefore clinical monitoring is recommended.

Additional effects in rats included pituitary basophil hypertrophy at ≥3 mg/kg/day after 13 or 26 weeks, decreased number of globule leukocytes in trachea, and adrenal angiectasis and haemorrhage at ≥3 mg/kg/day after 26 weeks and at 300 mg/kg/day after 13 weeks and acinar atrophy of the pancreas at ≥30 mg/kg/day after 26 weeks of dosing. These findings were also present at higher doses in rats after 13 weeks of treatment. Pancreatic oedema was noted in female mice given 1000 mg/kg/day after 13 weeks. It was suggested in the sponsor's "Nonclinical Overview" that these pancreatic changes were possibly related to the reduced food consumption in these animals. Mammary acinar atrophy was noted in a few male rats given 300 mg/kg/day in a 13 week toxicity study, but were not noted in the 26 week study at any dose. As noted in the sponsor's "Nonclinical Overview", VEGF receptors (R1 and R2) are expressed in endothelial cells of the adrenal cortex[12] and proliferation of vascular endothelial cells is a requirement for adrenal cortex development and differentiation[13]. Tracheal globule leukocytes (mucosal mast cells) are known to express VEGF and are involved in the permeability of nearby microvessels[14]. The adrenal and tracheal lesions are therefore likely associated with the VEGFR-2 inhibitory activity of pazopanib. It was suggested in the sponsor's "Nonclinical Overview" that the pituitary changes may be secondary to alterations in the pituitary-adrenal hormonal axis as a result of the adrenal lesions.

**Genotoxicity and carcinogenicity**

In accordance with current regulatory guidelines, pazopanib was tested in a standard battery of genotoxicity studies. Pazopanib was found to be non-mutagenic and non-clastogenic when

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[12] Vittet D, Ciais D, Keramidas M, De Fraipont F, Feige JJ (2000). Paracrine control of the adult adrenal cortex vasculature by vascular endothelial growth factor. *Endocrine Research,* 26:843-52.

[13] Katoh R (2003). Angiogenesis in endocrine glands: Special reference to the expression of vascular endothelial growth factor. *Microscopy Research and Technique,* 60:181-5.

[14] Fan L, Iseki S (1999). Immunohistochemical localization of vascular endothelial growth factor in the globule leukocyte/mucosal mast cell of the rat respiratory and digestive tracts. *Histochemistry and Cell Biology,* 111:13-21.

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, 300 µg/mL or 2000 mg/kg PO, respectively).  The weight of evidence provided by these *in vitro* and *in vivo* assessments suggests that pazopanib does not pose a genotoxic risk in humans.

An intermediate in the pazopanib synthesis process (designated GW776948X) does not contain any structural alerts for genotoxicity, and was not mutagenic in the Ames assay but was demonstrated to be genotoxic in the mouse lymphoma L5178Y TK+/- assay and the *in vivo* mouse micronucleus assay following intraperitoneal (IP) administration (NOEL 25 mg/kg). In the mouse lymphoma L5178Y TK+/- assay, the increase in mutant frequency was due to formation of both small and large colonies, suggesting that both clastogenicity and mutagenicity were contributing to the genotoxicity. GW776948X also induced micronuclei *in vitro* in a (non-GLP) mouse lymphoma (L5178Y TK+/- cells) micronucleus assay in a dose-dependent manner, and a kinetochore assay provided evidence that this clastogenicity occurred through an aneugenic mechanism. The CHMP guidance (CPMP/SWP/5199/02) indicates that for non-DNA reactive substances with sufficient evidence for a threshold-related mechanism (for example, aneuploidy) exposure levels which are without appreciable risk of genotoxicity can be established according to the procedure outlined for Class 2 solvents in ICH Q3C Note for Guidance on Impurities: Residual Solvents (Q3C(R3)).  This approach (taken by the Sponsor) calculates a "Permitted Daily Exposure" (PDE), which is derived from the NOEL in the most relevant (animal) study using "uncertainty factors" (UF).  In this case, this calculation results in a conservative PDE given that the *in vivo* micronucleus was conducted via the IP route and that exposure to GW776948X will occur via the oral route. In terms of what constitutes sufficient evidence for a threshold-related mechanism, it is noted that in the micronucleus study there was a dose-dependent increase in PCE with micronuclei, and which was 3-fold that seen in controls at 25 mg/kg, although the increase was not statistically significant. In the non-GLP mouse lymphoma kinetochore assay, there also was a concentration-dependent increase in micronucleus formation, and while this was not statistically significant at the lowest concentration (0.2 µg/mL), it was statistically significant at $\geq 0.8$ µg/mL, that is, at a clinically relevant concentration. Thus, the evidence for a threshold-related mechanism was not considered compelling.

The calculation of the PDE is given below.

PDE=  $\underline{\text{NOEL x Weight Adjustment}}$

$\qquad$ F1xF2xF3xF4xF5

F1 = extrapolation between species, 12 for mice to human

F2 = measure of variability in data, generally 10

F3 = length of study, 1 for rodent studies of 1 year of more, 10 for short term studies

F4 = severity of toxicity, assuming 10 for carcinogenicity, mutagenicity or teratogenicity

F5 = factor for NOEL if not determined, generally 1 when using a NOEL


The daily PDE for GW776948X was therefore determined as follows:

PDE =  $\underline{\text{25 mg/kg x 50 kg}}$

$\qquad$ (12)(10)(10)(10)(1)

PDE =  $\underline{\text{1250 mg}}$

$\qquad$ 12000

PDE =    0.10 mg

Thus, the PDE for GW776948X was calculated to be 0.1 mg/day.  However, the sponsor has noted that based on controls in the manufacturing process, measured levels of GW776948X in the final drug substance are below this limit, and that GlaxoSmithKline does not believe the presence of this impurity increases the risk for patients with RCC.

While this approach may be acceptable for the evaluation of this impurity when pazopanib is indicated for renal cell carcinoma, this impurity will need to be controlled to below the threshold of toxicological concern (1.5 µg/day) unless a more extensive qualification of this impurity has been conducted if pazopanib is indicated for another use.

Carcinogenicity studies have not been conducted to determine the tumourigenic potential of pazopanib when administered by the oral route.  Since pazopanib is indicated for the treatment of advanced RCC, where the life expectancy of the patient is short, this is consistent with the ICH Guideline on the Need for Carcinogenicity Studies (S1A, 1995), and such studies are therefore not required. However, in the 13-week study in mice, proliferative lesions (eosinophilic foci) were seen in the liver in 2 females and an adenoma in one female at 1000 mg/kg/day (2.5 times the human clinical exposure based on AUC). Therefore, carcinogenic potential of pazopanib cannot be ruled out, and may need to be investigated if pazopanib is indicated for another use.

### *Reproductive toxicity*

Reproductive toxicity studies consisted of male fertility, female fertility and early embryonic development and embryofetal development studies in rats (accompanied by appropriate dose range-finding studies), as well as dose range-finding embryofetal development studies (but no definitive study) in rabbits. No pre/postnatal studies were conducted. Toxicokinetic data were only obtained from pregnant rabbits.

In a male fertility study in rats, pazopanib administered for up to 108 days resulted in statistically significantly reduced seminal vesicle, testicular and epididymal weights (by >12%) at ≥30 mg/kg/day, as well as decreased sperm motility, and statistically significantly decreased (by ~40% relative to controls) sperm production rates and epididymal and testicular sperm concentrations at ≥100 mg/kg/day (~0.8 times the clinical exposure at a dose of 800 mg/day in humans based on AUC).  These data were consistent with the findings in repeat-dose toxicity studies in rats. After 26 weeks of dosing, atrophy/degeneration of the testes with aspermia, hypospermia and cribriform change in the epididymis was seen in rats given ≥30 mg/kg/day (~0.6 times the clinical exposure at a dose of 800 mg/day to humans based on AUC). Dose-dependent but reversible depletion of round spermatids in Stages I-V were also noted after 4 weeks of dosing in rats given ≥100 mg/kg/day followed by a 2 week recovery period. Regardless, no effects on embryo/fetal growth or survival, and no effects on mating or fertility were noted at doses up to 100 mg/kg/day, and the NOAEL for male reproductive effects was considered to be 3 mg/kg/day. However, the presence of VEGFR-2 has been shown on blood vessels in the human testis, epididymis, and prostate[15,16], and the findings were consistent with a pharmacological effect of pazopanib on the male reproductive system and therefore an effect of inhibition of VEGF activity on male fertility cannot be ruled out. Although histological effects

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[15] Ferrer FA, Miller LJ, Andrawis RI, Kurtzman SH, Albertsen PC, Laudone VP, Kreutzer DL (1997). Vascular endothelial growth factor (VEGF) expression in human prostate cancer: in situ and *in vitro* expression of VEGF by human prostate cancer cells. *J Urol*, 157:2329–2333.

[16] Ferrara N, Chen H, Davis-Smyth T, Gerber HP, Nguyen TN & Peers D, et al (1998).  Vascular endothelial growth factor is essential for corpus luteum angiogenesis. *Nat Med.* 4:336-340.

were not observed in the male reproductive organs of monkeys given pazopanib for 52 weeks nor in mice given pazopanib for 13 weeks, based on the effects on male reproductive organs in rats as well as on mechanistic considerations, pazopanib should be considered to have the potential to adversely affect male fertility, and this should be noted in the PI.

In female rats administered pazopanib for 2 weeks prior to and during mating, through to Day 6 *post coitum*, decreased implantations and decreased numbers of live fetuses per litter (due to embryolethality) were observed at doses of >30 mg/kg/day, and a decreased fertility index (number of females pregnant/number mated) at doses of 300 mg/kg/day. Fetal body weights were reduced (up to 16%) at >30 mg/kg/day.

The findings in the female fertility study were consistent with the findings in the repeat-dose toxicity studies. Effects on corpora lutea (sparse or absent) and increased incidence of ovarian cysts were seen in the ovaries of mice given pazopanib at ≥100 mg/kg/day (~2.2 times the clinical exposure at a dose of 800 mg/day to humans based on AUC) for 13 weeks. Coagulative necrosis of corpora lutea occurred at ≥100 mg/kg/day after 4 days in rats. Ovarian atrophy was seen at ≥300 mg/kg/day after 26 weeks. Decreased numbers of corpora lutea were also noted in the ovaries of female cynomolgus monkeys given pazopanib at 500 mg/kg (approximately equivalent to the clinical exposure at a dose of 800 mg/day to humans based on AUC) for 34 weeks. As noted in the sponsor's "Nonclinical Summary", since VEGF-dependent angiogenesis is crucial for follicular growth, corpus luteum formation and function, these ovarian changes are believed to be VEGF mediated and pharmacologically based[16], and have been reported to occur with other compounds in this class. Overall, pazopanib administration adversely affected the female reproductive system and female fertility in rats, and this should be noted in the PI.

Administration of pazopanib to pregnant rats from Days 6 to 17 *post coitum* resulted in maternal effects (decreased body weight), increased post-implantation loss (early resorptions, embryolethality) and decreased fetal body weight at dosages ≥10 mg/kg/day (0.3 –fold the exposure in humans at the recommended dose based on AUC). Pazopanib-related fetal cardiovascular malformations (including retroesophageal right subclavian arteries, missing innominate artery, aortic arch malformations and common truncus) and delayed ossification were observed at ≥3 mg/kg/day (0.1 –fold the exposure in humans at the recommended dose based on AUC). This dose was not associated with significant maternal toxicity, and therefore the findings were considered to be direct effects of pazopanib. The NOAEL for developmental toxicity in the rat was 1 mg/kg/day (0.03 –fold the exposure in humans at the recommended dose based on extrapolated AUC data).

In pregnant rabbits, 100 mg/kg/day (0.04 –fold the exposure in humans at the recommended dose based on AUC) was not tolerated, 30 mg/kg/day (0.01 –fold the exposure in humans at the recommended dose based on AUC) resulted in maternal toxicity (reduced food consumption and abortion) and all dosages including the lowest dose of 3 mg/kg/day (0.003 –fold the exposure in humans at the recommended dose based on AUC), resulted in reduced fetal weight. Investigation of fetal malformations in rabbits was restricted to external anomalies. The study was preceded by a non-GLP study in which pazopanib was administered to non-pregnant rabbits for 13 consecutive days. This resulted in reduced food consumption, body weight loss, mortality and/or early termination due to excessive body weight loss in rabbits given ≥300 mg/kg/day and reductions in food consumption and body weight at 100 mg/kg/day.

Overall, pazopanib reduced female fertility, resulted in adverse findings on the male reproductive system and was abortifacient, embryotoxic, fetotoxic and teratogenic in rats and abortifacient, fetotoxic and embryotoxic in rabbits (teratogenicity was not investigated in this species) at exposures well below clinical exposures (0.1 to 0.6 times the clinical exposure at a dose of 800 mg/day in humans based on AUC).

The scope of the reproductive toxicity investigations conducted was limited, but adequate. No toxicokinetic data were provided from pregnant rats but the data from the repeat dose toxicity studies were considered adequate for exposure comparisons, particularly since AUC data from pregnant and non-pregnant rabbits were comparable. However, the extent to which pazopanib crosses the placenta was not investigated. While there was no definitive embryo-fetal toxicity study in rabbits, this was not required due to the extensive findings in rats and the dose-range finding study in rabbits. No pre-postnatal study or studies with juvenile animals were conducted, and excretion into milk was not investigated. Breastfeeding should therefore be discontinued once treatment with pazopanib is initiated. Overall, the data were adequate to enable determination of the use in pregnancy category and for the inclusion of applicable reproductive toxicity statements in the PI.

### Use in children

No studies were submitted to support paediatric use, and it has been noted in the draft PI that the safety and efficacy of Votrient in children have not been established. Pazopanib has anti-angiogenic activity, and adverse effects have been shown in the toxicity studies on maturing and developing tissues as well as embryofetal toxicity, all at exposures well below the intended human clinical exposure. It was noted in the sponsor's "Nonclinical Overview" that rodent juvenile toxicology studies are not expected to provide additional information on the use of pazopanib in paediatric patients (ICH Guideline SWP/169215).  The omission of these studies is acceptable for the currently proposed indication, particularly since it is proposed that statements to indicate that it should not be used during pregnancy, lactation or in children are included in the PI. However the issue will need to be further investigated in the event that use in a paediatric population is proposed to be indicated.

### Local tolerance, Immunotoxicity, Excipients and Impurities

Pazopanib did not show potential for phototoxicity *in vitro* in the 3T3 cell neutral red uptake assay up to the limits of compound solubility. The study was conducted in accordance with ICH guidance on photosafety testing, since pazopanib absorbs light with a peak at 310 nm, and because a whole body autoradiography study in pigmented rats has shown that pazopanib-related radioactivity distributes to the uveal tissue and skin after oral administration and is retained longer than in other tissues. Moreover, following daily oral dosing in humans of 600 mg or more, pazopanib treatment has been associated with reversible depigmentation of hair in some patients, a finding (according to the sponsor's "Nonclinical Overview") likely related to c-Kit activity of pazopanib. However, according to the sponsor's "Clinical Overview", no patients who had taken the drug in the oral clinical program had shown any photosensitivity reactions at systemic exposures up to 924 μg.h/mL when treated for 2 to 12 months.

Immunotoxicity of pazopanib was not specifically investigated. There were few indications of immunotoxicity in the toxicity studies. Accumulation of (presumably pazopanib-related) crystalline material in the mesenteric lymph nodes was observed in repeat dose toxicity studies in rats and mice, but other histological findings in this tissue (lymphangiectasis and sinus histiocytosis at ≥ 30 mg/kg/day and histiocyte foci at 300 mg/kg/day) were only seen in the 3 month study in rats. As noted above, increases in WBC may have been secondary to inflammation associated with the dental changes or to altered food consumption. Clinically-relevant immunotoxicity was not seen in toxicity studies with other pharmacological agents in this class.

The genotoxicity of impurity GW776948X is discussed under the heading "Genotoxicity and carcinogenicity".

## Nonclinical Summary and Conclusions

- The sponsor has conducted mostly adequate studies on the pharmacodynamics, pharmacokinetics and toxicity of pazopanib, in accordance with the relevant guidelines, using appropriate *in vitro* and animal models. The reproductive toxicity investigations, while limited in scope, were adequate for the indication given the findings. Most toxicity studies were performed according to GLP conditions, and any non-GLP studies were generally adequately documented.

- Pazopanib was shown to inhibit the kinase activities of vascular endothelial growth factor receptors (VEGFR)-1, -2 and -3, platelet-derived growth factor (PDGFR)-α and −β, and stem cell factor receptor (c-Kit), with $IC_{50}$ values ≤0.1 μM, but had lower activity against Flt-3 receptors. Pazopanib also inhibited ligand-induced autophosphorylation of VEGFR-2, c-Kit and PDGFR- β receptors in cells *in vitro*. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation, angiogenesis, and the growth of 4 of 5 human renal carcinoma cell line tumour xenografts tested in mice. A number of other human tumour xenografts were also shown to be sensitive to pazopanib treatment. However, no significant effect on the growth of xenografts of the human renal cell carcinoma cell line CAKI-1 was observed. One metabolite had equivalent pharmacological activity to the parent molecule *in vitro*. *In vitro* and *in vivo* primary pharmacology data indicated potential for antitumour activity and were consistent with a mechanism involving tyrosine kinase inhibition at the targeted receptors at clinically relevant concentrations and doses.

- Radioligand and receptor binding assays indicated potential for binding to adrenoreceptors ($α_2$, $β_1$), $H_2$, $M_1$ and $5HT_{(1A, 5A and 7)}$ receptors at concentrations below the steady-state $C_{max}$ for pazopanib in patients receiving the proposed clinical dose. However, despite increasing the contractile force of rat isolated atria and showing potential to induce a non- β-adrenoreceptor mediated inotropic effect, no evidence of increased blood pressure was observed in the rat or cynomolgus monkey. There were no clinically significant findings in safety pharmacology studies covering the nervous, cardiovascular and respiratory systems. Pazopanib slightly but statistically significantly block the hERG $K^+$ channel, but the maximum concentrations used in the study were limited by solubility to less than the $C_{max}$. No effect was seen on cardiac repolarisation in dog Purkinje fibres. No electrocardiogram (ECG) changes were observed in any of the single- or repeat-dose studies in cynomolgus monkeys.

- Oral bioavailability in rats, dogs and cynomolgus monkeys was 50–70%. The terminal half-life of pazopanib was much shorter in the animal species (4–7 h) compared to humans (~30 h). There was evidence of non-linear pharmacokinetics, with less than dose-proportional exposure observed in every species examined, including humans. Studies with radiolabelled pazopanib indicated wide tissue distribution following oral administration. Transfer across the blood-brain barrier was limited. The extent of plasma protein binding by pazopanib in human plasma was very high (>98%) and similar to that in the mouse, rat, dog and cynomolgus monkey. The pharmacokinetics and metabolite profiles (consisting of minor metabolites only) of pazopanib were qualitatively comparable in the animal models.

- Unchanged pazopanib was the major contributor to the total plasma radioactivity AUC in all species (mice, rats, cynomolgus monkeys and humans) following oral administration of $^{14}$C-labelled drug, the metabolites contributing <10% each. The major metabolic pathways in humans were also prominent in the species used in the repeat-dose toxicity studies. Excretion was predominantly via the faeces in all species examined (rats, cynomolgus monkeys and humans). Renal excretion was more significant in rats (16% of radioactivity recovered) than in humans and cynomolgus monkeys (<4%).

- Pazopanib has the potential to affect the pharmacokinetics of concurrent medications that are substrates for various CYP enzymes (1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1), UGT1A1 and OATP1B1 in humans at clinically relevant concentrations. These are noted in

the draft PI. In *in vitro* studies pazopanib was a substrate but not inhibitor for the human P-gp transporter and the murine BCRP-1 transporter at clinically relevant concentrations. Two metabolites also did not inhibit human P-gp, but both inhibited human BCRP.

- Acute toxicity studies comprised an IV study in mice and a PO study in dogs. In both cases the study design and conduct precluded any significant conclusions from being made and neither met the requirements of the ICH guideline for single-dose toxicity.

- Repeat-dose toxicity studies were appropriate in terms of animal numbers and study duration (13 weeks in mice, 26 weeks in rats and 52 weeks in cynomolgus monkeys). Exposures were equivalent to or slightly exceeded those anticipated clinically, with maximum doses limited by severely reduced body weight gain and mortality.

- Dose-limiting toxicity occurred in the main species used in the repeated-dose studies (mice, rats, cynomolgus monkeys), resulting in low exposures to pazopanib. The main toxicologically significant findings in mice, rats and cynomolgus monkeys were consistent with exaggerated pharmacological effects arising from the inhibition of the relevant receptor kinases.
  Major toxic effects were evident in the teeth (altered dentin composition), bone (bone marrow hypocellularity and growth plate thickening in rats and cartilage degeneration in mice), nails (acanthosis and hyperkeratosis), gastrointestinal system, kidney (tubular degeneration and glomerulopathy), liver and male and female reproductive systems. Most of these changes are considered to be consistent with the primary pharmacological actions of pazopanib. Effects in a number of other organs, including pancreas, adrenals and spleen were also observed. Conclusions on the safety of pazopanib in humans from the nonclinical package were limited by the low relative exposures in the repeat-dose toxicity studies, which ranged from considerably lower to slightly higher than anticipated human clinical exposures, due to dosing being limited by toxicity in rats and cynomolgus monkeys.

- Pazopanib was negative for genotoxicity in an adequate battery of tests. The limit proposed for a genotoxic impurity (designated GW776948X) was considered acceptable given that it may be acting via an aneugenic mechanism, and considering the proposed indication. However, the need for more extensive qualification of GW776948X as well as submission of carcinogenicity studies may need to be considered if another indication is sought. The carcinogenic potential of pazopanib was not investigated, which is acceptable given the proposed indication.

- In rats, post-implantation loss, embryolethality, and decreased fetal body weight were noted in females administered doses ≥10 mg/kg/day, and increased pre-implantation loss and early resorptions were noted at doses ≥30 mg/kg/day, and total litter resorption was seen at 300 mg/kg/day. Decreased corpora lutea and increased ovarian cysts were noted in mice given ≥100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given ≥300 mg/kg/day for 26 weeks. Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to 34 weeks.

- Pazopanib did not affect mating or fertility in male rats, but following 15 and 26 weeks of dosing, there were decreased testicular and epididymal weights at ≥30 mg/kg/day. Atrophy and degeneration of the testes with aspermia, hypospermia and cribiform change in the epididymis was also observed in male rats given doses ≥30 mg/kg/day in the 26-week toxicity study. Reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations were observed at doses ≥100 mg/kg/day following 15 weeks of dosing.

- A full battery of reproductive toxicity studies was not conducted. However, the data were adequate to determine that pazopanib was embryotoxic, fetotoxic, abortifacient and teratogenic. Pazopanib should not be used during pregnancy, in children, and should not be used while breastfeeding. These issues are noted in the draft PI. Administration of pazopanib

to pregnant rats during organogenesis at ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification, increased pre- and post implantation loss, early resorptions, embryo lethality and reduced fetal body weight. In rabbits, reduced fetal weight was seen at ≥3 mg/kg/day, reduced maternal food consumption and increased post-implantation loss, and abortion were observed at doses ≥30 mg/kg/day (approximately 0.01 times the human clinical exposure, based on AUC). Associated exposure levels were below that anticipated clinically, and the effects were consistent with the primary pharmacological actions of pazopanib. Neither the placental transfer of pazopanib nor that of its metabolites was investigated. No pre-postnatal development studies were conducted.

- In rats, treatment with pazopanib resulted in adverse findings on the male and female reproductive systems, and adversely affected female fertility. Pazopanib therefore may impair fertility in human males and females. This has been noted in the draft PI.

- Given the targeted patient population, there is no nonclinical objection to the registration of pazopanib for the proposed indication. However, a number of toxicity issues will need to be resolved in the event that another indication or a change in targeted population is sought. The product information needs to be amended.

## IV. Clinical Findings

### Introduction

GSK initiated a comprehensive clinical development program in 2002 to investigate the efficacy and safety of pazopanib as monotherapy or in combination with other therapies for the treatment of various cancers. Since then, it has been evaluated in multiple Phase I, II, and III cancer trials. As of the cut-off date of 8 June 2008 for this submission, more than 1600 subjects (including healthy volunteers and subjects with various solid tumours) have been enrolled in these trials. Of these, 1155 subjects have received at least one dose of pazopanib 800 mg once daily, the dose for which this submission seeks approval. Pazopanib has also been studied in ophthalmic and dermatological indications using eye drop and ointment formulations, respectively.

#### *Phase I Studies*

As of this submission date, 20 Phase I studies have been conducted or are ongoing to characterise the clinical pharmacology of pazopanib in subjects with cancer. Among these studies are the dose ranging pharmacokinetics and pharmacodynamics study VEG10003; characterisation of absorption, distribution, metabolism and elimination study VEG10004; characterisation of food effect on pazopanib absorption study VEG10005; hepatocellular carcinoma study VEG107200; evaluation of drug-drug interactions studies VEG10006, VEG10007, VEG102857, VEG105427, VEG105424 and VEG108925; and the rollover protocol study VEG105430.

#### *Phase II/III Studies*

As of the submission date, a total of 12 Phase II or Phase III studies have been conducted or are ongoing in adult subjects with cancer. The clinical indications in these protocols include RCC, ovarian cancer, breast cancer, soft tissue sarcoma, cervical cancer, non-small cell lung cancer, multiple myeloma, and glioma. The studies included in the RCC program that are critical to this initial registration application are the pivotal Phase III study VEG105192, and two supportive Studies VEG102616 and VEG107769. In addition, a Phase III study comparing pazopanib with sunitinib in subjects with advanced metastatic RCC (VEG108844) began enrolment in August 2008. However, data will not be available until 2011.

Not all of the abovementioned 32 studies will be reviewed in this evaluation as some are ongoing and others are not directly relevant to the current application.

## Pharmacokinetics

### *Bioequivalence of Clinical Trials and Marketed Formulations*

In accordance with the principles discussed in European Medicines Evaluation Agency (EMEA) guidance entitled "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", *in vitro* dissolution testing was performed and data generated which showed that the changes between Phase III tablets and the proposed commercial tablets are minimal in nature and have no impact on performance of the tablets.

The composition of the Phase III and proposed commercial tablet cores are identical with the only differences being tablet shape, tablet debossing and the film coat colour.

In addition, the sponsor stated that dissolution data clearly demonstrated that the pazopanib tablets, 200 mg and 400 mg, used in Phase III clinical studies and the proposed commercial pazopanib tablets, 200 mg and 400 mg are comparable.

### *Pharmacokinetics in Healthy Subjects*

#### *Study MD1103367*

This was a single-masked, parallel group, placebo-controlled, randomised (with respect to placebo), 14-day repeat-dose, dose-rising study in healthy elderly subjects. Placebo and a total of 4 active doses of pazopanib were planned to be evaluated: 100mg, 300mg, 600mg, and 800mg.

*Results:* Only one cohort of 9 subjects (6 receiving pazopanib 100 mg once daily and 3 receiving placebo) was enrolled. The study was terminated prematurely due to observed increases in alanine aminotransferase (ALT) of $\geq$ 3 times the upper limit of normal in three subjects who received pazopanib 100 mg once daily. Two additional subjects were withdrawn from the study due to sinus arrest (1) and blood pressure increase (1). All adverse events reported in both pazopanib and placebo arms were mild to moderate in intensity.

Exposure to pazopanib was variable after a single dose in healthy volunteers, with area under the concentration versus time curve from 0 h to time of last blood sample ($AUC_{(0-t)}$) value ranging more than 10-fold from 11.0 $\mu$g*h/mL to 138 $\mu$g*h/mL. The range of observed maximum plasma concentration ($C_{max}$) values also was approximately 10 fold (0.867 $\mu$g/mL to 8.98 $\mu$g/mL). There was no correlation between high or low systemic exposures and the elevated ALT values. Pazopanib pharmacokinetic parameters after 14 days of once daily dosing were available from only one subject, who exhibited an accumulation ratio of approximately 1.4. The ratio of $C_{max}$ on Day 14 to $C_{max}$ on Day 1 was approximately 1.1.

#### Study MD7108238

This was a single-masked, placebo-controlled, randomised dose-rising study of pazopanib administered as eye drops in healthy adult subjects. The study was conducted in two parts: Subjects in Part A received a single dose of either 2 mg/mL or 5 mg/mL pazopanib solution in one eye. Subjects in Part B received either 2 mg/mL or 5 mg/mL pazopanib solution in one eye three times daily at 6 hour intervals for 14 days. Plasma pazopanib concentrations were measured on Day 1 in Part A and on Day 1 and Day 14 in Part B.

*Results:* Plasma pazopanib concentrations were observed in all subjects after single and repeated doses of pazopanib eye drops. A summary of relevant pharmacokinetic parameters from study MD7108238 is displayed in Table 5. Pazopanib was absorbed systemically after ocular

administration and accumulation in the plasma after repeated ocular doses was evident. Plasma pazopanib concentrations were at or near steady-state by Day 10 of three times daily ocular administration of the 2 mg/mL or 5 mg/mL solution.

**Table 5**. Geometric Mean (%CV) for Plasma Pazopanib Pharmacokinetic Parameters from Study MD7108238.

| | Treatment[1] | N | AUC(0-24) (µg·h/mL) | Cmax (µg/mL) | tmax (h)[2] |
|---|---|---|---|---|---|
| Part A Day 1 | 2 mg/mL | 3 | 0.0947 (23.8) | 0.00597(17.0) | 3.00 (3.00 - 4.00) |
| | 5 mg/mL | 3 | 0.486 (58.3) | 0.0315 (44.4) | 3.00 (2.00 - 6.00) |
| Part B Day 14 | 2 mg/mL | 10 | 0.835 (67.2) | 0.0353 (66.8) | 2.50 (0.08 – 3.08) |
| | 5 mg/mL | 10 | 1.68 (90.4) | 0.0724 (93.2) | 3.50 (0.25 – 4.00) |

Data Source: MD7108238 CPSR Pharmacokinetic Table 11.2, Table 11.3, Table 11.4, Table 11.5

1. Pazopanib solution was administered at 2 and 5 mg/mL as a single dose in Part A and three times daily dosing in Part B approximately 6 hours apart
2. Median (range)
NA = Not applicable

### *Pharmacokinetics in the Target Patient Population*

### *Study VEG10003*

This was a multicentre, Phase I, open-label, non-randomised, 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. Subjects received a single oral dose of pazopanib followed by repeated oral administration for the remainder of the study. Blood samples for the determination of plasma pazopanib concentrations were collected after a single dose for up to 96 hours (Day 1), and after repeated oral doses at predose on Day 8 and Day 15, and over 24 hours on Day 22. Oral pazopanib 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.

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.

*Results: Day 1 (single dose):* Plasma pazopanib concentrations were measurable in all subjects. Overall, mean $C_{max}$ and area under the concentration versus time curve from 0 to 24 h ($AUC_{(0-24)}$) on Day 1 increased as the pazopanib dose increased, with the highest mean values observed in the 2000 mg once daily dose group. However, mean $C_{max}$ and $AUC_{(0-24)}$ on Day 1 increased in a less than proportional fashion with increasing dose. Geometric mean pazopanib half-life ($t_{1/2}$) values ranged from 18.1 to 52.3 hours. The mean $t_{1/2}$ was 30.9 hours in the 800 mg once daily dose group, the monotherapy dose selected for administration in Phase II and Phase III clinical trials.

*Day 22 (repeated doses):* Mean plasma $AUC_{(0-24)}$ values on Day 22 of daily pazopanib administration were approximately 1.23- to 4.0-fold greater than mean 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. Steady state exposure to pazopanib appeared to plateau at doses of 800 mg once daily and higher. There were no apparent time-dependent changes in pazopanib pharmacokinetics through 22 days of 300 mg twice a day (bid) or 400 mg bid dosing.

Transient increases in plasma VEGF levels were observed during treatment with pazopanib. No consistent changes in other circulating biomarkers of angiogenesis were observed. Changes in DC-MRI were consistent with a decrease in tumour perfusion.

The steady-state trough plasma pazopanib concentration at which there was a 50% probability of developing hypertension was approximately 15 μg/mL (34 μM).

Ten of the twelve subjects with RCC enrolled in this study underwent scheduled disease assessments for evaluation of clinical response. Five of the six subjects (83%) with RCC 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. All four (100%) subjects with progressive disease achieved a steady-state trough concentration of <15 μg/mL.

In this study pazopanib was absorbed orally with median $t_{max}$ values ranging from 2.0 to 4.0 hours after single dose administration. Pazopanib was eliminated slowly and accumulation was observed upon repeated once daily administration. After single and repeated dose once daily administration, increases in pazopanib $C_{max}$ and AUC were less than dose proportional and 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.

### Study VEG10004

This was an open-label, two-part study to characterise the pharmacokinetics of a single intravenous dose of pazopanib and the absorption, distribution, metabolism and elimination of a single oral ^{14}C-labelled dose of pazopanib in subjects with solid tumour malignancies. Subjects enrolled in Part A received a single 400 mg oral radio-labelled 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 GSK1071306, GSK1268992, GSK1268997 and GW700201 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.

Subjects in Part B 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 10 hours on Day 10 of once daily oral administration (study Day 15).

*Results: Part A.* In the three subjects from whom data were available, recovery of the administered radio-labelled dose was 96.9%, 95.3%, and 62.4% through 168 hours postdose. Faecal recovery accounted for 96-98% of the recovered dose and urinary recovery accounted for 2-4% of the recovered dose. Unchanged pazopanib was the predominant component in blood and plasma, accounting for 79% to 95% of the total radioactivity. The major component in faeces was unchanged pazopanib, accounting for a mean of approximately 67% of the administered dose. Pazopanib metabolites in faeces accounted for 6% or less of the administered radioactivity dose.

*Part B.* Median pazopanib $t_{1/2}$ after intravenous administration was approximately 27.5 h which is similar to the geometric mean pazopanib $t_{1/2}$ of 30.9 h reported after oral administration of 800 mg once daily in study VEG10003. In the three subjects from whom data were available,

absolute bioavailability was 13.5%, 21.4%, and 38.9%, with corresponding clearances 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 at 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 suggested that 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 21%, the fraction of the orally bioavailable dose of pazopanib excreted in the urine as pazopanib and metabolites is ~20%.

It was shown that pazopanib is not extensively metabolised and first-pass metabolism is minor, consistent with its low plasma clearance and small volume of distribution. Renal impairment is unlikely to alter systemic exposure significantly.

### Study VEG10005

VEG10005 was an open-label, two-period, randomised crossover study designed to evaluate the effect of food on the pharmacokinetics of single doses of pazopanib in subjects with cancer. Subjects in a lead-in cohort received 400 mg pazopanib with a high-fat meal. Subjects in the randomised food-effect portion of the study received two 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 GSK1071306, GSK1268992, GSK1268997, and GW700201 were collected over 72 hours after administration of pazopanib.

*Results:* The effect of food on pazopanib pharmacokinetics was evaluated by comparing $C_{max}$ and $AUC_{(0-t)}$, truncated at a nominal 72 hours (actual 68-76 h) where possible. The statistical analysis included only subjects who completed both the fed and fasted treatments. 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 compared to administration in the fasted state.

The coefficient of variation (CV%) values for mean pazopanib area under the concentration versus time curve from 0 to 72 h ($AUC_{(0-72)}$) and $C_{max}$ were similar for the fed and fasted states within the high-fat and low-fat meal groups. These results suggest that the variability in pazopanib pharmacokinetics is not altered by administration with food.

Mean $AUC_{(0-t)}$ and $C_{max}$ of the pazopanib metabolites GSK1071306, GSK1268992, GSK1268997 and GW700201 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 time to maximum plasma concentration ($t_{max}$) values for all pazopanib metabolites, with the exception of GSK1071306 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.

***Comment: Administration of a single dose of pazopanib 800 mg with food in cancer subjects increased the bioavailability of pazopanib relative to administration in the fasted state. The $t_{1/2}$ values of pazopanib and metabolites did not change, indicating that food alters pre-systemic mechanisms of bioavailability, with no apparent systemic effects.***

### VEG20006

This was a Phase II, open-label study of pazopanib in patients with relapsed or refractory multiple myeloma. Subjects with relapsed or refractory multiple myeloma received 800 mg pazopanib daily for the duration of the study starting on Day 1. Subjects continued treatment until disease progression, intercurrent illness or unacceptable toxicity occurred.

*Results:* A total of 21 subjects received at least 1 dose of pazopanib. No subjects achieved a minimal, partial or complete clinical response during the course of the study. Data were sufficient to calculate pharmacokinetic parameters in only 11 subjects. Geometric mean pazopanib $AUC_{(0-24)}$, $C_{max}$, and plasma pazopanib concentration at 24 h after administration (C24 values) in Study VEG20006 were 487 μ g*h/mL, 27.5 μ g/mL, and 17.1 μ g/mL, respectively. These values were slightly less than the corresponding geometric mean values observed on Day 22 in VEG10003. Plasma pazopanib C24 values were greater than 20 μ g/mL in 7 of 11 subjects from whom pharmacokinetic parameters were available. No clinical responses were observed in subjects with multiple myeloma.

### *Population Pharmacokinetics Model*

A population pharmacokinetic model was developed with data combined from 5 Phase I studies (VEG10003, VEG10005, VEG10006, VEG10007, and MD1103367), 2 Phase II studies (VEG102616, VEG20006) and 1 Phase III study (VEG105192). The objectives of the population pharmacokinetic analyses were to characterise the population pharmacokinetics of pazopanib in healthy subjects and subjects with cancer and to identify covariates that influence the pharmacokinetics of pazopanib.

The effects of age, sex, body surface area, body weight, baseline Eastern Cooperative Oncology Group (ECOG) status, race (categorised as African American/African heritage, Asian, White, and Other), baseline calculated creatinine clearance (CLCR), concomitant administration of lapatinib, concomitant administration of CYP3A4 inhibitors, and concomitant administration of CYP3A4 inducers on pazopanib clearance (CL/F) were investigated. The effects of age, body weight, and sex on pazopanib volume of distribution (V/F) were investigated. The effects of concomitant administration of medications that affect gastric pH, administration of food, and the tablet formulation (50 mg, 100 mg, 500 mg tablets or 200 mg and 400 mg tablets) on the absorption rate constant (Ka), absorption lag time (ALAG) and bioavailability (F) also were investigated.

Data from 408 subjects were included in the population pharmacokinetics analysis of whom 258 were males and 150 were females. The majority of subjects were either White (N=325) or Asian (N=67). The ages of subjects ranged from 23 to 81 years with a weight range of 38.7 to 147 kg. Baseline CLCR values ranged from 30.8 to 150 mL/min. The following relationships were significant in the population pharmacokinetic model: ECOG baseline performance score (PERF) and lapatinib (LAP) concomitant administration (yes/no) on CL, drugs that increase gastric pH (MED3) and the effect of tablet formulation (TAB) on Ka and ALAG, the effect of dose (400 mg or 800 mg) on F, and the effect of food on Ka, F and ALAG.

The population estimates of CL/F, V/F and F are consistent with the values of CL and F obtained after oral and IV administration of pazopanib in study VEG10004.

Co-administration of lapatinib decreased the estimate of pazopanib clearance by approximately 36%. This result is consistent with the results from study VEG10006, where administration of lapatinib 1500 mg once daily increased geometric mean AUC by 50% relative to administration of pazopanib alone.

Results of the population pharmacokinetic modelling indicated that food affected pazopanib bioavailability, absorption rate, and absorption lag time. The increase in pazopanib bioavailability when administered with food of approximately 2.6-fold estimated by the population pharmacokinetic model was consistent with the 2-fold increase in pazopanib AUC observed when pazopanib was administered with food observed in Study VEG10005.

The lack of effect of CLCR on pazopanib CL is consistent with the results from VEG10004 that indicated that less than 4% of an oral dose is recovered in the urine as pazopanib-related radioactivity, and further suggests that renal impairment is unlikely to alter significantly systemic exposure to pazopanib.

The covariate analysis in the population pharmacokinetics analysis demonstrated that age, race, gender, and body weight were not significant predictors of pazopanib pharmacokinetics. There were insufficient data to determine the effects of CYP3A4 inhibitors and inducers on pazopanib pharmacokinetics as data from only four subjects with concomitant administration of CYP3A4 inhibitors and two subjects with concomitant administration of CYP3A4 inducers were included in the population pharmacokinetics analysis.

### Pharmacokinetics in Special Populations

### Effect of renal impairment

Results from Study VEG10004 indicated that less than 4% of an orally administered dose is recovered in the urine as pazopanib-related radioactivity. However, relative to the bioavailable dose (median absolute bioavailability of 21%), the fraction that is excreted in the urine as pazopanib and metabolites is approximately 20%. Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites. Results of the population pharmacokinetic modelling further indicate that renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics.

### Effect of hepatic impairment

The pharmacokinetics of pazopanib have not yet been evaluated in subjects with hepatic impairment. The effect of hepatic impairment currently is being investigated in Study NCI8063. Subjects in this study will be stratified into four groups or cohorts: normal liver function, mild liver dysfunction, moderate liver dysfunction, and severe liver dysfunction. Pazopanib will be administered once daily at starting doses of 100 mg, 200 mg, 400 mg, or 800 mg for the severe liver dysfunction, moderate liver dysfunction, mild liver dysfunction, and normal liver function cohorts, respectively. Pazopanib dose levels will be escalated up to 800 mg once daily based on safety and pharmacokinetics.

Despite the absence of these study results, it is anticipated that hepatic impairment could alter pazopanib disposition. Approximately 11% of an oral pazopanib dose was recovered as metabolites in faeces and 2% to 4% of the oral dose was recovered as pazopanib and metabolites in urine (Study VEG10004). If up to 4% of an oral dose was recovered in the urine as metabolites, then a maximum of 15% of an oral dose may be recovered as metabolites. These results suggest that relative to the bioavailable dose (median absolute bioavailability of 21%), the maximum fraction that is metabolised is approximately 71%. Complete loss of hepatic clearance may result in an approximately 3.5-fold increase in pazopanib AUC. Therefore, administration of pazopanib should be undertaken with caution in patients with hepatic impairment.

### Summary and Comments Relevant to Dose Selection

*Absorption:* Plasma concentrations of pazopanib peak from 2 to 4 hours following single dose administration. Pazopanib is absorbed orally with an absolute oral bioavailability of 13.5-38.9%. Exposure to pazopanib is increased approximately 2 fold by administration with a low-fat meal or a high-fat meal.

$C_{max}$ and AUC increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg after single dose and repeated once daily dose administration. 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.

*Distribution:* Pazopanib is extensively bound to human serum albumin (>99%) and to human
1-acid glycoprotein (AAG, 95%). After 5 mg IV administration, pazopanib displayed a volume of distribution of 9.2-13.1 L (<40% of total body water).

*Metabolism:* Pazopanib is the predominant species present in human plasma and recovered in faeces after oral administration. *In vitro* studies in human hepatocytes and hepatic microsomes indicate that pazopanib is metabolised primarily by CYP3A4 and to a lesser extent by CYP1A2 and CYP2C8.

*Excretion:* Faecal excretion is the predominant route of pazopanib elimination after oral administration. Less than 4% of the radio-labelled pazopanib oral dose was recovered in urine. Given the median absolute bioavailability of 21%, the fraction of the orally bioavailable dose of pazopanib that is excreted in the urine as pazopanib and metabolites amounts to ~20%. Pazopanib is eliminated slowly with geometric mean $t_{1/2}$ of approximately 30 h. Administration of pazopanib 50 to 2000 mg once daily for 22 days resulted in a 1.2 to 4.0-fold increase in $AUC_{(0-24)}$ values relative to single dose administration consistent with the average 30 h half-life.

*Pharmacokinetic Drug-Drug Interactions:* Ocular administration of a single dose of pazopanib with repeated oral dosing of ketoconazole (potent CYP3A4 and P-gp inhibitor) increased plasma pazopanib $C_{max}$ and $AUC_{(0-t)}$ 1.47-fold and 2.21-fold, respectively, compared to pazopanib administered alone. Co-administration of lapatinib 1500 mg once daily plus pazopanib 800 mg once daily resulted in 50% to 60% increases in $AUC_{(0-24)}$ and $C_{max}$ relative to administration of 800 mg pazopanib once daily alone. When co-administered with enzyme inducing anti-convulsants, pazopanib $AUC_{(0-24)}$ and trough concentrations were decreased by approximately 30% and 50%, respectively, relative to administration of pazopanib alone.

Effects of pazopanib on liver cytochrome P-450 (CYP) enzymes are described under *Drug-Drug Interactions* below.

Age, race, and gender had no effect on pazopanib pharmacokinetics.

Plasma pazopanib concentrations after single and repeated doses of 50 mg to 2000 mg were not correlated with the QT interval in subjects with cancer.

Pharmacodynamic data indicate that pazopanib, at a monotherapy dose of 800 mg once daily, results in effects consistent with inhibition of the VEGF receptors it was designed to target. Concentration-effect relationships were observed between trough plasma pazopanib concentrations and the development of hypertension in Study VEG10003 and the percent change from baseline in sVEGFR2 nadir in study VEG102616. The trough plasma pazopanib concentrations associated with one-half the maximal effect ($EC_{50}$) in both concentration-effect relationships were similar (21.3 µ g/mL and 15.3 µ g/mL) and demonstrated that there is a consistent inhibition of VEGF receptor(s) in subjects with cancer when plasma pazopanib concentrations are maintained above 15 µ g/mL.

Clinical responses were observed at plasma pazopanib concentrations associated with VEGFR inhibition in Study VEG10003 where a range of pazopanib doses was administered to subjects with RCC. Although clinical responses were not observed in all subjects with RCC in Study VEG10003 that achieved a trough plasma pazopanib concentration     15 µ g/mL, only subjects in whom trough concentrations were     15  g/mL achieved a clinical response. No clinical

responses were observed in subjects with RCC in whom trough plasma pazopanib concentrations were <15 $\mu$ g/mL.

Pazopanib C24 at steady-state was greater than 15 $\mu$ g/mL in 93% of subjects that received 800 mg once daily in study VEG10003. 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. The pharmacokinetic and pharmacodynamic results across clinical studies support that pazopanib 800 mg once daily is the appropriate monotherapy dose for subjects with RCC that provides optimal biologic and clinical effects associated with VEGFR inhibition.

## Drug Interactions

### *Study MD7110861*

This was an open-label, two-period, fixed-sequence study in healthy volunteers to evaluate the effects of repeat oral dosing of ketoconazole on the pharmacokinetics of a single dose of pazopanib administered as eye drops. Healthy subjects received a single ocular dose of pazopanib administered as 2 x 40 $\mu$ L drops of a 5 mg/mL solution on Day 1, followed by a washout period of approximately 12 days. Subjects then received 400 mg ketoconazole orally once daily for 8 days. On the fifth day of ketoconazole administration, subjects received an ocular dose of pazopanib administered as 2 x 40 $\mu$ L drops of a 5 mg/mL solution. Blood samples for the analysis of plasma pazopanib concentrations were collected over 96 hours after each administration of the pazopanib eye drops.

*Results:* Results of the statistical analysis of pazopanib pharmacokinetic parameters are shown in Table 6. Results suggested that oral absorption contributes to the systemic exposure to pazopanib after ocular administration. Compared to pazopanib administered alone, pazopanib administered with multiple doses of ketoconazole resulted in greater pazopanib $C_{max}$, AUC, and $t_{1/2}$ values.

**Table 6.** Effect of Ketoconazole on Pazopanib in Study MD7110861

| Parameter | Comparison of Interest | Ratio | 90% CI | CVw% [c] |
|---|---|---|---|---|
| AUC(0-t) [a] | B : A | 2.21 | (1.85, 2.63) | 35.3 |
| Cmax [a] | B : A | 1.47 | (1.24, 1.75) | 34.8 |
| t1/2 (h) [a] | B : A | 2.81 | (2.51, 3.15) | 21.8 |
| tmax (h) [b] | B - A | 0.00 | (-1.00, 1.00) | --- |

Data Source: MD7110861 CPSR Pharmacokinetic Table 12.1 and Table 12.2
a. Point estimate is the ratio of adjusted geometric means between regimens
b. Point estimate is the estimated median difference between regimens
c. CVw% represents a pooled estimate of within-subject variability across regimens
Regimen:
A = Pazopanib, single dose as 2 x 40 µL drops of 5 mg/mL solution
B = Ketoconazole, 400 mg oral dose on Days 1 - 8; Pazopanib, single dose as 2 x 40 µL drops of 5 mg/mL solution administered on Day 5

## Study VEG10006

Study VEG10006 was an open- label, safety, pharmacokinetic and pharmacodynamic study of multiple doses of pazopanib and lapatinib concomitantly administered in cancer patients. VEG10006 included a Dose-Escalation Phase and an expanded cohort phase. Subjects enrolled in the Dose-Escalation Phase (3 to 6 subjects per cohort) received lapatinib and pazopanib once daily for the duration of the study starting on Day 1. Pazopanib and lapatinib doses were escalated based on safety profiles observed in the first 21-day treatment cycle. Blood samples for

the determination of plasma pazopanib and lapatinib concentrations were collected according to a sparse blood sampling scheme on Day 22 in the Dose-Escalation Phase of this study.

Subjects in the Expanded Cohort Phase received either 1000 mg lapatinib once daily plus 400 mg pazopanib once daily or 1500 mg lapatinib once daily plus 800 mg pazopanib once daily. Subjects received either pazopanib or lapatinib alone for 15 days, followed by addition of the other agent. The steady-state pharmacokinetics of the combined administration was assessed on Day 37 and compared to the steady-state pharmacokinetics of each agent alone on Day 15.

***Results: Dose-Escalation Phase.*** Geometric mean plasma pazopanib C24 values did not increase in a dose-proportional fashion across the dose cohorts studied. There was no obvious trend in median plasma pazopanib trough concentrations as the lapatinib dose increased. Geometric mean plasma lapatinib C24 was variable across the dose levels studied. There was no trend in median lapatinib trough plasma concentration values as the daily dose of pazopanib increased.

***Expanded Cohorts.*** Lapatinib 1000 mg once daily had no marked effect on pazopanib pharmacokinetics after administration of 400 mg once daily. In contrast, lapatinib 1500 mg once daily plus pazopanib 800 mg once daily resulted in an approximately 50% to 60% increase in geometric mean $AUC_{(0-24)}$ and $C_{max}$ relative to administration of 800 mg pazopanib once daily alone. Pazopanib 400 mg once daily had no consistent effect on lapatinib pharmacokinetics after administration of lapatinib 1000 mg once daily. The small number of subjects from whom data were available (N=4) and the variability in plasma lapatinib concentrations precluded interpretation of the effect of pazopanib on lapatinib pharmacokinetics. However, there was no apparent effect of co-administration of pazopanib 800 mg and lapatinib 1500 mg on lapatinib pharmacokinetics.

***Comment: Administration of lapatinib 1000 mg once daily had no consistent effect on the pharmacokinetics of pazopanib 400 mg once daily relative to administration of pazopanib alone. However, concentrations of lapatinib achieved after administration of 1500 mg once daily were sufficient to increase the bioavailability of pazopanib 800 mg once daily. This increase in pazopanib bioavailability is consistent with increased absorption due to inhibition of CYP3A4 in the gut and/or inhibition of systemic pazopanib metabolism by CYP3A4.***

### Study VEG102857

This is an ongoing Phase I/II, open-label, multicentre trial of pazopanib in combination with lapatinib in adult patients with relapsed malignant glioma. Subjects on a stable regimen of enzyme inducing anticonvulsants (EIACs) received pazopanib and lapatinib starting on Day 1 in the Phase I portion of the study. Blood samples for the determination of plasma pazopanib and lapatinib concentrations were collected on Day 15 in all subjects. Escalation of pazopanib and lapatinib doses was based on the safety profile observed during the first 21-day cycle and the plasma pazopanib and lapatinib concentrations observed on Day 15.

***Results:*** Data from the Phase I portion of the study were provided. At the cut-off date, data were available from subjects administered 200 mg pazopanib once daily plus 1500 mg lapatinib once daily (N=4), 800 mg pazopanib once daily plus 1500 mg lapatinib once daily (N=6), and 800 mg pazopanib once daily plus 500 mg lapatinib twice daily (N=3).Geometric mean and median trough plasma pazopanib concentrations (C24) in all dose cohorts studied to date were less than the target of 15 μ g/mL that demonstrated clinical activity and biologic effects in Study VEG10003.

In addition, in cohorts where 800 mg of pazopanib was administered once daily in the presence of lapatinib and EIACs, geometric mean pazopanib $AUC_{(0-24)}$ and plasma concentration at 24-

hour (C24, trough level) values were 30% and 50% less, respectively, than the geometric mean values observed on Study Day 22 of pazopanib 800 mg once daily in Study VEG10003.

Dose-escalation is ongoing, however, pazopanib doses >800 mg once daily and lapatinib doses >1500 mg once daily or >500 mg twice daily may be required to achieve target trough concentrations in the presence of EIACs.

### Study VEG10007

This was a multicentre, open-label, multiple-probe drug interaction study to determine the effects of pazopanib on the metabolism of cytochrome (CYP) P450 probe drugs in patients with solid tumours. It was a non-randomised crossover study. Subjects received a single dose of midazolam 3 mg orally (CYP3A4) on Days 1 and 23, and a cocktail of caffeine 200 mg (CYP1A2), omeprazole 40 mg (CYP2C19), dextromethorphan 30 mg (CYP2D6), and warfarin 10 mg (CYP2C9) on Days 2 and 24. Pazopanib 800 mg once daily administration began on Day 6 and continued for the duration of the study. Blood and urine samples for bioanalysis of the probe drugs were collected for 6 days after each administration of midazolam on Day 1 and Day 23. Plasma pazopanib and pazopanib metabolite concentrations were determined on Day 22 and Day 24.

*Results:* Relevant pharmacokinetic parameters for the CYP probe drugs are summarized in Table 7. Geometric mean plasma pazopanib $C_{max}$ values observed in study VEG10007 after 800 mg once daily were more than 7- to 16-fold greater than the in vitro $IC_{50}$ values for inhibition of CYP enzymes. However, pazopanib 800 mg once daily is only a weak inhibitor of CYP3A4 and CYP2D6 *in vivo*. Pazopanib 800 mg once daily had no effect on CYP2C9, CYP1A2, or CYP2C19 metabolism *in vivo*.

**Table 7.** Effects of Pazopanib on CYP Probe Substrates *In Vivo* in Study VEG10007.

| Analyte(s) | | Parameter | N | Ratio[1] of Geometric Least Squares Means | 90% CI for the Ratio |
|---|---|---|---|---|---|
| Midazolam (CYP34) | | AUC(0-∞) (ng.h/mL) | 14 | 1.32 | 1.11, 1.57 |
| 1-hydroxymidazolam | | AUC(0-t) (ng.h/mL) | 21 | 1.27 | 1.06, 1.53 |
| S-Warfarin (CYP2C9) | | AUC(0-∞) (ng.h/mL) | 9 | 0.82 | 0.64 ,1.06 |
| Omeprazole/ 5-hydroxyomeprazole (CYP2C19) | | Concentration ratio at 2 hours | 12 | 0.92 | 0.61, 1.37 |
| Caffeine (CYP1A2) | | AUC(0-10) | 20 | 1.00 | 0.77, 1.30 |
| Urine Dextromethorphan to 1-Dextrorphan Ratio (CYP2D6) | | Concentration ratio 0-4 hours | 16 | 1.33 | 0.99, 1.77 |
| | | Concentration ratio 4-8 hours | 15 | 1.64 | 1.16, 2.32 |
| | | Concentration ratio 8-10 hours | 17 | 1.62 | 1.13, 2.34 |
| | | Concentration ratio 10-24 hours | 17 | 1.45 | 1.02, 2.07 |

Data source: VEG10007 CPSR pharmacokinetic Table 11.97 and Table 11.99
1. Ratio is the estimate of the ratio of geometric means for the PK parameter for the probe drugs administered in combination with pazopanib versus the probe drug administered alone.

### Study VEG105427

Study VEG105427 was a 3-part, Phase I, open-label study of the safety, tolerability, and pharmacokinetics of pazopanib in combination with paclitaxel in subjects with cancer. Subjects in Part 1 received paclitaxel intravenously as a 1-hour infusion on Days 1, 8, and 15 every 28 days. Pazopanib dosing began on Day 2 and continued throughout the duration of the study. Pazopanib and paclitaxel doses were escalated to determine the maximum tolerated regimen (MTR). Blood samples for determination of plasma paclitaxel and pazopanib concentrations were collected on Day 1 (paclitaxel only), Day 8 (paclitaxel and pazopanib), and Day 15 (paclitaxel and pazopanib) of Cycle 1.

*Results:* The MTR was determined to be 80 mg/m$^2$ paclitaxel IV on Days 1, 8, and 15 every 28 days and 800 mg pazopanib once daily. Geometric mean plasma paclitaxel area under the concentration versus time curve from 0 h to infinity (AUC$_{(0-\infty)}$), increased approximately 26% after administration of 80 mg/m$^2$ plus 800 mg pazopanib once daily relative to administration of 80 mg/m$^2$ paclitaxel alone. Statistical analyses of paclitaxel clearance (CL) and dose-normalised C$_{max}$ across subjects who received 800 mg pazopanib once daily are presented in Table 8. Pazopanib 800 mg once daily is a weak inhibitor of CYP2C8 and/or CYP3A4.

**Table 8**. Effect of Pazopanib on Paclitaxel Clearance and Dose-Normalized C$_{max}$ in Study VEG105427.

| Parameter | N | Geometric Least Squares Mean | | | 90% Confidence Interval |
|---|---|---|---|---|---|
| | | Day 1 | Day 15 | Ratio | |
| CL (L/h/m²) | 17 | 21.7 | 18.6 | 0.86 | 0.72 – 1.02 |
| Cmax/Dose (µg/mL/mg) | 20 | 0.427 | 0.560 | 1.31 | 1.03 – 1.67 |

### Drug-Drug Interactions

Pazopanib produced moderate to marked in vitro inhibition of CYP enzymes [1A2, 3A4,2B6, 2C8, 2C9, 2C19, 2D6 and 2E1] with IC$_{50}$ values ranging from 7.9 µ M (2C9) to 18 µ M (2D6).

These concentrations are 2- to 4-fold below the 34 µ M (15 µ g/mL) trough plasma pazopanib concentration associated with clinical activity and biologic effects. Therefore, pazopanib could inhibit multiple CYP enzymes at target concentrations.

Results from Study VEG10007 indicated that pazopanib 800 mg once daily was a weak inhibitor of CYP3A4 (midazolam) and CYP2D6 (dextromethorphan) and had no clinically relevant effect on the probes for CYP1A2 (caffeine), CYP2C9 (warfarin), or CYP2C19 (omeprazole). Pazopanib 800 mg once daily increased paclitaxel (80 mg/m$^2$, a substrate for CYP2C8, CYP3A4, and P-gp) mean AUC$_{(0-\ )}$ by 26% relative to administration of paclitaxel alone in study VEG105427.

Results from studies VEG102857 and MD7110861 indicate that co-administration of compounds that inhibit or induce CYP3A4 will alter the pharmacokinetics of pazopanib. Oral absorption contributes to the systemic exposure to pazopanib after ocular administration, and pazopanib oral absorption is not dose-dependent at doses of 800 mg and less. Therefore, a similar increase in systemic exposure to pazopanib is expected after oral administration of 800 mg with strong CYP3A4 inhibitors. A dose reduction of 400 mg of pazopanib is recommended if co-administration of a strong CYP3A4 inhibitor is warranted.

## Pharmacodynamics

### Study VEG102616

This was a Phase II Study of pazopanib using a randomised discontinuation design in subjects with locally recurrent or metastatic clear-cell renal cell carcinoma. Adult subjects with renal cell carcinoma (RCC) received pazopanib 800 mg administered once daily. Serial blood samples for the determination of plasma pazopanib concentrations were collected at the clinic visit on Week 4 of treatment, before and 1-8 h posttreatment. In addition, a blood sample was obtained pre-dose (within 22 to 26 h from previous dose of pazopanib) at the clinic visit at Week 8 and Week 12. Blood samples for the determination of plasma sVEGFR2 concentrations were collected at the Week 1 clinic visit (prior to pazopanib administration) and prior to pazopanib administration at the Week 4, Week 8, and Week 12 clinic visits. The nadir in plasma sVEGFR2 was identified

for each subject, and the percent change from the baseline sVEGFR2 concentration prior to pazopanib administration was calculated.

***Results:*** The geometric mean plasma pazopanib trough concentration at Week 4 was greater than the target of 15 μ g/mL, suggesting that plasma pazopanib concentrations associated with clinical and biologic activity were achieved in the majority of subjects. An Emax model[17] described the relationship between the predose plasma pazopanib concentration measured at the Week 4 clinic visit and the percent change from baseline in the sVEGFR2 nadir. The Week 4 predose plasma concentration at which the decrease from baseline in the sVEGFR2 nadir was 50% of the maximum value was approximately21 μ g/mL. It was shown that pazopanib decreases sVEGFR2, a marker for VEGF receptor inhibition, in a concentration-dependent fashion.

### Study VEG104450

This was a Phase II, open-label study evaluating the effect of pazopanib in subjects with ovarian cancer. VEG104450 was a multicentre, open-label study of pazopanib in adult female subjects with ovarian epithelial, fallopian tube or primary peritoneal cancer. Treatment consisted of 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 by a repeated measurement no earlier than 21 days after initial response was observed. Blood samples for determination of plasma pazopanib concentrations were obtained within 60 minutes prior to pazopanib administration on Day 1 of Treatment Periods 2 and 3.

***Results:*** Thirty-six women were enrolled into the study. Thirty-one percent of subjects experienced a CA-125 response to pazopanib. The mean and median predose plasma pazopanib concentrations on Day 1 Period 2 were 32.3 μ g/mL and 28.3 μ g/mL, respectively. Predose plasma pazopanib concentrations on Day 1 Period 2 were greater than 15 μ g/mL (the concentrations associated with clinical activity and biologic effects in study VEG10003) in 25 of the 29 (86%) subjects from whom data were available in study VEG104450. These results suggest that the majority of subjects enrolled in VEG104450 achieved plasma pazopanib concentrations associated with clinical activity and biologic activity. However, a total of 31% of subjects experienced a CA-125 response to pazopanib, which suggests that factors other than plasma pazopanib concentration likely influence the CA-125 response.

### Pazopanib-Concentration-QT Interval Relationship

A pharmacokinetic/pharmacodynamic model was developed to describe the relationship between pazopanib plasma concentrations and the QT interval using data from 2 studies. Plasma pazopanib concentrations were obtained at the time of ECG measurements in Study VEG10003 and Study VEG10005.

There was no apparent relationship between plasma pazopanib concentrations and the mean QTcF[18] interval within each plasma pazopanib quantile analysed. Results of the mixed-effects modelling suggest that there was no relationship between plasma pazopanib concentrations and the QT interval.

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[17] A three-parameter logistic equation or sigmoid $E_{max}$ model (four-parameter if inhibitory sigmoid) or modified Hill equation.

[18] The QT interval was corrected for heart rate using the Fridericia's (**QTcF**) formula which takes into account the physiologic shortening of the QT interval which occurs as the heart rate increases, permitting comparison of the QT interval across a range of rates. It is mathematically defined as: QTcF = QT/CubeRootRR(seconds) and theoretically corrects the QT interval to that which would be observed at a heart rate of 1 cycle per second.

## Efficacy

The primary data to support pazopanib clinical efficacy in advanced RCC were from the pivotal Phase III study, VEG105192. Supportive efficacy data were also provided from the Phase II study VEG102616 and the extension study VEG107769.

### Pivotal Study VEG105192

### Study Design and Objectives

VEG105192 was the pivotal Phase III, randomised, double-blind, placebo-controlled, multicentre study. The primary objective of the study was to evaluate and compare the progression-free survival (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 rate (RR), rate of complete response (CR) + partial response (PR) + 6-month stable disease (SD), safety and tolerability. Additional objectives included pharmacokinetics, quality of life assessments and pharmacogenetics.

The key eligibility criteria were: subjects have locally advanced or metastatic RCC, were treatment-naïve or cytokine-pretreated; had clear cell or predominantly clear cell histology; measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST); Eastern Cooperative Oncology Group performance status (ECOG PS[19]) of 0 or 1; and protocol specified criteria for acceptable organ function. Eligible subjects were first stratified according to the following stratification factors:

1) prior systemic therapy: treatment-naïve versus cytokine-pretreated

2) baseline ECOG PS 0 versus 1, and

3) prior nephrectomy status: yes versus no.

Subjects were then centrally randomised in a 2:1 ratio of pazopanib: placebo to receive 800 mg pazopanib daily dosing or matching placebo. Subjects continued on the investigational product until disease progression, death, unacceptable toxicity or withdrawal of consent.

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 the 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. Eligible subjects who progressed on placebo had the option to receive pazopanib by enrolling into Study VEG107769.

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[19] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 - Dead

A cross-study Independent Data Monitoring Committee (IDMC) was established for VEG105192 and VEG102616 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 was comprised of 6 board-certified radiologists, performed a blinded review of all scans for randomised 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). The first planned analysis of the study was when the final PFS analysis occurred, which also included the interim analysis on overall survival. The final analysis on OS will occur when the required number of death events (n=287) for the OS analysis has accrued.

A major Protocol Amendment was issued on 09 May 2006. Major revisions included:

*1. Expansion of the study population to include treatment-naïve advanced RCC subjects.*

The initial protocol finalised in November 2005 was to enrol subjects with advanced RCC who had received one prior cytokine-based therapy. This was because cytokine-based therapies were considered the standard of care at this time despite their limited benefit and serious toxicities. Following the approvals of sorafenib and sunitinib by the FDA for advanced RCC in December 2005 and January 2006, respectively, GSK discussed with the FDA in March 2006, prior to the first subject being enrolled in VEG105192, expanding the study population to include subjects with treatment-naïve advanced RCC. This was based on the following rationales: 1) it was broadly recognised that cytokines have limited clinical efficacy and substantial toxicity, therefore, best supportive care was most appropriate for treatment-naïve patients in many countries prior to the availability of anti-angiogenic agents, and 2) with the emerging data from anti-angiogenic agents and the diminishing use of cytokine-based therapy for advanced RCC it was reasonable to evaluate pazopanib in both treatment-naïve and cytokine-pretreated subjects.

*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 progressed disease (PD) events to be achieved from each subgroup prior to the final PFS analysis.

Two interim OS analyses were scheduled with the initial design: the first interim OS analysis was to occur at the time of final PFS analysis with approximately 33% of the final death events (287); the second interim OS analysis was to occur when 67% of the final death events accrued. With the revision of final PFS analysis to be based on 127 PD events from each treatment-naïve and cytokine-pretreated subgroups, it was projected that at the time of final PFS analysis, 70% of the final required death events would have been achieved and therefore only one interim OS analysis was necessary.

*3. Allow crossover of subjects in the placebo arm to receive pazopanib treatment.*

The protocol was initially designed without a crossover. However, with emerging data from other agents in this class demonstrating clinical benefit in advanced RCC, and per investigators' request, GSK amended the protocol to allow subjects randomised to the placebo arm, who progressed, to receive pazopanib as a treatment option through the open label extension study VEG107769.

***Statistical methods*:** Although the primary endpoint in this study was PFS, the sample size calculation was based on 90% power to detect a 50% improvement in median OS with pazopanib treatment compared with placebo treatment. Given 1 interim analysis 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 with a 2:1 randomisation.

This sample size allowed at least 90% power (1-sided alpha of 0.025) to detect a 100% improvement of PFS in the overall study population (intent-to-treat, ITT, population) as well as the treatment-naïve and cytokine-pretreated subgroups. To achieve this power, the final PFS analysis was planned to occur after 90 PFS events had accumulated in each of the subgroups. PFS was summarised using Kaplan-Meier survival curves, and compared between treatment arms using a stratified log-rank test. The primary analysis of PFS was based on IRC assessments. Nine sensitivity analyses of PFS were performed to confirm the robustness of the primary result including analyses based on disease assessment by the investigator, using the scan date, adjusted or unadjusted for stratification factors and so on. Subgroup analyses were performed using the same methods.

OS was summarised using Kaplan-Meier survival curves, and compared between treatment arms using a stratified log-rank test. RR was compared between treatment arms using a Fisher's exact test. Approximate 95% confidence intervals (CI) for the difference in RRs were calculated. Duration of response and time to response were summarised descriptively using medians and quartiles.

The ITT population was the primary population used for the analysis of efficacy data. The ITT population comprised all randomised subjects which were analysed based on the assigned randomised treatment and not based on actual treatment received. Sub-populations of interest, including treatment-naïve and cytokine-pretreated subgroups, were also analysed as prespecified in the RAP.

### Study Populations

A total of 435 subjects were enrolled between 18 April 2006 and 24 April 2007, from 23 countries/regions in Europe, South America, Asia and Pacific regions. This included 233 treatment-naïve subjects and 202 cytokine-pretreated subjects who received one prior interleukin 2 (IL-2) or interferon-alfa (IFN  )-based therapy. Two hundred and ninety subjects were randomised to the pazopanib arm and 145 subjects were randomised to the placebo arm. The clinical cut off date for this report was 23 May 2008. At the time of the submission, the study was still on-going to collect additional safety and survival data.

As OS was the principal secondary endpoint, study completion for a subject was defined as when death had been reported for a subject or when the study was closed. At the time of cut off, deaths were reported for 38% subjects in the pazopanib arm and 46% in the placebo arm. Twenty-two percent subjects in the pazopanib arm and 10% in the placebo arm were still on study treatment.

The majority of subjects had discontinued the investigational product at the time of clinical cut-off. The main reason for discontinuation of the investigational product was disease progression

(pazopanib: 51% and placebo: 77%). A higher proportion of subjects in the pazopanib arm compared with the placebo arm discontinued the investigational product prematurely (that is, with reasons other than disease progression or death), with 14% discontinued because of AEs and 10% for other reasons in the pazopanib arm as compared to 3% discontinued because of AEs and 3% for other reasons for the placebo arm.

The safety and ITT populations were identical for both pazopanib and placebo treatment groups. The proportions of treatment-naïve and cytokine-pretreated subjects in each arm were balanced due to stratification.

### *Demographics and Other Baseline Characteristics*

Demographic characteristics were similar between the treatment groups. Overall, most subjects were White (86%), male (71%), and the median age was 59 years.

Demographic characteristics were similar between subgroups by prior systemic therapy for both the pazopanib and placebo treatment groups.

Baseline disease characteristics were balanced between the two treatment groups. Subjects had either clear cell histology (90%) or predominantly clear cell histology (9%). Forty-three percent presented with Stage IV disease at initial diagnosis. At screening, all subjects had Stage IV (metastatic) disease. The most common metastatic sites were lung (74%), lymph nodes (56%), followed by bone (27%), liver (25%) and kidney (23%). More than 50% of subjects had tumour lesions involving 3 or more organs, indicating a relatively large tumour burden in these subjects. The proportion of subjects with a favourable Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk was lower than those with an intermediate prognostic risk (39% versus 54%). In addition, 3% of subjects were in the poor prognostic group.

The disease characteristics were generally similar between the treatment-naïve and cytokine-pretreated subjects (see Table 9). As expected, the time since initial diagnosis of RCC and the time since diagnosis of Stage IV disease were longer in the cytokine-pretreated subgroups compared with the treatment-naïve subgroups. Prior and current medical conditions were similar in the two study groups. The co-morbid condition of hypertension is common in subjects with advanced RCC. Overall, 40% of subjects had hypertension at the start of the study, 38% of subjects in the pazopanib arm and 44% of subjects in the placebo arm.

Similar proportions of subjects in each arm were treatment-naïve and cytokine-pretreated. In the cytokine-pretreated subgroup, in the pazopanib group, 75% had received interferon treatment, 17% had received combination IL-2 and interferon treatment and 8% had received IL-2 treatment and in the placebo group, these percentages were 67%, 19% and 12%, respectively.

Similar proportions of subjects in each arm had prior nephrectomy (89% and 88% in the pazopanib and placebo arms, respectively) and/or prior radiotherapy (22% and 15% in the pazopanib and placebo arms, respectively). In the cytokine-pretreated subgroup, the best response to prior therapy was CR or PR for 10 (5%) subjects.

With respect to the most common concomitant medications that were started after the first dose of the investigational product, more subjects in the pazopanib compared with the placebo arm began using anti-diarrhoeals (for example, loperamide) and anti-hypertensives (for example, amlodipine) during the study.

**Table 9.** Study VEG105192 - Summary of Selected Baseline Disease Characteristics in Treatment-naïve and Cytokine-pretreated Subgroups (ITT Population) (M5, CSR, p66)

| Parameters | Treatment-naïve | | Cytokine-pretreated | |
|---|---|---|---|---|
| | 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]** | | | | |
| Favorable 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) |

Data Source: Table 6.29, Table 6.30, Table 6.35, Table 6.36, Table 7.101 and Table 7.102.

ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloan-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

*Efficacy Results*

*Progression Free Survival*

*Primary analysis*

The primary analysis on PFS in VEG105192 was based on imaging assessment results from the IRC review. In the ITT population, which included treatment-naïve and cytokine-pretreated subjects, a clinically and statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm, with an hazard ratio (HR) of 0.46 (95% confidence interval, CI, 0.34 to 0.62, p <0.0000001) (see Figure 6). 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.

**Figure 6.** Kaplan-Meier Graph of PFS per IRC Assessment (VEG105192: ITT Population)
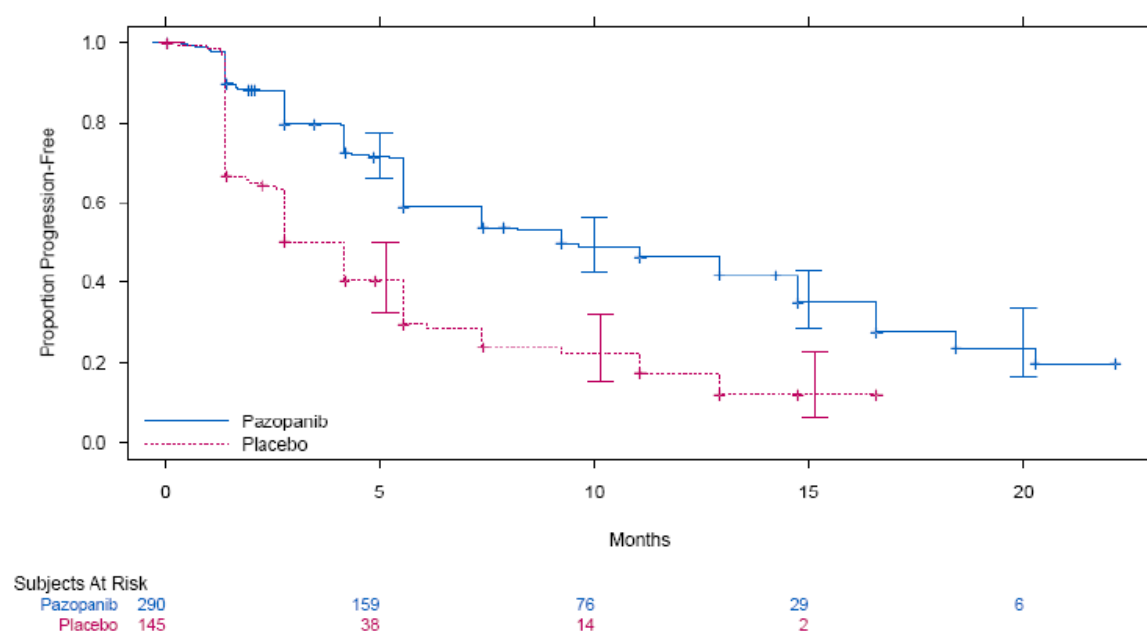


By IRC assessment, the percentage of subjects who were censored with follow up ended was balanced between the two treatment arms (31% [90/290] in the pazopanib arm and 29% [42/145] in the placebo arm). The majority of these subjects had ended follow-up because they were assessed as PD by the investigator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

Progression events were recorded for almost half of all such subjects by both the investigator and the IRC, reducing the possibility for bias with data censored for this reason. There was no evidence of systematic bias in timing of disease assessments and subjects in both treatment arms generally came in for visits on time.

***Sensitivity analyses on PFS***

***PFS by investigator assessment***

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.

The results of this investigator analysis are supportive of the improvement in PFS observed in the primary analysis. The conduct of the study and the results suggests no evidence of systematic bias in estimation of the treatment effect. The investigators were blinded to study treatment. Further, there was no evidence of systematic bias in timing of disease assessments and subjects in both treatment arms generally came in for visits on time. There were only 3 subjects with progression due to symptomatic deterioration, where the subjects did have objective evidence of PD (death) shortly after. A sensitivity analysis which excludes these three symptomatic progressions as events showed consistent results.

In addition, efforts were made to follow subjects, who withdrew from the investigational product (IP) for reasons other than progressive disease or death, until progression. Progression events were recorded for 50% of all such subjects, leading to relatively few subjects who were censored for investigator assessed progression because of the above reasons (13% in the pazopanib arm

and 4% in the placebo arm). Both were lower than the percentage of cases censored with follow-up ended by the IRC assessment. The differences between the two arms in the investigator censored cases (13% in the pazopanib arm versus 4% in the placebo arm) were due to the following reasons: 1) There was a higher percentage of subjects in the pazopanib arm who were censored due to progression after an extended period of inadequate assessment (that is, PFS event occurred more than 12 weeks after the previous adequate assessment); and, 2) There was a higher rate of subjects in the pazopanib arm who discontinued the investigational product due to AE or other reason and did not continue disease assessments until PD was documented. The fact that pazopanib subjects were on treatment and were progression-free for longer made it more likely that they would experience either of these situations.

The Kaplan-Meier graph of PFS by both IRC and investigator's assessments showed a high degree of overlap in the pazopanib arm as well as in the placebo arm by both assessments. The consistency in the overall results between the IRC and Investigator analyses supports the results of the primary analysis. The overall agreement between IRC and investigator (categorically) on PD or censoring was 68.3% of subjects in each of the pazopanib and placebo arms.

### *Other sensitivity analyses*

The 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 large highly statistically significant improvement in PFS with pazopanib compared with placebo (Figure 7). In most cases, larger estimates of treatment effect, that is, lower HRs, were observed with the sensitivity analyses compared with the primary analysis.

There was no evidence of systematic bias in timing of disease assessments. The primary analysis used progression and censoring dates based on the protocol defined assessment schedule in order to correct for any bias associated with subjects coming in for assessments off the protocol defined schedule. This analysis method proved unnecessary because the majority (94%) of response assessments (scans) occurred no more than 1 week earlier or 1 week later than the protocol defined window (that is, within 2 weeks of a scheduled time point) and these rates were the same for both treatment arms.

**Figure 7.** Forest Plot of Primary and Sensitivity Analyses of PFS (VEG105192: ITT Population)
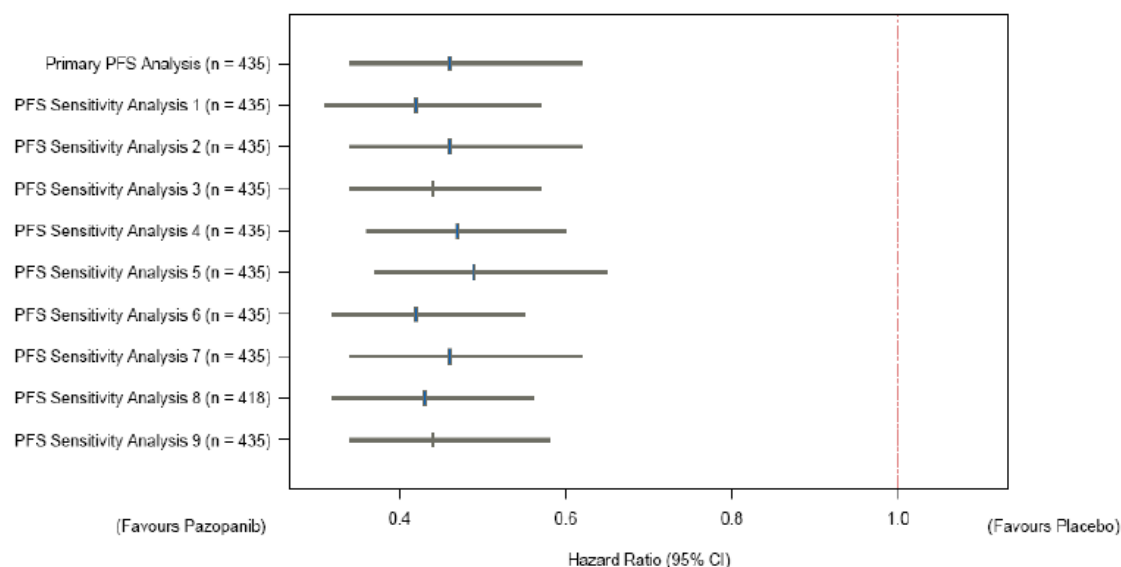


Data Source: VEG105192, Figure 7.6

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).

*Analysis of covariates*

In sensitivity analysis 9, PFS was analysed using a Cox proportional hazards model with the stratification factors (baseline ECOG PS, prior systemic therapy status, and prior nephrectomy) and treatment analysed as covariates. All covariates were included in the final model and each was tested for a significant relationship to PFS. Even after conditioning for the stratification factors, pazopanib treatment was still highly significant in the model. In addition, the covariate of ECOG PS was statistically significant ($p=0.012$), with a longer PFS in subjects with a baseline ECOG PS of 0 compared with those with a ECOG PS of 1. Importantly, with the significant factors of treatment with pazopanib and ECOG PS in the model, there was no statistically significant effect according to whether subjects had received prior systemic therapy ($p=0.990$) or if they had a prior nephrectomy ($p=0.413$).

*Overall Survival*

Overall survival (OS) was the principal secondary efficacy endpoint in VEG105192. The final OS analysis will be performed when 287 death events have been accumulated from the study. For this report, 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. 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 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; Figure 8). However, the results did not reach the prespecified O'Brien-Fleming significance level for the interim analysis (one-sided p 0.004 for superiority and one sided p >0.201 for futility).

**Figure 8**. Kaplan Meier Overall Survival Curves: (VEG105192: ITT population)
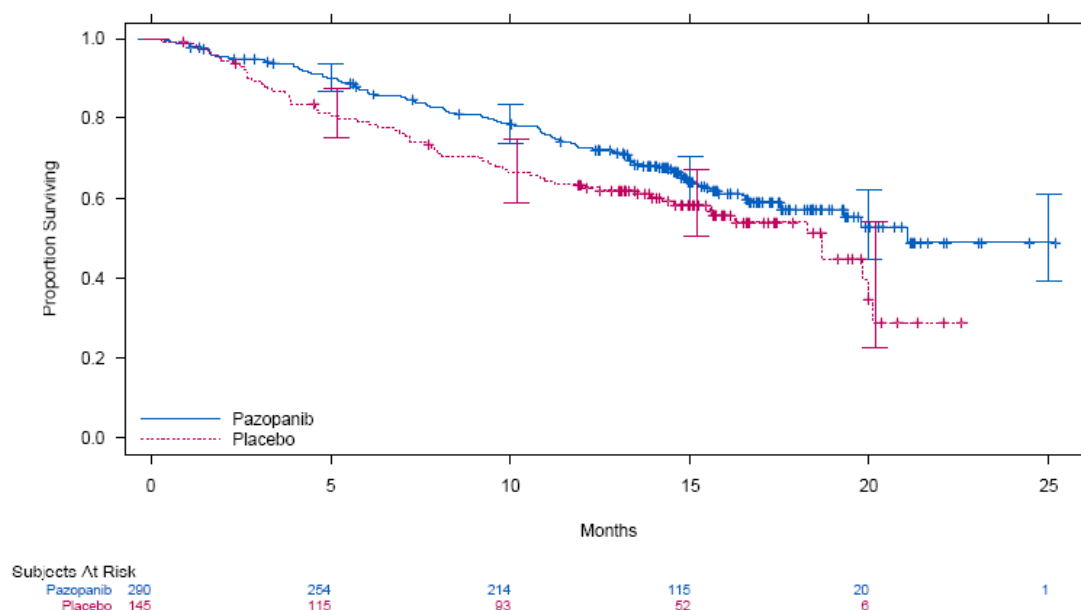


The estimate of the first 12 months of the OS curve is unlikely to change significantly at the final analysis since data were censored and follow-up ongoing for only 10 subjects (6 in the pazopanib arm and 4 in the placebo arm) over this period. The estimate of OS at 1 year was 72.3% (95% CI 66.7%, 77.2%) in the pazopanib arm and 62.7% (95% CI 54.2%, 70.0%) in the placebo arm.

*Sensitivity Analysis*

Overall survival, as analysed using a Cox proportional hazards model, was consistent with the primary analysis of OS (HR: 0.73; 95% CI, 0.54, 0.99; one-sided p=0.021).

*Covariate Analysis*

In the analysis of OS using the Cox proportional hazards model, in addition to the treatment effect, 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 statistically significant effect by prior systemic therapy (p=0.931).

### Subsequent Anti-cancer Therapy

Results for OS in VEG105192 may be influenced by subsequent anti-cancer therapies received by some subjects 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. For these 70 subjects, the median time from the date of randomisation into VEG105192 to the first dose of pazopanib in VEG107769 was 6.4 months (range: 1 month to 18 months). A smaller percentage (28%) of subjects in the pazopanib arm compared with the placebo arm received further anti-cancer therapy post-discontinuation.

### Response Rate and Duration of Response

The response rate (RR) was defined as the percentage of subjects who achieved either a confirmed CR or PR according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria. In the pivotal study, VEG105192, RR, IRC-assessed, was significantly higher in the pazopanib compared with 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 duration of response was defined as the time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to RCC, in subjects with CR or PR. In VEG105192, 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.

Time to response was evaluated in VEG105192 and the median time to response with pazopanib treatment was 12 weeks.

The rate of CR, PR or 6 month SD was significantly higher in the pazopanib compared with placebo arm (see Table 10). The difference was 31.7%, $p < 0.001$, both by IRC and investigator assessment.

**Table 10**. Summary of CR+PR+6-months SD Rate per RECIST by the IRC and Investigator (ITT population).

| | Independently-Evaluated | | Investigator-Evaluated | |
|---|---|---|---|---|
| | Placebo (N=145) | Pazopanib (N=290) | Placebo (N=145) | Pazopanib (N=290) |
| **Best Response, n (%)** | | | | |
| Complete Response | 0 | 1 (<1) | 0 | 4 (1) |
| Partial Response | 5 (3) | 87 (30) | 9 (6) | 99 (34) |
| 6-months Stable disease[a] | 17 (12) | 48 (17) | 23 (16) | 53 (18) |
| Progressive Disease | 84 (58) | 92 (32) | 102 (70) | 98 (34) |
| Unknown | 39 (27) | 62 (21) | 11 (8) | 36 (12) |
| **CR+PR+6-months SD Rate, n (%)** | 22 (15) | 136 (47) | 32 (22) | 156 (54) |
| 95% CI | 9.3, 21.0 | 41.2, 52.6 | 15.3, 28.8 | 48.1, 59.5 |
| **Difference in CR+PR+6-months SD (%)** | 31.7 | | 31.7 | |
| 95% CI for Difference | 23.5, 39.9 | | 22.9, 40.6 | |
| P-value | <0.001 | | <0.001 | |

Data Source: Table 7.35 and Table 7.38.

CR: complete response; IRC: Independent review committee; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

a    Note, this table summarizes subjects by their best response, so subjects with a best response of CR or PR would not be counted as subjects with 6 months SD.

### Subgroup Analyses

In VEG105192, PFS was analysed based on prior systemic therapy treatment, MSKCC risk category, ECOG PS, age and gender. All subgroup analyses on PFS were based on IRC assessments. Analyses by race were planned but not conducted due to insufficient sample sizes in major race categories. Interim OS was analysed by prior systemic therapy and MSKCC risk category. Tumour responses were analysed in subgroups based on the three stratification factors: prior systemic therapy, baseline ECOG PS and prior nephrectomy, and were analysed based on both IRC and investigator assessments.

### Efficacy of Pazopanib in Treatment-Naïve and Cytokine-Pretreated Subgroups

### Progression free survival

In VEG105192, the study was adequately powered to allow detecting a clinically meaningful improvement in PFS in the pazopanib arm compared with the placebo arm in each of the treatment-naïve and cytokine-pretreated subgroups. The subgroup PFS analyses were performed using stratified log-rank tests.

In treatment-naïve subgroup, the median PFS in the pazopanib and placebo arms was 11.1 months and 2.8 months, respectively, with an HR of 0.40 (95% CI 0.27 to 0.60, p <0.0000001). In the cytokine pre-treated subgroup, the median PFS in the pazopanib and placebo arm was 7.4 months and 4.2 months respectively with a HR of 0.54 (95% CI: 0.35, 0.84, p <0.001).

The Kaplan-Meier graphs of PFS for the treatment-naïve and cytokine-pretreated subgroups are displayed in Figures 9 and 10, respectively. These figures display results in these subgroups using both the dates defined for the primary analysis (visit-based) and the dates defined for Sensitivity Analysis 1 (scan-based).

**Figure 9A.** Kaplan Meier Graph of PFS in Treatment-naïve Subgroup per IRCAssessment (VEG105192: ITT Population).



A: Dates as in Primary Analysis (visit-based)
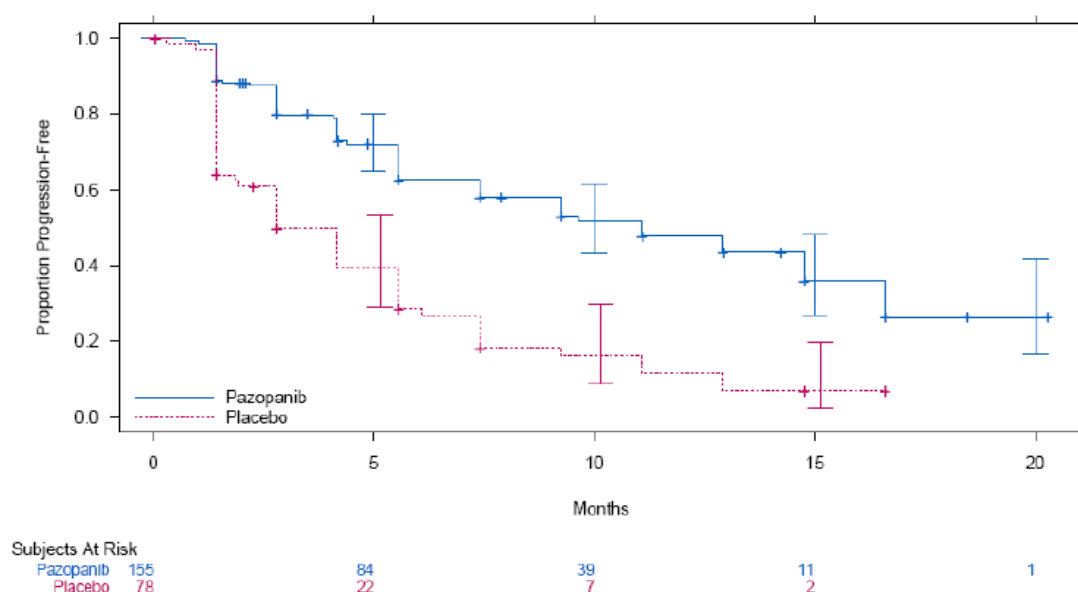
**Figure 9B.**

B: Dates as in Sensitivity Analysis 1 (scan-based)



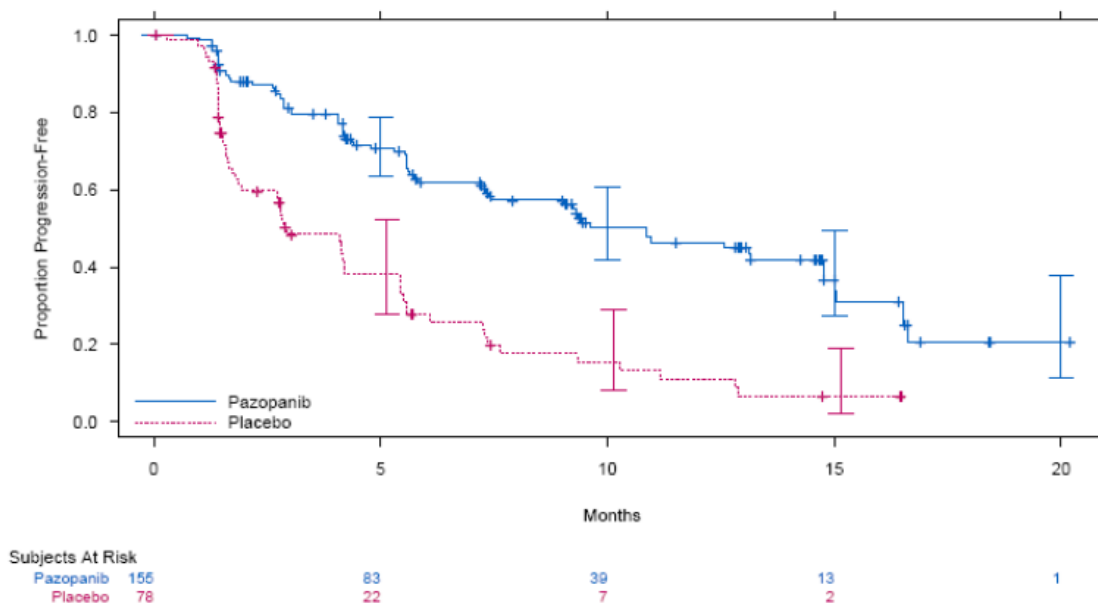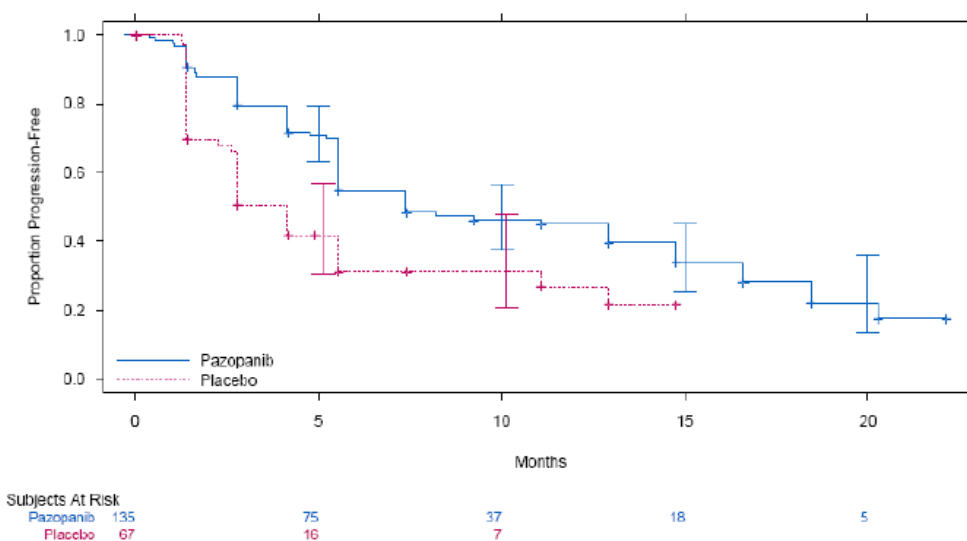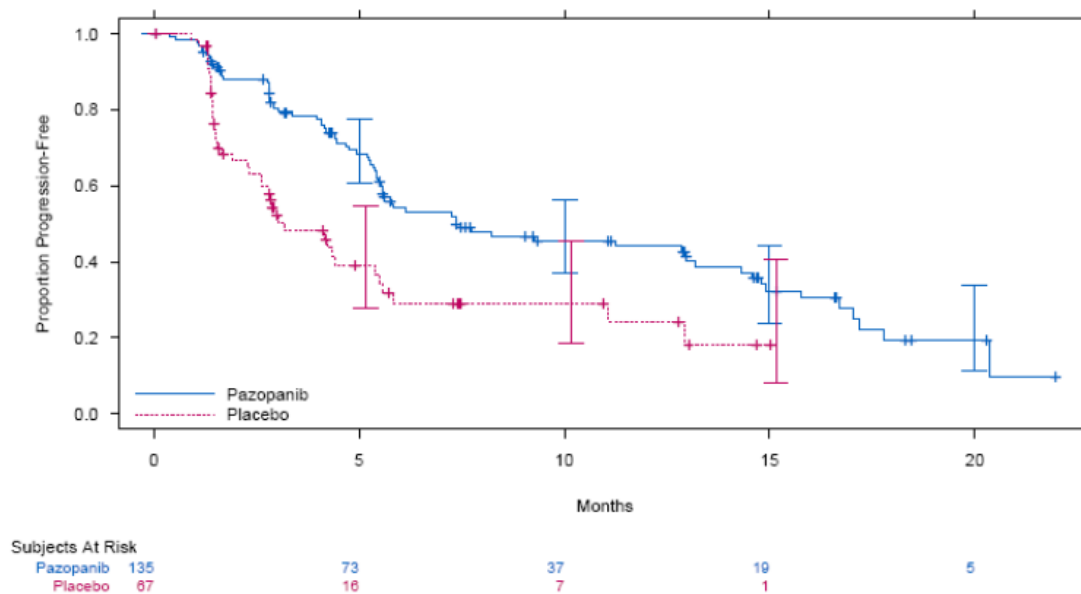**Figure 10A.** Kaplan-Meier Graph of PFS in Cytokine-pretreated Subgroup per IRC assessment (VEG105192: ITT Population).

A: Dates as in Primary Analysis (visit-based)

**Figure 10B.**

B: Dates as in Sensitivity Analysis 1 (scan-based)



Although the PFS medians estimated using visit-based analysis appear to indicate that the placebo arm in the cytokine-pretreated subgroup had a longer PFS than that of the placebo arm of the treatment-naïve subgroup (4.2 months versus 2.8 months), this difference is due to the sensitivity of these data at the median and the timing of the assessments, rather than an actual difference in PFS in these two subgroups. The median for the treatment-naive placebo subjects is 2.8 months (Week 12) because the proportion progression-free at 2.8 months is 49.9%, just below the 50% mark (Figure 9). In comparison, the proportion of subjects that are progression-free at 2.8 months (Week 12) in the cytokine pretreated subgroup is 50.5%, just over the 50% mark required to estimate a median (Figure 10). Given the analysis uses the visit time points for most dates, the next event does not occur until the Week 18 visit or at 4.2 months. Thus, the estimate of the median is 6 weeks later, despite that the percentages progression-free at 2.8 months are within 1% of each other.

An adhoc analysis of these subgroups using the dates based on the actual scan dates defined for Sensitivity Analysis 1 also supports that there is not an underlying difference in these two groups at the median. The median PFS in the treatment-naïve subgroup is slightly longer at 2.9 months and the median PFS for the cytokine-pretreated subgroup is only 3.2 months.

***Overall survival (interim analysis)***

The interim analysis of OS in the pivotal study VEG105192 on the overall ITT population was based on 176 death events, which was 61% of the death events for the final OS analysis. The interim OS data on the overall ITT population was, therefore, not fully mature. The interim analysis of OS on the treatment-naïve and cytokine-pretreated subgroups was further limited, with only 90 and 86 deaths events, respectively. OS appeared 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). Estimates of median OS were immature.

The Kaplan- Meier graphs of OS for the treatment-naïve and cytokine-pretreated subgroups are displayed Figures 11 and 12, respectively. As shown in the Kaplan-Meier graph of OS analysis

in the treatment-naïve subgroup the curve was relatively mature up to 12 months. Beyond 12 months, the curve was much less mature with many subjects censored. The immaturity in the median was also reflected in the fact that the 95% CI could not completely be determined due to the lack of events after the median.

**Figure 11.** Graph of Kaplan Meier Overall Survival Curves (Treatment-naive Stratum, VEG105192).
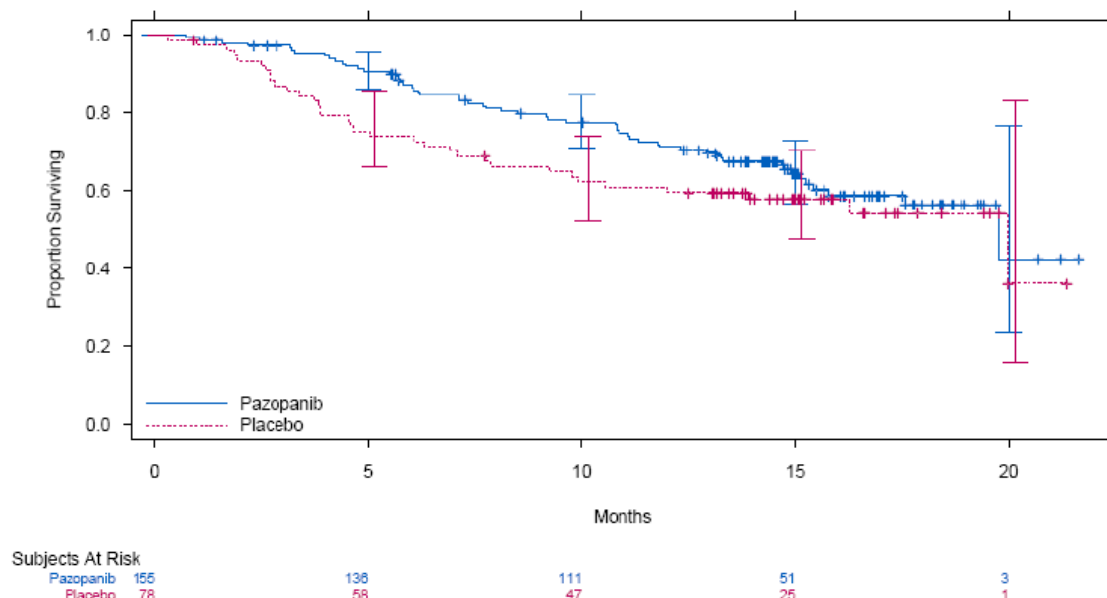


**Figure 12.** Graph of Kaplan-Meier Overall Survival Curves (Cytokine-pretreated Stratum, VEG105192).
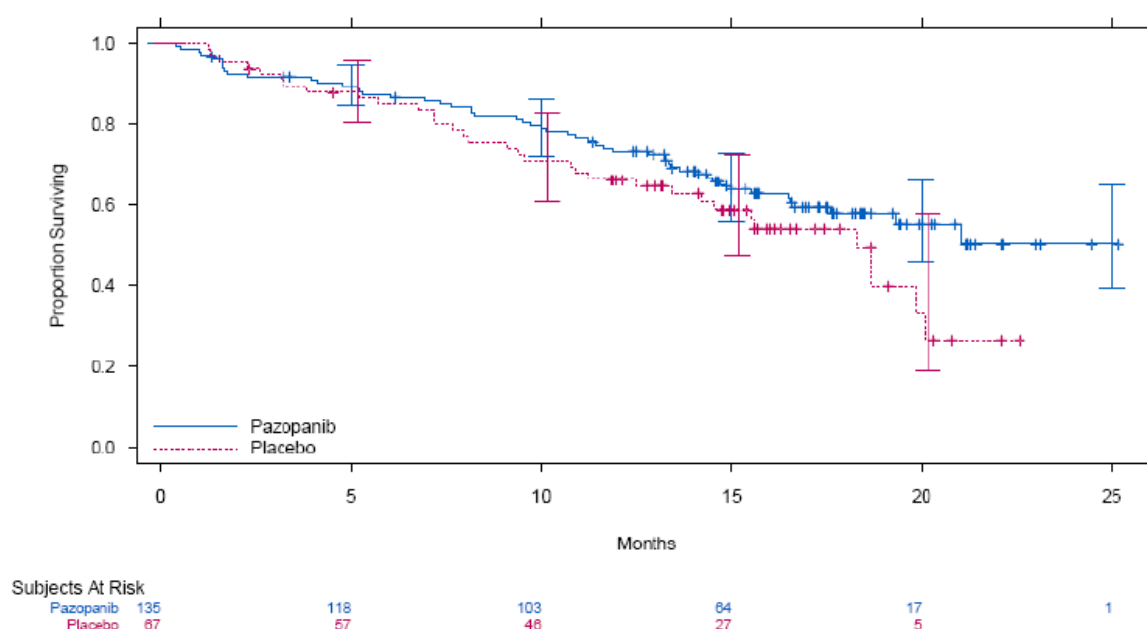


Similarly, in the cytokine pre-treated subgroup, the Kaplan-Meier curve was relatively mature up to 12 months and beyond 12 months was immature with many subjects censored. However, in this subgroup, survival data from the placebo arm were more mature with 50% of subjects in the placebo arm having died, allowing estimation of the median and 95% CI).

Of the placebo-treated subjects in VEG105192, 42% of subjects in the treatment-naïve subgroup, and 55% of subjects in the cytokine-pretreated subgroup, received pazopanib in VEG107769, therefore, the cross-over is likely to impact each of these two subgroups.

*Response analyses*

The RR was analysed in the treatment-naïve and cytokine-pretreated subgroups by both IRC and investigator assessments in VEG105192 (Table 11). The RRs by investigator's assessment were slightly higher in both arms in each subgroup compared with the IRC 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.

**Table 11.** Response Rate per RECIST in Treatment-naïve and Cytokine-pretreated Subgroups (VEG105192: ITT Population, VEG102616: All Enrolled Population).

| Response Rate (CR+PR), % | Assessment | VEG105192 | | VEG102616 |
|---|---|---|---|---|
| | | Placebo (N=145) | Pazopanib (N=290) | Pazopanib (N=225) |
| Treatment-naive | IRC | 4 | 32 | 33.5 |
| | Investigator | 6 | 39 | - |
| Cytokine-pretreated | IRC | 3 | 29 | 37.1 |
| | Investigator | 6 | 32 | - |

-=not performed.

### Efficacy of Pazopanib by Age, Gender, ECOG PS and MSKCC Risk Category

PFS was analysed in all subgroups based on the IRC assessment, with the HR and p-values from a log-rank test unadjusted for the stratification factors. Tumour response was analysed in the ECOG PS subgroups of 0 or 1. Interim OS was analysed in the MSKCC favourable and intermediate risk subgroups.

### PFS by Age, Gender, ECOG PS and MSKCC Risk Category

The treatment effects of pazopanib on PFS that were observed in all the subgroups analysed were consistent with the primary result, with 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. In all the subgroup analyses, the p value for the log rank test comparing pazopanib to placebo was less than 0.001.

### Interim Analysis of OS by MSKCC Risk Category

As these are subgroup analyses, analyses by MSKCC score were not powered to detect differences in OS by treatment arm. In the subgroup of patients with a favourable score, the HR was 0.81 (95% CI, 0.44, 1.51) (that is, in favour of pazopanib compared with placebo) but was slightly larger than in the overall population. In the subgroup of patients with an intermediate score, the HR was 0.67 (95% CI, 0.45, 1.01), slightly lower than in the overall population. There were too few subjects (14) in the poor risk group for a meaningful statistical analysis.

### Health Outcomes

Analysis of health outcomes was an objective in Study VEG105192. The European Organization for Research and Treatment of Cancer HRQL (health-related quality of life survey), EORTC-QLQC30, was included in this study in order to provide for an overall assessment of global health status/quality of life in addition to measures on 5 functional scales and selected symptoms.

The EQ-5D[20] was included in this study for the purpose of obtaining utilities for use in health economic model evaluations. Additionally, this instrument provides assessments of overall health status and functioning that may also be very relevant in the assessment of HRQOL in RCC advanced subjects.

### EORTC QLQ-C30 (VEG105192)

Results from a mixed model repeated measures (MMRM) analysis for change from baseline consistently showed no statistical difference between pazopanib and placebo arms at each assessment time point (Weeks 6, 12, 18, 24 and 48) in global health status/HRQOL. Additionally, the between-group differences are smaller than minimally important difference (MID) of 5 to 10. The within-group differences were also smaller than MID, suggesting that declines from baseline were not clinically meaningful in either arm.

### EuroQoL-5D (VEG105192)

Results from a mixed-model repeated measures analysis for change from baseline consistently showed no statistical difference between pazopanib and placebo arms at each assessment time point in EQ-5D utility score[20]. 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.

### Supportive Study VEG102616

### Study Design and Objectives

VEG102616 was a Phase II, multicentre study to evaluate the efficacy and safety of pazopanib. The key eligibility criteria were similar to those in the pivotal study VEG105192; including subjects with advanced/metastatic RCC who were either treatment-naïve or had progressed following one prior cytokine-based systemic therapy for advanced/metastatic RCC; had clear cell or predominantly clear cell histology; measurable disease per RECIST; ECOG PS of 0 or 1; and protocol-specified criteria for adequate organ function. The study also allowed subjects who had progressed from one prior bevacizumab treatment to be enrolled.

The study was originally designed as a randomised discontinuation study because of the assumption that pazopanib would act more like a cytostatic agent that would suppress tumour growth rather than cause tumour reduction. The design was subsequently revised into an open-label, single arm study based on activity observed at the planned interim analysis upon IDMC recommendation.

### Original Design and Outcome from Interim Analysis

The original randomised discontinuation design included a 12-week open-label lead-in phase and a double-blind randomised phase following the Week 12 imaging-based disease assessment. In the 12-week Lead-in Phase all enrolled subjects received oral pazopanib, 800 mg once daily. Based on the outcome from the Week 12 disease assessment, subjects could continue the open label pazopanib treatment if they had a CR or PR or be randomised to receive 16-week blinded treatment with either pazopanib or placebo if they had a SD at Week 12. Subjects who progressed prior to or at Week 12 would be discontinued from pazopanib treatment.

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[20] The *EQ-5D* consists of a health descriptive system and a visual analog scale (EQ-VAS) for respondents to self-classify and rate their health on the day of administration of the instrument. The descriptive system has 5 items/dimensions (that is, mobility, self-care, usual activities, pain/discomfort and anxiety/depression), and for each item, there are three response levels (that is, no problems, moderate problems and extreme problems). The items can be used individually or in combination (as a health profile) as descriptive measures in clinical studies. From http://www.hqlo.com/content/1/1/7.

Imaging based disease assessments were performed at baseline, Week 8 and Week 12 for all subjects during the lead-in phase. Subjects who continued past Week 12 had disease assessments every 8 weeks until PD. Imaging scan of disease assessments from all subjects were submitted to the IRC for review.

The primary objectives were to compare the PD rate 16 weeks after randomisation in subjects who were randomised to pazopanib compared with placebo; and, at the interim analysis, to determine SD rate at 12 weeks in the Lead-in phase. The secondary efficacy objectives were to assess PFS and duration of response. The sample size was calculated based on: 1) having a 90% power to detect a PD risk that is 4 times larger in the placebo arm compared with the pazopanib arm (40% versus 10%); 2) the Week 12 SD rate was <50% but >40%. With these assumptions, 80 subjects with SD at Week 12 needed to be randomised and 160 to 230 subjects needed to be enrolled.

This initial design included a planned interim analysis to assess the Week 12 SD rate for futility when 60 subjects had been followed for 12 weeks in the lead-in phase, but there were no formal stopping rules for efficacy. This planned interim analysis also allowed for adjustment of sample size based on the observed SD rate if the futility boundary (defined as Week 12 SD rate of <40%) was not crossed.

The results from the interim analysis on the first 60 subjects showed a 47% SD rate at Week 12, indicating that the study did not cross the pre-specified boundary for futility. At interim analysis, the response rate for these 60 subjects was also analysed as an ad hoc analysis with a RR rate of 32% per investigator and 38% by IRC assessment. The interim efficacy data together with safety data from 161 subjects were provided to the IDMC that had been established for both VEG102616 and VEG105192. Upon evaluating both efficacy and safety data, the IDMC indicated that pazopanib was highly active, a randomised discontinuation design to assess PFS was no longer necessary, nor would it provide additional useful information. The IDMC also indicated that there were no safety signals to warrant a change in dose or safety monitoring. The IDMC recommended halting randomisation, unblinding the study, and offering pazopanib treatment to all subjects who were in the randomisation phase of the study. The IDMC also recommended amending the study to an open-label single-arm study and to allow subjects who had consented to be screened and enrolled.

The preliminary efficacy of pazopanib had been established by the interim data from VEG102616, so the pivotal Phase III study VEG105192 was continued to definitively confirm the clinical efficacy per IDMC recommendation.

Following the Protocol Amendment 1 to an open-label, single-arm design to evaluate efficacy and safety of pazopanib the efficacy endpoints were as follows:

*Efficacy endpoints*

Primary efficacy endpoints: RR and Week 12 SD rate.

- RR: defined as the percentage of subjects who achieved either a confirmed CR or confirmed PR using RECIST criteria, as analysed by central independent review (IRC)
- Week 12 SD rate: defined as the percentage of subjects having SD at 12 weeks after the first dose of pazopanib.

Secondary efficacy endpoints: were duration of response and PFS.

- Duration of response: defined as the time from first documented response (CR or PR) until the first documented PD or death due to any cause, whichever was first.
- PFS: defined as the date of first dose of pazopanib until the first documentation of disease progression or death due to any cause, whichever was first.

### Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were similar to those in study VEG 105192. Subjects were eligible for the study if they were at least 21 years of age, had histologically or cytologically confirmed diagnosis of RCC which was metastatic or locally recurrent, had either no prior systemic therapy or failed only 1 prior cytokine-based or bevacizumab-based therapy, had evidence of documented measurable disease by RECIST criteria, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate bone marrow/hepatic/renal function, and coagulation. Women with childbearing potential had a negative serum pregnancy test and agreed to use adequate contraception. Men with a female partner of childbearing potential agreed to use a barrier method of contraception or abstinence during the study and for 28 days following the last dose.

### Statistical Methods for the Revised Design

RECIST was used to assess clinical activity and disease status. For all efficacy endpoints, analyses were performed based both on IRC assessment and investigator assessment. Revision of the study design occurred after 55 subjects were randomised into the double-blinded treatment phase, with 28 subjects randomised to the placebo arm. The time period on placebo for these 28 subjects was expected to negatively affect the efficacy assessments on RR and PFS in the revised single arm design if no adjustments were made in the analyses, as tumours were expected to grow after a subject was off pazopanib. Therefore, adjustments were made in the analyses of RR and single arm PFS to attempt to estimate the results that would have been achieved if subjects were continuously dosed with pazopanib.

Two populations were used in the efficacy analyses:

*All Enrolled Population*: included all subjects treated with pazopanib.

*Randomised Efficacy Population*: included all subjects randomised, regardless of whether a subject had actually received the assigned treatment. A PFS analysis was performed on this population, in which subjects were analysed according to the treatment arm that they were randomised to, regardless of whether or not the placebo subjects eventually crossed over to pazopanib therapy after the protocol amendment. In addition, RR and PFS were analysed for the two subgroups: treatment-naïve and subjects who received prior systemic therapy.

### Primary efficacy analyses (response rate)

### Response Rate

Due to the fact that 28 subjects had received placebo treatment for various periods of time and might have had tumour enlargement during this time, the baseline for evaluating tumour response was reset for those who were on placebo treatment for longer than 28 days and subsequently received pazopanib based on the following: If a subject's most recent assessment before crossover to pazopanib indicated that the disease status was worsened compared to the original baseline assessment (for example, increased sum of longest diameters for the target lesion, worsening of non-target lesion or new lesions), the most recent disease assessment before the crossover would be used as the new baseline to assess tumour response for the subject. For all the other subjects, the original baseline assessments continued to be used as the baseline for tumour response assessment.

The estimated RRs were calculated along with corresponding unadjusted exact 95% CIs. Subjects with unknown or missing response were treated as non-responders, that is, they were included in the denominator when calculating the percentage.

### Stable disease rate at Week 12

Initially this analysis was to be performed at the interim analysis only. However, after Protocol Amendment 1, it was also performed for all 225 subjects enrolled in the final analysis. The estimated SD rate was calculated along with corresponding unadjusted exact 95% CIs. Subjects with unknown or missing disease status at Week 12 were treated as non-SD, that is, they were included in the denominator when calculating the percentage. Both IRC and investigator assessed SD rate at Week 12 were reported.

### Progression Free Survival

Median PFS was estimated using Kaplan-Meier techniques (including the Kalbfleisch- Prentice extension for weighted analysis). Approximate 95% confidence limits were calculated. Duration of response and time to response were summarised descriptively using medians and quartiles.

## Study Population

A total of 225 subjects were enrolled in the study. Of the 225 subjects, 55 subjects participated in the randomised phase from Week 12 to Week 28 of the original study design. A total of 170 subjects were not eligible for the randomised phase as, at the time of randomisation, they did not have SD, or were enrolled after the IDMC recommendation. These 170 subjects received open label pazopanib throughout the duration of their participation in the study.

As of 24 March 2008, 43 subjects (19%) were still receiving the investigational product. Progression of disease and AEs were the most common reasons for discontinuation of IP.

Demographic characteristics were similar between the treatment groups in VEG105192 and VEG102616. Overall, most subjects were White, male, and the median age was 60.0 years.

Disease characteristics were not analysed by prior cytokine treatment in VEG102616. In VEG102616, 63 (28%) subjects were enrolled from the USA. The disease characteristics of the USA subgroup and the overall study population of VEG102616 were comparable. Time since initial diagnosis of RCC was 14.6 months (USA) versus 18.7 months (overall); percentage of subjects had Stage IV disease at initial diagnosis was 43% (USA) versus 36% (overall); baseline ECOG PS of 0:1 was 70%:30% (USA) versus 65%: 35% (overall); MSKCC prognostic risk category of favourable risk: intermediate risk was 49%: 41% (USA) versus 43% versus 41% (overall). In USA subjects, the most common metastatic sites were lung (89%), lymph nodes (56%), kidney (27%) and bone (22%), similar to the overall study population of VEG102616.

### Prior medical conditions

There were no imbalances between treatment arms in VEG105192 in terms of prior medical conditions. There were no notable differences in prior or current medical conditions amongst subjects enrolled in the VEG105192 and VEG102616.

The number of treatment-naïve subjects in VEG102616 was 155. In VEG102616, the percentage of treatment-naïve subjects was higher (69%) than in VEG105192 (53%). The numbers of cytokine-pretreated subjects in VEG102616 was 70. Similar proportions of subjects in each arm in VEG105192 and in VEG102616 had prior nephrectomy and/or prior radiotherapy.

### Efficacy Results

Overall survival was not an endpoint in VEG102616.

### Progression Free Survival

PFS was a secondary endpoint in VEG102616. Prior to the study design changing to an open label design, 55 subjects had randomised into the Randomisation Phase. Due to the fact that 28

(12% of total enrolled) subjects were randomised to the placebo arm, a weighted analysis was undertaken to estimate PFS adjusting out the effect of placebo. Twelve out of the 28 placebo subjects progressed by both IRC and investigator's assessment while they were in the randomised phase as compared to only 2 of 27 by IRC and 5 of 27 by investigator in the pazopanib arm.

In the weighted analysis, the data from the 28 placebo subjects was removed, but in its place is an estimate of the expected contribution of the placebo subjects had they continued to treated with pazopanib after Week 12. This was done by using the outcome from all subjects who were either randomised to the pazopanib arm at Week 12 before randomisation was closed (n=27) or who had SD at Week 12 and received open label pazopanib treatment because randomisation had been closed (n=51). Overall the contribution of subjects with Week 12 SD should have been 106 subjects, meaning that the contribution of the 78 subjects who continued on pazopanib after randomisation or week 12 SD needed to be upweighted by approximately 36%. That is, each data point associated with one of these subjects would be treated as approximately 1.36 subjects in the analysis.

The median PFS estimate adjusted for randomisation to placebo was 11.9 months per IRC and 9.9 months per investigator. This estimate is likely to represent a less biased estimate of PFS in the cohort of pazopanib treated subjects relative to the median PFS estimate that includes subjects randomised to placebo (median of 10.4 months per IRC and 8.5 months per investigator). Both sets of PFS results were consistent with the PFS observed in the pazopanib arm in VEG105192.

### Response Rate and Duration of Response

The RR was defined as the percentage of subjects who achieved either a confirmed CR or PR according to RECIST criteria. RR was significantly higher with pazopanib than placebo treatment in VEG105192. The RR with pazopanib treatment in study VEG102616 was consistent with the pazopanib arm of VEG105192 (Table 12).

**Table 12.** Response Analysis per RECIST (VEG105192: ITT Population, VEG102616: All Enrolled Population, VEG107769: ATS Population).

| | VEG105192[a,b] | | VEG102616[a] | VEG107769[a] |
|---|---|---|---|---|
| | Placebo (N=145) | Pazopanib (N=290) | Pazopanib (N=225) | Pazopanib (N=71) |
| **Best Response, n (%)** | | | | |
| Complete Response | 0 | 1 (<1) | 3 (1) | 0 |
| Partial response | 5 (3) | 87 (30) | 75 (33) | 23 (32) |
| Stable disease[b] | 59 (41) | 110 (38) | 101 (45) | 25 (35) |
| Progressive disease | 58 (40) | 51 (18) | 24 (11) | 10 (14) |
| Unknown[c] | 23 (16) | 41 (14) | 22 (10) | 13 (18) |
| **Response Rate (CR+PR), n (%)** | 5 (3) | 88 (30) | 78 (35) | 23 (32) |
| 95% CI | 0.5, 6.4 | 25.1, 35.6 | 28.4, 40.9 | 21.5, 43.3 |
| **Duration of response, weeks** | NC | 58.7 | 68.0 | NC |
| 95% CI | | 52.1, 68.1 | 53.7, NC | |
| **Difference in Response (CR+PR) (%)** | 26.9 | | NA | NA |
| 95% CI for Difference | 20.8, 33.0 | | | |
| P-value | <0.001 | | | |

CR=-complete response; NA=not applicable; NC=not calculable; PR=partial response.

a. IRC-assessed for VEG105192 and VEG102616, and investigator-assessed for VEG107769 (as IRC review was not performed for VEG107769).

c. In order to qualify as a best response f stable disease, a response of stable disease had to be observed a minimum of 12 weeks in VEG105192 and VEH107769 and 8 weeks in VEG102616.

d. A subject was classified as unknown if they never had progressive disease, and did not have stable disease for long enough to be classified as stable disease. This includes subjects with no follow-up and some subjects who had not progressed by the IRC, where the investigator called the disease progression.

In the supportive study VEG102616, tumour response was a primary endpoint. In VEG102616, RR per IRC was 35% (95% CI: 28.4% to 40.9%), similar to that reported in the pazopanib arm of VEG105192. RR per investigator review was also similar (34% [95% CI: 27.6% to 40.0%]).

In VEG102616, the median duration of response was slightly higher than in the pazopanib arm of VEG105192. It was 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 12 weeks in VEG102616.

### SD rate at Week 12

In VEG102616, a protocol defined endpoint was to assess SD of the first 60 subjects at Week 12. This assessment was to be performed at the interim analysis. This Week 12 assessment identified a RR of 38% by IRC assessment and 32% per investigator. These data were reviewed by the IDMC. An adhoc analysis of all 225 subjects at Week 12 determined the overall RR to be 27.6% and SD to be 47.1% by IRC review. This calculation for the percentage of subjects with response at Week 12 includes subjects who had either a confirmed or unconfirmed response. The progressive disease rate (PD + unknown) was 12.0% (IRC assessment).

### Subgroup Analyses

### Response Analyses

The RR was analysed in the treatmenth-naïve and cytokine-pretreated subgroups by IRC assessments in VEG102616. The RR with pazopanib treatment was similar to study VEG105192. In the supportive study VEG102616, prior systemic treatment did not correlate with RR (the primary endpoint) (p=0.651).

### Efficacy of Pazopanib by Age, Gender, ECOG PS and MSKCC Risk Category

PFS was analysed in all subgroups based on the IRC assessment, with the HR and p-values from a log-rank test unadjusted for the stratification factors. Tumour response was analysed in the ECOG PS subgroups of 0 or 1.

### PFS by Age, Gender, ECOG PS and MSKCC Risk Category

Results of exploratory subgroup analyses identified the following factors to affect overall response rate (CR + PR): ECOG performance status 0 better than 1 (p=0.003), haemoglobin ≥ lower limit of normal (LLN; p<0.001), metastasis to lymph nodes (p=0.032).The following baseline characteristics did not correlate (p>0.05) with response rate (CR+PR): age (p=0.354), race (p=0.390), sex (p=0.879), prior nephrectomy (p=0.462), prior systemic therapy (p=0.651), sites of metastasis [bone (p=0.059), kidney (p=0.738), lung (p=0.084), liver (p=0.711), adrenals (p=0.264), abdomen/viscera (p=0.817), pancreas (p=0.050)], MSKCC criteria (p=0.294), lactose dehydrogenase (LDH; p=0.273), serum calcium (p=0.856), time since recurrence (p=1.000), time from diagnosis to treatment (p=0.252).

### Comparison of efficacy by study region

The efficacy of pazopanib on tumour response and PFS was compared between the USA and non-USA subjects in the supportive study VEG102616. In the study 63 (28%) subjects were enrolled in 12 USA sites and 162 (72%) subjects were enrolled in 31 non-USA sites.

A comparison based on the endpoints of RR and PFS (adjusted for randomisation to placebo) showed that efficacy was consistent for USA versus non-USA subjects. Response rate was similar in USA and non-USA subjects by IRC assessment (31.7% for USA and 35.8% for non-USA subjects) and investigator assessment (39.7% for USA and 31.5% for non-USA subjects). For the non-USA subjects, the percentage that was non-evaluable for response was higher than for USA subjects.

The median PFS (adjusted for randomisation to placebo) based on IRC assessment was similar for the USA (51.6 weeks) and non-USA subjects (52.1 weeks). The median PFS based on investigator assessments was 10 weeks longer for the USA subjects (49.4 weeks) compared with the non-USA subjects (39.3 weeks). It is unclear what contributed to the differences.

### Supportive Study VEG107769

### Study Design and Objectives

VEG107769 was an open-label extension study to VEG105192. Subjects who were randomised to the placebo arm and subsequently progressed with objective evidence of disease progression could be enrolled in VEG107769 to receive pazopanib treatment at a dose of 800 mg once daily. A maximum of 145 subjects could be enrolled (the number of subjects in the placebo arm of VEG105192). Enrolment criteria were as for VEG105192 except that subjects with an ECOG PS of 2 were also eligible.

The primary objective was to evaluate the safety and tolerability of pazopanib. Secondary objectives included evaluation of the RR (CR + PR), the rate of CR + PR + 6-months SD, PFS and OS. Tumour response was assessed by the investigator using RECIST; no IRC assessments were conducted.

As for Study VEG105192, the IDMC monitored safety during the course of the study. Disease assessments were performed for all subjects every 6 weeks until Week 24, and every 12 weeks until discontinuation of treatment. Regular safety assessments were performed for all subjects. Dates of death were recorded in VEG107769, but survival was followed up via VEG105192.

### Endpoints

Efficacy was a secondary objective. The efficacy endpoints included RR, and rate of CR + PR + 6 months SD, PFS and OS. RR and rate of CR + PR + 6-months SD were defined as per VEG105192 except that only investigator assessments of imaging scans were performed. PFS and OS were defined as per VEG105192 except that the time was calculated from first dose rather than randomisation.

### Statistical Methods

The All Treated Subjects (ATS) population comprised all enrolled subjects who received at least one dose of open label investigational product. The ATS population was used for the analysis of all efficacy data.

Response rates were displayed along with 95% CIs. The original protocol stated that exact binomial CIs were required, but this was later determined to be unnecessary given the expected number of subjects (based on Study VEG105192 enrolment) and the rate (based on VEG102616 response rate).

Analyses of duration of response and time to response were not performed as the number of responses observed was not sufficient for a meaningful analysis.

PFS was summarised descriptively using Kaplan-Meier estimates for the median, quartiles and PFS rates at 6 months, 12 months, and 18 months. Investigator assessed PFS for ATS was reported. Approximate 95% CIs were calculated, based on Greenwood's formula for the standard error of the Kaplan-Meier estimate.

OS death data came from the Study VEG105192 death data set. For subjects who did not die, OS was censored at the time of last contact. Last date of contact was defined as the maximum date of any visit date or the survival follow-up date. The OS was summarised descriptively using Kaplan-Meier estimates for the median, quartiles and OS rates at 6 months, 12 months and 18 months.

### Study Population

The first subject was enrolled on 29 September 2006. A total of 71 subjects were enrolled in the study at the clinical cut off of 23 May 2008. This included 70 subjects from the placebo arm of VEG105192 and 1 subject from the pazopanib arm.

At the time of clinical cut off, 40 (56%) subjects discontinued the investigational product, 31 (44%) subject were still receiving the investigational product. Disease progression was the most frequent reason for discontinuation of the investigational product (24 [34%] subjects). An AE led to discontinuation of the investigational product in 7 (10%) subjects. Demographic characteristics were similar between the treatment groups in VEG105192 and VEG107769. Overall, most subjects were White, male, and the median age was 59.0 years.

Baseline disease characteristics are summarised in Table 13. Disease characteristics were not analysed by prior cytokine treatment in VEG107769.

**Table 13.** Summary of Disease Characteristics at Baseline (VEG105192 ITT, VEG102616 All Enrolled, VEG107769 ATS Population).

| Diagnosis parameters | Number (%) of subjects | | | | |
|---|---|---|---|---|---|
| | VEG105192 | | | VEG102616 | VEG107769 |
| | Placebo (N=145) | Pazopanib (N=290) | Total (N=435) | Pazopanib (N=225) | Pazopanib (N=71) |
| **Histology at Initial Diagnosis[a]** | | | | | |
| Clear Cell or Predominantly Clear Cell | 145 (100) | 289 (100) | 434 (100) | 225 (100) | 71 (100) |
| **Stage of Disease at Initial Diagnosis** | | | | | |
| I | 13 (9) | 22 (8) | 35 (8) | 22 (10) | 9 (13) |
| II | 24 (17) | 43 (15) | 67 (15) | 39 (17) | 15 (21) |
| III | 46 (32) | 93 (32) | 139 (32) | 78 (35) | 21 (30) |
| IV | 61 (42) | 127 (44) | 188 (43) | 82 (36) | 26 (37) |
| Missing | 1 (<1) | 5 (2) | 6 (1) | 4 (2) | 0 |
| **Time Since Initial Diagnosis (months)** | | | | | |
| Median | 13.8 | 15.7 | 15.3 | 18.7[e] | 26.4[f] |
| Range | 1 to 152 | 0 to 184 | 0 to 184 | 1 to 226 | 4.7 to 161.7[f] |
| **Time Since Diagnosis of Stage IV Disease (months)** | | | | | |
| Median | 5.8 | 6.1 | 6.0 | - | 14.6[f] |
| Range | 0 to 89 | 0 to 149 | 0 to 149 | - | 3.7 to 96.7[f] |
| **Most Frequent Locations of Disease at Baseline[b]** | | | | | |
| Lung | 106 (73) | 214 (74) | 320 (74) | 176 (78) | 57 (80) |
| Lymph Nodes | 86 (59) | 157 (54) | 243 (56) | 96 (43) | 40 (56) |
| Bone | 38 (26) | 81 (28) | 119 (27) | 62 (28) | 18 (25) |
| Liver | 32 (22) | 75 (26) | 107 (25) | 39 (17) | 12 (17) |
| Kidney | 36 (25) | 66 (23) | 102 (23) | 49 (22) | 11 (15) |
| **Number of organs involved[b]** | | | | | |
| 1 | 20 (14) | 53 (18) | 73 (17) | - | 8 (11) |
| 2 | 50 (34) | 78 (27) | 128 (29) | - | 26 (37) |
| ≥3 | 75 (52) | 159 (55) | 234 (54) | - | 37 (52) |
| **ECOG Performance Status** | | | | | |
| 0 | 60 (41) | 123 (42) | 183 (42) | 147 (65) | 23 (32) |
| 1 | 85 (59) | 167 (58) | 252 (58) | 78 (35) | 37 (52) |
| 2 | 0 | 0 | 0 | 0 | 10 (14) |
| Unknown | 0 | 0 | 0 | 0 | 1 (1) |
| **MSKCC Risk Category[c]** | | | | | |
| Favourable Risk | 57 (39) | 113 (39) | 170 (39) | 97 (43) | 29 (41) |
| Intermediate Risk | 77 (53) | 159 (55) | 236 (54) | 92 (41) | 33 (46) |
| Poor Risk | 5 (3) | 9 (3) | 14 (3) | 5 (2) | 1 (1) |
| Unknown[d] | 6 (4) | 9 (3) | 15 (3) | 31 (14) | 8 (11) |

Data Source: VEG105192, Table 6.14, Table 6.15, Table 8.53, Table 8.54; VEG102616, Table 6.15, Table 6.16, Table 6.17, Table 8.40; VEG107769, Table 6.11, Table 6.12, and Table 8.37.

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

a. VEG105192: placebo arm: 89% clear cell, 11% predominantly clear cell; Pazopanib arm: 91% clear cell, 9% predominantly clear cell (Histology at initial diagnosis was missing for Subject 757; in the pazopanib arm in VEG105192); VEG107769: 92% clear cell, 8% predominantly clear cell

b. As defined by the Investigator.

c. 108 of the assignments in VEG105192, 162 in VEG102616, and all 71 subjects in VEG107769 required the use of total calcium measurements because of missing baseline albumin levels for calculation of corrected calcium.

d. Subjects who were missing data on 1 or more of the 5 risk factors and thus did not have sufficient data to be assigned to a risk category.

e. N=223.

f. Months were calculated from weeks or days as displayed in the source data by multiplication by a factor of 0.23 for weeks and 0.0328 for days.

The numbers of cytokine-pretreated subjects in VEG107769 was 37. One subject received pazopanib in both VEG105192 and VEG107769.

### Efficacy Results

Subgroup analyses were not conducted in VEG 1007769.

### Progression Free Survival

In VEG107769, the primary objective was to evaluate the safety of pazopanib treatment. PFS was a secondary endpoint. PFS was analysed based only on the disease assessments by the investigators; there was no IRC assessment in this study. At the time of the clinical cut-off, 33 (46%) subjects had progressed or died. The median PFS was 8.3 months (95% CI: 6.1 to 11.4 months).

### Overall Survival

Overall survival was a secondary endpoint in VEG107769. At the time of data cut-off, 21 (30%) subjects had died. Median OS was 16.8 months (95% CI: 16.3, not calculable). One-year survival was 73% (95% CI: 61% to 85%).

### Response Analyses

In the supportive study, VEG107769, RR was a secondary endpoint. Disease assessment was by investigator review only. The RR was 32% (95% CI: 21.5% to 43.3%). Duration of response was not calculated in VEG1007769. The rate of CR + PR + 6 month SD was 49.3% (95% CI: 37.7, 60.9).

### Clinical Information Relevant to Dosing Recommendations

The proposed regimen for the treatment of subjects with advanced RCC is pazopanib 800 mg once daily. This is the treatment regimen used in all three efficacy studies. The concentration-effect relationships and clinical effects observed in study VEG10003 and VEG102616 suggest that plasma pazopanib concentrations must be maintained above 15 µg/mL for the entire dosing interval for optimal clinical and biologic activity. Twenty-four hour pazopanib concentrations at steady-state were greater than 15 µg/mL in 93% of subjects that received 800 mg once daily in Study VEG10003. 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.

### Persistence of Efficacy and/or Tolerance Effects

In VEG102616, 55 subjects who had SD at Week 12 after treatment with pazopanib were subsequently randomised to the blinded treatment of pazopanib or placebo prior to the change in study design. The PFS between these two groups were compared.

PFS was statistically significantly longer (p=0.013) in the pazopanib arm compared with the placebo arm. Median PFS was 51.6 weeks (95% CI, 43.6 weeks to not calculable) in the pazopanib arm, almost twice that in the placebo arm (27.1 weeks [95% CI, 19.9 to 47.3 weeks]), as assessed by the IRC. By investigator assessment, median PFS was 59.4 weeks (95% CI, 35.3 to 87.7 weeks) in the pazopanib arm and 37.0 weeks (95% CI, 19.7 to 61.0 weeks) in the placebo arm (p=0.217).

PFS in both arms was similar until the first post-randomisation assessment at Week 20, after which a larger number of subjects in the placebo arm progressed. Between Week 20 and Week 28, most of the remaining progression-free placebo subjects had crossed back over to pazopanib

due to the IDMC recommendation. These data indicate that continued treatment with pazopanib is needed to maintain anti-tumour activity and delay progression.

### *Summary of Efficacy*

The primary evidence of pazopanib clinical efficacy was demonstrated in the pivotal Phase III study, VEG105192, by the following findings:

- The primary analysis of the primary endpoint, PFS, revealed a large and highly statistically significant improvement in PFS in pazopanib-treated subjects compared to placebo-treated subjects (HR 0.46; 95% CI: 0.34 to 0.62; p<0.0000001). The median PFS in the pazopanib arm was more than double that in the placebo arm
- PFS was significantly improved by pazopanib treatment compared to placebo in the two pre-specified subgroups of interest: the treatment naïve subgroup (HR: 0.40; 95% CI 0.27, 0.60; p<0.0000001) and the cytokine pre-treated subgroup (HR: 0.54; 95% CI 0.35, 0.84; p<0.001)
- The pre-planned interim OS analysis indicated that the overall survival appeared to be prolonged in the pazopanib arm relative to the placebo arm, although the p-value (p =0.02) did not meet the pre-specified significance level for the interim analysis and p >0.201 for futility
- A RR of 30% was observed in the pazopanib-treated subjects. Responses were durable, with a median duration of response greater than 1 year. A similar RR was observed in the treatment-naïve (32%) and cytokine-pretreated (29%) subgroups.

Subgroup analyses in VEG105192 demonstrated that the treatment effect of pazopanib on PFS in all the subgroups analysed was consistent with the primary analysis, including subgroups by gender, age, ECOG PS, and the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk category, with HRs ranging from 0.40 to 0.52 (all with a p-value of <0.001).

The robustness of the primary analysis of PFS was confirmed by multiple sensitivity analyses including PFS based on the investigator's assessment, using the scan date, adjusted or unadjusted for stratification factors.

Efficacy data from the Phase II study VEG102616 and the extension study, VEG107769 supported the results of the pivotal study. Consistent with VEG105192, the RR in VEG102616 and VEG107769 was 35% and 32% respectively.

Among the pazopanib-treated subjects with tumour response, a median duration of response greater than 1 year was achieved in the Phase III study, VEG105192, and the Phase II study VEG102616. The PFS results from VEG102616 and VEG107769 are supportive of the pivotal study, allowing for differences in the disease characteristics of the study populations.

Comparisons of clinical efficacy in VEG102616 on tumour response and PFS, in USA subjects versus non-USA subjects, suggest no differences between these two regions.

*Comment: The pivotal study was appropriately designed and conducted to evaluate efficacy of pazopanib in treatment of patients with RCC. The study population enrolled was representative of the population that is to be treated in the indication proposed by the sponsor. Overall, the evaluator considered that the data submitted for evaluation support adequately support that pazopanib is effective for treatment of patients with advanced and/or metastatic renal cell carcinoma.*

## 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 tumours, and subjects with psoriasis or macular degeneration) have been exposed to pazopanib in clinical trials, including 16 monotherapy studies (including the 3 RCC studies that are the focus of this summary), 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. Overall, 1155 subjects have received pazopanib as 800 mg, which is the dose for which this submission seeks approval. Many of these studies are ongoing; therefore, this information represents the data available as of the cut-off date of 8 June 2008.

The most important safety data are provided from the 3 RCC studies: the pivotal trial VEG105192 and 2 supportive trials VEG102616 and VEG107769. These data will be discussed in this evaluation along with additional safety information from 8 monotherapy studies for which interim reports are available.

Safety data to be discussed are from the following studies:

### Core safety data

- VEG105192: N=435; pazopanib arm n=290 and placebo arm n=145 with locally advanced and/or metastatic RCC.

- VEG102616 : N=225 with advanced RCC.
- VEG107769: N=71.

### Additional Safety Data

- VEG10003, a Phase I, dose escalation study in subjects with solid tumours (n=63).
- VEG10004, a Phase I PK study in subjects with solid tumour malignancies (n=10).
- VEG10005, a Phase I PK study in cancer subjects (n=35).
- VEG10007, a Phase I drug interaction study to determine the effects of pazopanib on the metabolism of cytochrome P450 probe drugs in subjects with solid tumours (n=24).
- VEG104450, a Phase II study in subjects with ovarian cancer (n=36).
- VEG20002, a Phase II study in subjects with relapsed or refractory soft tissue sarcoma (n=142).

- VEG20006, a Phase II study in subjects with relapsed or refractory multiple myeloma (n=21).
- VEG105281, a Phase II study to evaluate pazopanib/lapatinib combination therapy in subjects with FIGO Stage IVB cervical cancer (n=60).

## Extent of Exposure

In Study VEG105192, the median duration of treatment was nearly doubled in the pazopanib arm compared with the placebo arm (7.4 months versus 3.8 months). Approximately half (46%) of the subjects in the placebo arm withdrew from study treatment within 3 months compared with 23% of subjects in the pazopanib arm. In the pazopanib arm, 32% of the subjects remained on treatment for over 12 months compared with 15% of subjects receiving placebo. The mean daily dose of the investigational product administered, including dose interruptions, was 787 mg in the placebo arm and 700 mg in the pazopanib arm.

Dose reductions were required for 106 (37%) subjects in the pazopanib arm and 9 (6%) subjects in the placebo arm. In the pazopanib arm, 75 (26%) subjects had 1 dose reduction, 21 (7%) had 2 dose reductions, 8 (3%) had 3 dose reductions, 1 subject had 4 dose reductions and 1 subject had

6 dose reductions. AEs leading to dose interruption in >5% subjects in the pazopanib arm included ALT increased (17 [6%] subjects), diarrhoea (16 [6%] subjects), and aspartate transaminase (AST) increased (15 [5%] subjects).

Across RCC studies 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. 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.

### Adverse Events

### Common Adverse Events

In Study VEG105192, the overall incidence of AEs reported during the study was higher in the pazopanib arm (92%) as compared with placebo (74%). The AEs reported by >20% subjects in the pazopanib arm were diarrhoea (52%), hypertension (40%), hair colour changes (depigmentation) (38%), nausea (26%), anorexia (22%) and vomiting (21%) (see Table 14). These were all reported at a higher incidence than in the placebo arm. Most AEs were of Grade 1 or 2 toxicity. More Grade 3 AEs were reported for the pazopanib arm (33%) compared with 14% in the placebo arm. Grade 4 AEs were reported in 7% of subjects in the pazopanib arm and 6% in the placebo arm. The most frequent toxicities of Grade 3 or 4 in the pazopanib arm were ALT increased, AST increased, hypertension and diarrhoea.

**Table 14.** Adverse Events Reported for at Least 10% of Subjects by Any Grade, and by Grade 3 and 4 Toxicity (Safety Population) in Study VEG105192.

| Preferred Term | Number (% of subjects) | | | | | |
|---|---|---|---|---|---|---|
| | Placebo (n=145) | | | Pazopanib (n=290) | | |
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| Any AE[a] | 107 (74) | 21 (14) | 8 (6) | 268 (92) | 96 (33) | 20 (7) |
| Diarrhea | 13 (9) | 1 (<1) | 0 | 150 (52) | 9 (3) | 2 (<1) |
| Hypertension | 15 (10) | 1 (<1) | 0 | 115 (40) | 13 (4) | 0 |
| Hair color changes | 4 (3) | 0 | 0 | 109 (38) | 1 (<1) | 0 |
| Nausea | 13 (9) | 0 | 0 | 74 (26) | 2 (<1) | 0 |
| Anorexia | 14 (10) | 1 (<1) | 0 | 65 (22) | 6 (2) | 0 |
| Vomiting | 11 (8) | 3 (2) | 0 | 61 (21) | 6 (2) | 1 (<1) |
| Fatigue | 11 (8) | 2 (1) | 2 (1) | 55 (19) | 7 (2) | 0 |
| ALT increased | 5 (3) | 1 (<1) | 0 | 53 (18) | 18 (6) | 3 (1) |
| AST increase | 5 (3) | 0 | 0 | 43 (15) | 13 (4) | 1 (<1) |
| Asthenia | 12 (8)[b] | 0 | 0 | 41 (14) | 8 (3) | 0 |
| Abdominal pain | 2 (1) | 0 | 0 | 32 (11) | 6 (2) | 0 |
| Headache | 7 (5) | 0 | 0 | 30 (10) | 0 | 0 |

Data Source: Study VEG105192 Table 8.21
a. AEs are ranked by incidence in the pazopanib arm. Any AE, any grade includes Grade 5 (fatal) events (12 [4%] subjects in the pazopanib arm and 4 [3%] subjects in the placebo arm). Fatal events by preferred term are described separately (see Section 2.1.3.1.1).
b. One placebo subject had Grade 5 asthenia.
Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase

The percentage of subjects with AEs in the treatment-naive and cytokine pre-treated subjects were similar to the overall population: treatment-naive group, 141 (91%) subjects in the pazopanib group and 58 (74%) subjects in the placebo experienced at least 1 AE during the study compared to cytokine pretreated subjects, 127 (94%) subjects in the pazopanib group and 49

(73%) subjects in the placebo experienced at least 1 AE during the study. AE frequencies according to maximum common toxicity criteria (CTC) grade were also similar between these 2 subgroups.

For the RCC studies overall, the most common AEs reported in subjects receiving pazopanib were similar to those observed in the VEG105192 Study and included diarrhoea (54%), hypertension (41%), hair colour changes (40%), nausea (31%), fatigue (29%), anorexia (23%), vomiting (20%), and ALT increased (16%). Most of these events were Grade 1 or 2 using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Commonly reported AEs with the most frequent Grade 3 classification were hypertension (36 subjects, 6%), ALT increased (31 subjects, 5%), and AST increased (21 subjects, 4%).

### Treatment-Related Adverse Events

In Study VEG105192 more AEs were considered by the investigator to be treatment-related in the pazopanib arm compared with the placebo arm (257 [89%] subjects and 56 [39%] subjects, respectively). Treatment-related AEs reported for >10% subjects in the pazopanib arm included diarrhoea, hair colour change, hypertension, nausea, anorexia, vomiting, fatigue, ALT increased and AST increase (see Table 15).

**Table 15.** Treatment-related Adverse Events Reported for at Least 10% of Subjects by Any Grade, and by Grade 3 and 4 Toxicity (Safety Population) in Study VEG105192.

| Preferred Term | Number (% of subjects) | | | | | |
|---|---|---|---|---|---|---|
| | Placebo (n=145) | | | Pazopanib (n=290) | | |
| | Any Grade[a] | Grade 3 | Grade 4 | Any Grade[a] | Grade 3 | Grade 4 |
| Any AE | 56 (39) | 5 (3) | 1 (1) | 257 (89) | 74 (26) | 11 (4) |
| Diarrhea | 9 (6) | 1 (1) | 0 | 128 (44) | 9 (3) | 2 (<1) |
| Hair color changes | 5 (3) | 0 | 0 | 107 (37) | 1 (<1) | 0 |
| Hypertension | 13 (9) | 1 (1) | 0 | 106 (37) | 12 (4) | 0 |
| Nausea | 8 (6) | 0 | 0 | 63 (22) | 2 (<1) | 0 |
| Anorexia | 6 (4) | 0 | 0 | 49 (17) | 4 (1) | 0 |
| Vomiting | 5 (3) | 1 (1) | 0 | 48 (17) | 6 (2) | 1 (<1) |
| Fatigue | 2 (1) | 0 | 0 | 46 (16) | 5 (2) | 0 |
| ALT increased | 3 (2) | 0 | 0 | 43 (15) | 15 (5) | 2 (<1) |
| AST increase | 4 (3) | 0 | 0 | 38 (13) | 9 (3) | 1 (<1) |

Data Source: Study VEG105192 Table 8.11, Table 8.69.

a. Any AE, any grade includes Grade 5 (fatal) events (4 [1%] subjects in the pazopanib arm and 0 subjects in the placebo arm). Fatal events by preferred term are described separately (see Section 2.1.3.2.1).

For the RCC studies, 530 subjects (90%) treated with pazopanib had at least 1 AE that was considered at least possibly related to the investigational product by the investigator. The most common treatment-related AEs were similar to events noted for Study VEG105192 and included diarrhoea, hair colour changes, hypertension, nausea, and fatigue.

### 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 serious adverse events (SAEs).

Four subjects died within 28 days of first dose, 1 in the placebo group and 3 in the pazopanib group. The deaths were considered as related to the disease under study for all subjects.

Forty-two subjects died within 28 days of last dose which included the 4 subjects who died within 28 days of the first dose. This included 29 (10%) subjects in the pazopanib arm and 13 (9%) subjects in the placebo arm. The deaths were considered related to the disease under study for the majority of subjects in both treatment groups (all except 3 subjects in the placebo arm and all except 9 subjects in the pazopanib arm).

As of the clinical cut-off dates, a total of 51 subjects died within 28 days of the first dose and/or last dose of pazopanib overall in RCC studies. Deaths due to disease progression were not to be reported as SAEs.

### *Serious Adverse Events*

In Study VEG105192, the incidence of fatal serious adverse events (SAEs) was similar in the pazopanib group (4%) and the placebo group (3%), although the causes of fatal events were not similar. Fatal SAEs were considered by the investigator to be related to the investigational product for 4 of the subjects in the pazopanib arm and none in the placebo arm. The events considered treatment-related included abnormal hepatic function and rectal haemorrhage, abnormal hepatic function, peritonitis and ischaemic stroke. Haemoptysis and hepatic function abnormal were the only events reported for more than 1 subject in the pazopanib group (2 subjects each).

The incidence of SAEs (including fatal and non-fatal events) was 24% and 19% in the pazopanib and placebo groups, respectively. Diarrhoea 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. By combining preferred terms for events of interest, more cases of SAEs of liver abnormalities, arterial thromboembolic events (that is, myocardial infarction/ ischaemia, cerebral ischemic event, peripheral vascular disease (PVD), transient ischaemic attack (TIA), and other arterial thrombotic events) and haemorrhagic events were reported in the pazopanib arm compared with the placebo arm. However, no individual preferred term in these categories was reported in more than 1 subject except for hepatotoxicity.

In Study VEG105192, 34 (12%) subjects in the pazopanib arm and 3 (2%) subjects in the placebo arm had SAEs which in the investigator's opinion were treatment-related. Treatment-related SAEs reported in 2 or more subjects in the pazopanib arm were diarrhoea (2%), anaemia (1%), hepatic function abnormal (1%), hepatotoxicity (1%), hypertension (<1%), and vomiting (<1%). The causes of the treatment-related SAEs were similar to those noted for the all causality SAEs.

Overall for the RCC studies, the incidence of fatal SAEs was 3% for pazopanib-treated subjects as of the clinical cut-off date. Similar to Study VEG105192, dyspnoea, haemoptysis, and hepatic function abnormal were the only events reported for more than 1 subject.

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 diarrhoea (9 subjects [2%]). 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: diarrhoea (1%), vomiting (<1%), gastrointestinal haemorrhage (<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%), anaemia (<1%), leucopenia (<1%), thrombocytopenia (<1%), pulmonary embolism (<1%), hypertension (<1%), and hyponatremia (<1%).

### Discontinuations and Dose Modifications due to Adverse Events

For Study VEG105192, AEs leading to permanent discontinuation of the 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 hyperbilirubinaemia) led to discontinuation of the 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 (Amendment 5) in the study protocol (after all subjects had been enrolled) to include stopping for any AST/ALT >8x upper limit of normal (ULN) or for AST/ALT >3x ULN in the presence of hypersensitivity symptoms or concomitant bilirubin elevation to 2xULN.

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 diarrhoea, AST increased, and asthenia. AEs associated with liver function/enzyme abnormalities led to discontinuation of the investigational product for 23 (3.9%) subjects.

More subjects in the pazopanib arm had AEs which led to dose reductions than in the placebo arm (24% versus 3%). AEs that led to dose reduction in >5% subjects in the pazopanib arm included hypertension (21 [7%] subjects) and diarrhoea (16 [6%] subjects).

Overall, 115 (20%) of pazopanib-treated RCC subjects had AEs that led to dose reductions. As with Study VEG105192, the most common events leading to dose reductions were hypertension (30 subjects [5%]) and diarrhoea (26 subjects [4%]).

### Adverse Events of Special Interest

### Hepatic Enzyme Abnormalities

An integrated analysis of hepatic enzyme abnormalities was conducted across the RCC and monotherapy program.

Table 16 provides a summary of liver enzyme abnormalities. The comparison of Study VEG105192, RCC and all monotherapy populations demonstrates that the percentage of subjects who experienced hepatic enzyme abnormalities was consistent across a broad range of studies.

**Table 16.** Summary of Hepatic Enzyme Elevations Across the Pazopanib RCC and Monotherapy Program.

| Laboratory Criteria, n (%) | Study VEG105192 | | RCC | Monotherapy |
| | Placebo (n=145) | Pazopanib (n=290) | Pazopanib (N=586) | Pazopanib (N=977) |
|---|---|---|---|---|
| AT >3xULN and total bilirubin >1.5xULN | 2 (1) | 13 (4) | 20 (3) | 23 (2) |
| AT >3xULN, total bilirubin >2xULN, and ALP <2xULN or missing | 1 (<1) | 3 (1) | 4 (<1)[a] | 4 (<1)[a] |
| ALT >20xULN | 0 (0) | 5 (2) | 7 (1) | 7 (<1) |
| ALT >10xULN | 1 (< 1) | 13 (4) | 21 (4) | 27 (3) |
| ALT >5xULN | 2 (1) | 35 (12) | 61 (10) | 80 (8) |
| ALT >3xULN | 4 (3) | 52 (18) | 104 (18) | 138 (14) |
| Total bilirubin >1.5xULN | 5 (3) | 48 (17) | 83 (14) | 100 (10) |

Data Source: Study VEG105192 Table 8.60; Integrated SCS Table 8.42 and Table 8.43

a.   An additional subject meeting these criteria was identified upon review of the SAE database.  Study VEG102616 Subject 618.

Based on the FDA Draft Guidance for Drug-Induced Liver Industry: Premarketing Clinical Evaluation (October 2007)
Abbreviations: ULN = Upper Limit of Normal; AT= aminotransferase (ALT or AST); ALT = Alanine aminotransferase; ALP= alkaline phosphatase
Subjects are counted in more than one category if they fulfil multiple criteria.

While isolated ALT and isolated bilirubin elevations are seen in 10 to 18% of pazopanib treated subjects, ALT elevations >10xULN and combined ALT and bilirubin elevations are much less common, ranging from <1% to 4% among the groups reflected.

The majority of liver enzyme elevations are detected in the first 18 weeks of treatment with pazopanib. By Week 18, 56.9% of subjects had an ALT/AST elevation, which was 332/359 (92.5%) of all ALT/AST elevations that occurred, and by Week 24, 58.8% of subjects had an ALT/AST elevation, which was 343/359 (95.5%) of all ALT/AST elevations that occurred, in RCC trials. Thus over 90% of all ALT/AST elevations of any grade occurred by Week 18.

While approximately half of all subjects who receive pazopanib experience some elevations in transaminases, few subjects (4%) had increases to 10xULN or greater and <1% had concurrent ALT and bilirubin elevations without significant alkaline phosphatase elevations suggestive of possible impairment of hepatic function.

Outcomes of subjects who developed ALT of    3x ULN (n=106) were evaluated across the RCC population. In no case did a subject with transaminase elevations (with or without bilirubin elevations) have evidence of persistent enzyme abnormalities upon discontinuation of the drug, nor did persistent elevation in liver enzymes lead to hepatic failure in any subject. These analyses demonstrate that pazopanib treatment is commonly associated with asymptomatic hepatobiliary laboratory abnormalities, which can be monitored and managed and are reversible. Hepatic failure and fatal hepatic events are rare and occurred in the setting of progressive disease or significant underlying liver disease.

Most subjects with transaminase elevations in whom dosing was interrupted could be successfully re-challenged.

### Hypertension

### Analysis of Hypertension in Study VEG105192

In the pazopanib arm, of subjects with a baseline systolic blood pressure (SBP) within the range of 90 to 139 mmHg, 47% and 8% had post-baseline SBP shifts ranging from 140 to 169 mmHg and     170 mmHg, respectively. In the placebo arm, of subjects with a baseline SBP within the range of 90 to 139 mmHg, 32% and 1% had a SBP shift ranging from 140 to 169 mmHg and     170 mmHg, respectively.

In the pazopanib arm, of subjects with a baseline diastolic blood pressure (DBP) value within the range of 50 to 89 mmHg, 52% and 3% had post-baseline DBP shifts ranging from 90 to 109 mmHg and     110 mmHg, respectively. In the placebo arm, of subjects with a baseline DBP value within the range of 50 to 89 mmHg, 19% and 0% had a DBP shift ranging from 90 to 109 mmHg and     110 mmHg, respectively.

Subjects in the pazopanib arm had a higher incidence of AEs of hypertension or worsening of hypertension during study treatment compared with subjects in the placebo arm (40% versus 10%), and more subjects treated with pazopanib required adjustment of anti-hypertensive medications compared to those in the placebo arm (49% versus 20%). Most of the events occurred early in the study; by Week 18, 47% of pazopanib subjects had at least 1 occurrence of hypertension.

The cumulative incidence of hypertension across the 3 primary RCC studies was similar to the pazopanib-treated subjects in the VEG105192 study.

### Cardiac and Vascular Events

### Cardiac and Vascular Events in Study VEG105192

Cardiac and vascular AEs reported in this study were categorised as follows:

1. Non-vascular cardiac events which include arrhythmia and myocardial dysfunction

(cardiomyopathy), and

2. Vascular events which include: arterial thromboembolic events (myocardial infarction/ ischaemia, cerebral vascular event, PVD, TIA, and other arterial thrombotic events), and venous thromboembolic events (pulmonary embolism [PE], deep vein thrombosis [DVT] and other venous thrombotic events).

Twenty-eight subjects (10%) in the pazopanib arm and 8 subjects (6%) in the placebo arm experienced at least 1 cardiac and/or vascular AE. Exposure-adjusted cardiac and vascular events rate were analysed for both treatment arms using a 100 patient-years rate. While the exposure-adjusted incidence rate 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), the exposure-adjusted incidence rate for Grade 5 events was higher on the placebo arm (1.28 versus 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. However, 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).

### Cardiac and Vascular Events Across RCC Studies and Monotherapy Studies

Exposure-adjusted incidence rate for cardiac and vascular events was analysed for pazopanib-treated subjects in the 3 primary RCC studies using a 100 patient-years rate. The overall incidence rate of the cardiac and vascular events was 13.21 per 100 patient-years (CI 9.97, 16.45), which is similar to the exposure adjusted incidence rate of 11.99 observed for the VEG105192 pazopanib arm (comparing to 10.22 in the placebo arm). For any Grade 5 cardiac or vascular events, the overall incidence rate was 0.83 per 100 patient-years. The incidence rate for nonvascular cardiac events was 7.84 (CI 5.35, 10.33), with an exposure-adjusted rate for Grade 5 events of 0.41. For arterial thromboembolic events, the exposure-adjusted incidence rate was 3.3 (CI 1.68, 4.92) across RCC studies and the rate of venous thromboembolic events were 2.48 (CI: 1.08, 3.88). These exposure-adjusted incidence rates for these event categories were similar to those calculated for Study VEG105192.

Across all monotherapy studies, the overall exposure-adjusted incidence rate of the cardiac and vascular events was 16.08 (CI 13.00, 19.16). Similar to the RCC studies analyses, the overall incidence rate for Grade 5 cardiac or vascular events was 0.61 per 100 patient-years. The incidence rate for non-vascular cardiac events (9.03 [CI 6.73, 11.33]) is comparable to the rate observed for the RCC studies (7.84 [CI 5.35, 10.33]). The incidences of arterial thromboembolic events and of venous thromboembolic events were also similar to the rates calculated for the 3 RCC studies.

### Haemorrhagic Events

### Hemorrhagic Events in Study VEG105192

Thirty-seven (13%) subjects in the pazopanib arm of Study VEG105192 and 7 (5%) subjects in the placebo arm experienced at least 1 haemorrhagic AE. The most common haemorrhagic events in the pazopanib arm were haematuria (n= 11, 4%), epistaxis (n= 5, 2%), haemoptysis (n= 5, 2%) and rectal haemorrhage (n= 4, 1%). Nine subjects in the pazopanib arm experienced serious haemorrhagic events. Among these 9 subjects, the haemorrhagic events in 6 subjects were assessed by investigator as associated with their underlying disease. Among the remaining 3 subjects, the SAEs were assessed as possibly related to study drug. Two of these subjects had underlying kidney tumours and developed retroperitoneal haemorrhage and haematuria, respectively. The remaining subject had a rectal haemorrhage with bleeding oesophageal varices. Two subjects in the placebo arm experienced serious hemorrhagic events.

### Hemorrhagic Events Across RCC Studies and Monotherapy Studies

Across all monotherapy studies (977 subjects), the most frequent haemorrhagic incidents were epistaxis (7.35/100 patient-years), haematuria (3.22/100 patient-years), haemoptysis (2.76/100 patient-years) and lower GI tract haemorrhages (haematochesia, haemorrhoidal and rectal haemorrhages for 1.38, 1.07 and 1.84/100 patient-years, respectively). The relatively high incidence of haematuria in this population is not unexpected given that over half of the subjects included in the monotherapy population had RCC.

Across RCC studies, the haemorrhagic AE profile was relatively similar to all monotherapy studies.

### Thyroid Function Abnormalities

Increases in thyroid stimulating hormone (TSH) were commonly noted in RCC subjects receiving pazopanib (29%). Most of these subjects do not appear to develop clinically overt hypothyroidism. Overall, clinical hypothyroidism manifested as elevated TSH and low thyroxine

(T4) was noted in 6% of subjects. The hypothyroidism AE incidence rate was also low (4-7%) and similar between VEG105192 and across the RCC studies for pazopanib-treated subjects.

Hyperthyroidism occurs infrequently (1%) and the incidence was not significantly different in subjects receiving pazopanib compared to those receiving placebo in Study VEG105192.

### *Amylase/Lipase Elevations and Pancreatic Events*

Pancreatic monitoring was incorporated in the clinical program because degranulation of the acinar cells was observed in long term toxicology studies. Laboratory grade increases in amylase values were observed for 42/184 subjects (23%) in VEG102616, and increased blood amylase was reported as an AE for 6/225 subjects (3%), all Grade 1 or Grade 2 in severity. Laboratory grade increases in lipase values were observed for 48/181 subjects (27%). Elevations in lipase were reported as an AE for 10 subjects (4%) and were rated Grade 3 for 6 subjects and Grade 4 for 1 subject.

There were no reports of pancreatitis on the placebo controlled Phase III study VEG105192. The only other 2 pancreatic events reported as AEs in the monotherapy studies occurred in Study VEG107769 and Study VEG10007. In VEG107769, 1 subject had a Grade 3 SAE of pancreatitis that was considered unrelated to pazopanib treatment. This event did not result in any changes to dosing. For Study VEG10007, 1 subject had a Grade 2 pancreatitis event that was considered a pazopanib-related SAE.

While elevations in amylase and lipase are common, pancreatitis is rare (<1% across all monotherapy studies), and the relationship of these events to pazopanib is uncertain.

### *Bowel Perforations and Enteral Fistulae*

For VEG105192, 1 subject in the pazopanib arm experienced a fatal SAE of perforative peritonitis which was considered related to the investigational product. Two other subjects in the pazopanib arm had enteral fistulas.

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

### *Proteinuria*

No AEs for nephrotic syndrome were reported in the RCC studies. Proteinuria is a recognised AE with this class of tyrosine kinase inhibitor (TKI) agents. The incidences of AEs of proteinuria were similar between Study VEG105192 (9%) and the combined RCC study populations (8%) and most events were Grades 1 or 2.

### *Adverse Events from Biopharmaceutic and Clinical Pharmacology Studies*

Pazopanib, in monotherapy or in combination with lapatinib or paclitaxel, was generally well tolerated in the Phase I studies in healthy and cancer patients. The most commonly reported AEs in subjects with cancer in the Phase I studies were diarrhoea, hypertension, hair colour changes (depigmentation), nausea, anorexia, fatigue, vomiting, headache, and dysgeusia. The most commonly reported drug-related AEs in the Phase I studies were also diarrhoea, hypertension, hair depigmentation, nausea, anorexia, fatigue, vomiting, headache, and dysgeusia. In general, most events were Grade 1-3; there were very few Grade 4-5 AEs in these studies. In general, SAEs and deaths were consistently due to disease progression.

The most frequently reported SAEs were diarrhoea and abdominal pain, reported by 28 subjects each. Vomiting, hypertension, pyrexia, dyspnoea, pulmonary embolism, dehydration, anaemia, and fatigue were also among the most frequently reported SAEs. The pattern of SAEs is consistent with the pattern observed for the pivotal study VEG105192 and across the RCC studies.

The most frequently reported treatment-related SAEs were diarrhoea, hypertension, vomiting, neutropenia, fatigue, ALT increased, anaemia, dehydration, pulmonary embolism, and thrombocytopenia. A similar pattern of treatment-related SAEs was observed for the pivotal study VEG105192 and across the RCC studies.

### Clinical Laboratory Evaluations

### Haematologic Assessments

### Haematologic Assessments in Study VEG105192

The worst case haematologic toxicity grade shift from baseline is shown in Table 17. Most toxicity grade shifts were to Grade 1 or 2 in both groups. The incidences of leucopenia, 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 haematologic parameters were similar in the pazopanib and placebo arms.

**Table 17.** 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 grade[a] | Grade 3 | Grade 4 | N | Any grade[a] | 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 |

Data Source: Study VEG105192 Table 8.64
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.

### Haematologic Assessments Across RCC Studies

For the RCC studies, the worst case hematologic toxicity grade shift from baseline is displayed in Table 18. Overall, most haematology abnormalities were of Grade 1-2 severity and Grade 4 toxicities were uncommon. The incidences of leucopenia, neutropenia, thrombocytopenia, lymphocytopenia, and anaemia in the RCC subjects were similar to those observed in the pazopanib arm of Study VEG105192.

**Table 18.** Summary of Worst-case Hematologic Toxicity Grade Shift from Baseline (Pazopanib-treated Subjects) in RCC Studies.

| Hematologic Toxicity | Number (%) of subjects | | | |
|---|---|---|---|---|
| | Pazopanib (N=586) | | | |
| | N | Any grade[a] | Grade 3 | Grade 4 |
| Leukopenia | 572 | 204 (36) | 5 (<1) | 0 |
| Neutropenia | 572 | 178 (31) | 6 (1) | 8 (1) |
| Thrombocytopenia | 572 | 169 (30) | 5 (<1) | 5 (<1) |
| Lymphocytopenia | 572 | 214 (37) | 29 (5) | 8 (1) |
| Anemia | 572 | 138 (24) | 7 (1) | 6 (1) |

Data Source: Integrated SCS Table 8.57
a. Any grade increase from baseline.

### Clinical Chemistry Assessments

### 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%). 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%), hypoglycaemia (17% versus 3%), hypokalaemia (9% versus 2%), and hypomagnesaemia (26% versus 14%). Overall, the majority of the toxicity grade shifts in clinical chemistry were to Grade 1 or Grade 2 in both arms.

### Chemistry Assessments Across RCC Studies

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 lab abnormalities in RCC subjects was similar to the rates observed in the pazopanib arm of VEG105192.

### Urinalysis, Vital Signs, Physical Findings and Other Observations

For Study VEG105192, there were no significant changes in urine red blood cells and glucose levels from baseline in both arms.

In VEG105192, in the pazopanib arm, the percentage of non-clinically significant abnormal ECG findings increased from baseline (37%) to anytime post-baseline (62%). Eight subjects (3%) had clinically significant abnormal ECG findings post-baseline including: Grade 1 sinus tachycardia, Grade 1 lateral subepicardiac ischaemia and Grade 1 atrio-ventricular blockage, Grade 1 bradycardia and cardiac arrhythmia, abnormal ECG due to long standing hypertension, Grade 1 sinus bradycardia, Grade 1 QTc prolongation, and QTc prolongation.

In VEG105192, nine (3%) subjects in the pazopanib arm and 3 (2%) subjects in the placebo arm had a post-baseline QTc value shift from <480 msec at baseline to QTc values of 480 to 499 msec post-baseline. Three subjects in the pazopanib arm had a post-baseline QTc value of >500 msec but no associated AE reports. One subject had an SAE of QT prolongation.

Across RCC studies. two pazopanib-treated subjects had clinically significant abnormal ECG values (>480 msec) at baseline. Twelve subjects had a shift from <480 msec to 480 to 499 msec. Eight subjects (1%) had post-baseline values between 500 to 549 msec and 2 subjects (<1%) had post-baseline values    550 msec.

### Safety in Special Groups

### Age

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. However, statistical analyses suggested that on-therapy increases in ALT are significantly correlated with age. Older subjects have a higher tendency for ALT elevations.

### Gender, race and ECOG Status

Overall, no clinically significant differences in the safety profile, as assessed by AEs, SAEs, and hepatic enzyme laboratory abnormalities, were noted based on gender, race or ECOG status.

### Overdose, Withdrawal and Rebound

There is no specific antidote for overdosage of pazopanib, and treatment of overdose should consist of general supportive measures. Pazopanib doses up to 2000 mg daily have been evaluated in clinical trials without dose-limiting toxicity.

The potential for drug abuse or dependence has not been investigated.

There were no reports of withdrawal or rebound effects from these studies.

### Other Ongoing or Planned Clinical (Pharmacology) Studies

### Study MD7108240

This is a multicentre, double-masked, randomised, parallel-group dose-ranging study of repeat topical ocular doses of pazopanib in subjects with primary or recurrent active subfoveal neovascular age-related macular degeneration.

No pharmacokinetic data were reported to the cut-off date. As of the cut-off date of 08 June, 2008:

- No deaths were reported in the study.
- 1 Serious Adverse Event (SAE) was reported (atrial fibrillation) which was considered not related to study drug.

### Study VEG109599

This is an open-label, two-arm, Phase I, dose escalation study to evaluate the safety and tolerability and optimum tolerated regimen (OTR) of pazopanib in combination with gemcitabine (Arm A), or of pazopanib in combination with gemcitabine and cisplatin (Arm B) in subjects with advanced solid tumours.

No pharmacokinetic data were reported to the cut-off date. As of the cut off date, 08 June 2008, no subject had died. One SAE was reported in 1 subject during the reporting period. The SAE, chest pain, was considered by the investigator to be related to study drug.

### Study VEG109607

This is an open-label, two-arm, multicentre, Phase Ib, dose escalation study to evaluate the safety and tolerability and to determine the maximum tolerated dose (MTD) of pazopanib in combination with erlotinib (Arm A) or of pazopanib in combination with pemetrexed (Arm B) in subjects with advanced solid tumours.

No pharmacokinetic data were reported to the cut-off date. As of the data cut-off date of 08 June 2008, 15 subjects have been enrolled; 7 subjects in Arm A and 8 subjects in Arm B. As of the cut off date, there were no deaths reported per the investigator.

### Study VEG109693

This is a Phase I, open-label multiple dose of pazopanib alone and in combination with lapatinib in Japanese patients with solid tumours.

No pharmacokinetic data were reported to the cut-off date. As of the data cut-off date of 08 June, 2008:

- No deaths were reported in the study.
- Pazopanib monotherapy (Part A): 4 subjects reported 5 SAEs; 1 SAE, pneumonitis, was considered to be possibly related to the study drug.
- Pazopanib and lapatinib combination (Part B): 2 subjects reported 2 SAEs, neither was considered related to the study drugs.

### Study VEG105424

This is an open-label, pharmacokinetic study of the safety and tolerability of pazopanib in combination with Folfox 6 or CapeOx in subjects with colorectal cancer.

No pharmacokinetic data were reported to the cut-off date. As of the data cut-off, 08 June 2008 3 deaths have been reported for this study, and 24 subjects experienced 63 SAEs.

### VEG105430

This open-label study will enable cancer subjects who are currently receiving benefit from pazopanib either as monotherapy or as part of a combination regimen in a GSK-sponsored Phase I or II study that has met its study objectives, to continue to receive treatment until commercial pazopanib supplies are locally available. Treatment will be pazopanib 400 mg to 800 mg PO, once or twice daily and, if applicable, other medication as previously defined from prior study. Subjects may continue in the study until disease progression.

### Study VEG107200

This is a Phase I, non-randomised, open-label, dose-escalation, multicentre study to evaluate the administration of oral pazopanib in adult subjects with hepatocellular cancer (HCC). Treatment will be pazopanib, PO, once daily, Days 1-21 of each cycle until discontinuation:

No pharmacokinetic data were reported to the cut-off date. As of the cut-off date, 08 June, 2008 4 deaths were reported. All 4 deaths occurred after each subject had been off study drug for at least 6 weeks and were not considered related to study drug. Four serious adverse events (SAEs) were reported.

### Study VEG110190

This is an open-label, two-arm, multicentre feasibility study to evaluate the safety and tolerability of pazopanib in combination with carboplatin and paclitaxel in female subjects with newly diagnosed, advanced gynaecological tumours. No pharmacokinetic data were reported to the cut-off date.

### Summary of Safety

- The most common AEs in the RCC population treated with pazopanib include diarrhoea, hypertension, hair colour changes, nausea, fatigue, anorexia and vomiting. Most events are Grade 1-2 and few led to permanent discontinuation of study drug.
- The most common Grade 3/4 events were hypertension, ALT increased, diarrhoea, AST increased and fatigue.
- More cases of SAEs of liver abnormalities, arterial thromboembolic events and hemorrhagic events were reported in the pazopanib arm compared with the placebo arm of the pivotal study VEG105192.
- The incidence of fatal SAEs was similar in pazopanib-treated subjects in VEG105192 in comparison with placebo.
- In the placebo-controlled trial VEG105192, the most common laboratory chemistry abnormalities occurring more frequently on pazopanib than placebo included ALT, AST and bilirubin elevations, hypophosphataemia, hypoglycaemia, hypokalaemia, and hypomagnesaemia. Most of these were Grade 1/2.
- The most common Grade 3/4 laboratory abnormalities were for ALT and AST. Leukopenia, neutropenia and thrombocytopenia were more common on pazopanib than placebo but Grade 3/4 cytopenias were uncommon.
- Liver enzyme abnormalities were noted early in pazopanib clinical development and have been extensively evaluated. While approximately half of all subjects who received pazopanib experienced some elevations in transaminases, few subjects (4%) had increases to 10x ULN or greater and <1% had concurrent ALT and bilirubin elevations without significant alkaline phosphatase elevations suggestive of possible impairment of hepatic function.
- Elevations in transaminases typically occurred in the first 18 weeks of treatment. Hepatobiliary AEs that were not laboratory abnormalities were less common, and liver failure and fatal hepatic events were rare.
- Most subjects with transaminase elevations in whom dosing is interrupted can be successfully re-challenged.
- Rare but severe AEs previously described for VEGFR inhibitors including cardiac/cerebral ischaemia, haemorrhage, and bowel perforation (Rini, 2007)[21] were observed on pazopanib treatment. QT prolongation (>500 msec) was also observed (1.8% of subjects across RCC studies); Torsades de Pointes was reported in <1% of subjects across the monotherapy studies. The sponsor stated that a study evaluating the effect of pazopanib on QT interval was planned for early 2009.

*Comment: In summary, pazopanib treatment in subjects with RCC was generally well tolerated with an AE profile similar to other VEGFR inhibitors. Most AEs were mild to moderate in severity and were reversible upon interruption or discontinuation of pazopanib.*

### POST-MARKETING EXPERIENCE

No post-marketing data were submitted for evaluation.

## Clinical Summary and Conclusions

In this application the sponsor is seeking approval for registration of pazopanib (Votrient) film-coated tablets 200 mg & 400 mg for the proposed indication as follows:

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[21] Rini, BI. (2007). Vascular endothelial growth factor-targeted therapy in renal cell carcinoma: current status and future directions. *Clin Cancer Res* 13:1098-1106.

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

The primary evidence in support of clinical efficacy of pazopanib was from the pivotal Phase III study, VEG105192.In this study the primary analysis of the primary endpoint, PFS, revealed a large and highly statistically significant improvement in PFS in pazopanib-treated subjects compared to placebo-treated subjects (HR 0.46; 95% CI: 0.34 to 0.62; p<0.0000001). The median PFS in the pazopanib arm was more than double that in the placebo arm. PFS was significantly improved by pazopanib treatment compared to placebo in the two pre-specified subgroups of interest: the treatment naïve subgroup and the cytokine pre-treated subgroup. The pre-planned interim OS analysis indicated that the overall survival appeared to be prolonged in the pazopanib arm relative to the placebo arm, although the p-value (p =0.02) did not meet the pre-specified significance level for the interim analysis and p >0.201 for futility.

A RR of 30% was observed in the pazopanib-treated subjects. Responses were durable, with a median duration of response greater than 1 year. A similar RR was observed in the treatment-naïve (32%) and cytokine-pretreated (29%) subgroups.

Subgroup analyses in VEG105192 demonstrated that the treatment effect of pazopanib on PFS in all the subgroups analysed was consistent with the primary analysis, including subgroups by gender, age, ECOG PS, and the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk category, with HRs ranging from 0.40 to 0.52 (all with a p-value of <0.001).

The robustness of the primary analysis of PFS was confirmed by multiple sensitivity analyses including PFS based on the investigator's assessment, using the scan date, adjusted or unadjusted for stratification factors.

Efficacy data from the Phase II study VEG102616 and the extension study, VEG107769 support the results of the pivotal study. Consistent with VEG105192, the RR in VEG102616 and VEG107769 was 35% and 32% respectively.

Among the pazopanib-treated subjects with tumour response, a median duration of response greater than 1 year was achieved in the Phase III study, VEG105192, and the Phase II study VEG102616.

In relation to safety, pazopanib treatment in subjects with RCC was generally well tolerated with an AE profile similar to other VEGFR inhibitors. Most AEs were mild to moderate in severity and were reversible upon interruption or discontinuation of pazopanib. The risk/benefit profile appears favourable.

It is the opinion of the clinical evaluator that the data presented in this application provide adequate evidence of efficacy of pazopanib when used as treatment for advanced RCC.

***Recommendation:*** At present, and on the basis of the data evaluated, it is recommended that pazopanib ***should be approved*** for the proposed indication as follows:

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

## V.   Pharmacovigilance Findings

### Risk Management Plan

The adverse event profile of pazopanib is clinical trials was consistent with other VEGFR inhibitors used for RCC (sunitinib and sorafenib).

The following safety risks have been identified by the sponsor in its submission:

| Important identified risk | • Hepatic dysfunction<br>• Haemorrhagic events<br>• GI perforations and fistula<br>• Cardiac arrhythmia<br>• Cardiac ischaemia<br>• Cerebrovascular ischaemic events<br>• Hypertension<br>• Hypothyroidism<br>• Diarrhoea<br>• Fatigue<br>• Asthenia |
|---|---|
| Potential risks | • Cardiac dysfunction<br>• Venous thromboembolic events<br>• Hypoglycaemia<br>• Interactions with substrates of cytochrome P450<br>• Interaction of pazopanib with inhibitors of CYP3A4<br>• Food effect<br>• Reproductive effects<br>• Potential for carcinogenicity |
| Missing information | • Use in patients with hepatic dysfunction<br>• QT effects, including torsades de pointes |

The sponsor proposes routine pharmacovigilance for all safety issues highlighted above. This includes monthly review of post-marketing reports with a particular focus on paediatric and elderly patients, overdose effects and reports of drug interactions.

In addition, the sponsor proposes the following additional pharmacovigilance activities:

- Active surveillance using a variety of USA medical claims databases to monitor the events of liver chemistry abnormalities, ischaemia (myocardial infarct (MI), angina, cerebro-vascular accident/stroke (CVA), transient ischaemic attack (TIA), and torsade de pointes;
- Active surveillance of hepatic events via the Varian Electronic Medical Record system, an oncology-specific electronic medical record epidemiological database;
- NCI study 8063: A Phase I and Pharmacokinetic Single Agent Study of Pazopanib in Patients with Advanced Malignancies and Varying Degrees of Liver Function;
- VEG111485: A Phase I, Randomized, Double-Blinded,Placebo-Controlled Study to Evaluate the Effect of Repeat Oral Doses of Pazopanib (GW786034) on Cardiac Conduction in Subjects with Solid Tumors;
- Two-year carcinogenicity studies in rats and mice are to be performed in the future to assess the carcinogenic potential of pazopanib.

In addition to recommendations regarding the Product Information document, the following issues have been identified by the Office of Medicines Safety Monitoring (OMSM):

1) There appears to be an apparent under-representation of the elderly in active surveillance measures to monitor torsade de pointes, and ischaemic cardiac events such as myocardial infarction, cerebrovascular accidents, transient ischaemic attack, and unstable angina. The sponsor was asked to clarify and justify anticipated number of elderly patients

to be entered into the proposed databases, or to consider alternative databases in order to maximise the capture of data most applicable to the intended population.

## Sponsor's Response:

To compensate for under-representation of the elderly (ie, aged 65 years and over) in US medical claims data, the applicant will augment the healthcare claims database study with the PHARMO Dutch linked registry system. The PHARMO Dutch linked registries include patients of all age groups, and has a similar age distribution as the overall age distribution of the Netherlands. The viability of using this data source, however, will depend on gaining regulatory approval in the EU and whether it is placed on formulary.

2) The sponsor stated that a two-year carcinogenicity studies in rats and mice is planned for the future to assess the carcinogenic potential of pazopanib. The anticipated time frame and milestones for this study were requested.

## Sponsor's Response:

Carcinogenicity studies in rats and mice with pazopanib are currently planned to initiate in September 2011 in support of an estimated marketing authorization in late 2014 for chronic adjuvant indications of Votrient. These studies are not considered necessary or warranted for the current indication in advanced RCC in accordance with the recently adopted ICH S9 guidance (Section 2.7). The guidance states 'The appropriateness of a carcinogenicity assessment for anticancer pharmaceuticals is described in ICH S1A. Carcinogenicity studies are not warranted to support marketing for therapeutics to treat patients with advanced cancer.' [22]

3) The anticipated time frame and milestones for the NCI study 8063 was also requested from the sponsor.

## Sponsor's Response.

NCI 8063 is a phase I pharmacokinetic single agent study of pazopanib in patients with advanced malignancies and varying degrees of liver dysfunction.

The main clinical milestones achieved to date are as follows:

- Enrollment and completion of 'normal' hepatic function cohort: maximum tolerated dose (MTD) defined as 800 mg
- Enrollment and completion of 'mild' hepatic dysfunction cohort: MTD defined as 400 mg
- Enrollment and completion of 'moderate' hepatic dysfunction cohort: MTD defined as 200 mg

Enrollment of the 'severe' hepatic dysfunction cohort is ongoing.

Submission of the final study report for NCI 8063 is anticipated by August 2010.

4) The sponsor was asked to clarify the conditions of a proposed analysis in the pharmacovigilance plan which sets out to monitor prescriber behaviour to ensure

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[22] ICH S9, EMEA/CHMP/ICH/646107/2008, Nonclinical Evaluation for Anticancer Pharmaceuticals.

ICH S1A. Guideline on the needs for carcinogenicity studies of pharmaceuticals.

compliance with labelling recommendations around hepatic monitoring using medical claims databases.

## Sponsor's Response:

To clarify, the prescriber compliance analysis will be carried out in an electronic medical records database (not in medical claims databases as stated in the question). The information from medical claims databases will only be used for the cardiovascular monitoring surveillance study.

The details of the proposed prescriber compliance analysis are as follows:

The frequency and timing of liver chemistry tests before and during the period of pazopanib exposure will be characterized and the proportion of patients who receive/do not receive liver chemistry tests at least once every 4 weeks for the first 4 months of treatment will be enumerated. The proportion of patients with additional periodic monitoring after the first 4 months of treatment will also be calculated. Any instances of severe elevations will also be flagged ((transaminase elevations >8X upper limit of normal (ULN); and transaminase elevations >=3X ULN with bilirubin elevations >=2X ULN and alkaline phosphatase <3X ULN)). Among pazopanib users with severe elevations, the proportion who discontinued use and who had subsequent monitoring of liver function, as well as the proportion whose liver chemistries returned to baseline values will be described.

This algorithm is based on the liver monitoring guidelines contained in the proposed pazopanib prescribing information.

The sponsor's assessment of the requirement to provide a risk minimisation plan concluded that routine risk minimisation activities were sufficient for all safety issues is accepted. No additional risk minimisation activities are necessary beyond presentation of risks in the Product Information.

There were no objections raised to the sponsor's proposed risk minimisation plan by the OMSM.

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

The quality evaluator had no objections to registration.

## Nonclinical

There are no nonclinical objections to registration. Repeat dose toxicity was studied in mice, rats and cynomolgus monkeys. The adverse effects noted were generally consistent with the mechanism of action of pazopanib.

## Clinical

The clinical evaluator has recommended approval of the application.

**Pharmacodynamics** In a phase II study in patients with RCC (VEG102616), pazopanib administration was associated with reductions in circulating soluble VEGFR-2 (an endogenous inhibitor of VEGF), suggesting inhibition of angiogenesis.

**Pharmacokinetics** Absolute bioavailability data were only available for 3 subjects. The median value was 21%. $T_{max}$ occurred at 2-4 hours. Administration with food resulted in an approximate 2-fold increase in $C_{max}$ and AUC. The proposed PI recommends administration 1 hour before or 2 hours after food, which is consistent with the dosing used in the pivotal clinical study.

Pharmacokinetics were non-linear, with decreasing systemic exposure at higher doses. Systemic exposure appeared to plateau at a dose 800 mg once daily.

Following IV administration, the volume of distribution (in the three available subjects) was between 9.2 – 13.2 L. Protein binding was 95 - 99%.

Following oral administration of a radiolabelled dose, less than 4% of the radioactivity was excreted in the urine (with less than 0.5% being in the form of unchanged pazopanib), suggesting that the drug is not renally cleared. Pazopanib was the major species in blood and plasma (79-95% of circulating radioactivity). *In vitro* data indicated that the drug is metabolised predominantly by CYP3A4.

Following IV administration, clearance was between 0.206 and 0.347 L/hr in the three subjects studied. Half-life was between 26.7 and 39.3 hours. Elimination was predominantly via faeces (96 - 98%).

Administration with a cytochrome P450 (CYP450) inhibitor (ketoconazole) resulted in 2.2 fold increase in pazopanib AUC. In a study in glioma patients receiving enzyme-inducing anticonvulsant agents, pazopanib AUC values were 30% lower than expected. Interaction studies suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2D6 and CYP2C8.

A study in patients with hepatic impairment is ongoing with results not available until August 2010. No study has been conducted in renal impairment.

**Efficacy** The justification for the choice of 800 mg once daily as the recommended dose was found to be acceptable by the clinical evaluator.

Evidence for efficacy comes primarily from one phase III, randomised (2:1), double-blind, placebo controlled trial (**study VEG105912**). The study has been published (JCO January 25, 2010) and a copy of the publication is included in the agenda papers. Subjects enrolled had locally advanced or metastatic disease, with clear cell histology. Subjects could have been naïve to systemic treatment, or could have had one prior cytokine-based therapy.

The primary endpoint was progression-free survival (PFS). Pazopanib treatment was associated with a significant improvement in PFS (Hazard Ratio 0.46; 95% CI 0.34 – 0.62; $p < 0.0000001$). Median PFS was prolonged by approximately 5 months (9.2 versus 4.2 months).

Overall survival (OS) was a secondary endpoint. Data were immature as less than 50% of subjects had died. There was no significant difference between treatment groups. Patients allocated to the placebo group were permitted to crossover to the active group on progression and 48% did receive pazopanib. The OS results may therefore have been confounded by this crossover. The sponsor was requested to provide any updated survival data, if available, in their pre-ACPM response.

Pazopanib treatment was associated with a significantly greater response rate (30% versus 3%). There were no differences between treatments on quality of life measures.

Subgroup analyses of PFS suggested that the efficacy benefit was observed across all subgroups examined.

Two supportive studies were included in the submission. **Study VEG107769** was an open uncontrolled extension study of 71 subjects who had received placebo in the pivotal study and had developed progressive disease. The observed response rate was 32%, which is consistent with that seen in the pazopanib arm of the pivotal study. Study **VEG102616** was another open uncontrolled study in 225 RCC subjects. The observed response rate was 35%.

**Safety** A total of 1645 subjects were included in the submitted studies. Of these 1155 were treated with 800 mg once daily. A total of 586 RCC subjects were treated. Median duration of

treatment was 7.4 months. Approximately 180 RCC subjects were treated for more than 12 months.

The most informative safety data come from the pivotal study, which was a randomised (2:1), double blind comparison with placebo. The overall safety profile in terms of incidence of adverse events is summarised in the following table.

**Table 19.** Overall safety profile.

|  | **Pazopanib** | **Placebo** |
| --- | --- | --- |
| Adverse events (AEs) | 92 % | 74 % |
| Treatment – related AEs | 89 % | 39 % |
| Grade 3 or 4 AEs | 40 % | 20 % |
| Treatment – related Grade 3 or 4 AEs | 30 % | 4 % |
| Serious adverse events (SAEs) | 24 % | 19 % |
| Treatment – related SAEs | 12 % | 2 % |
| Fatal AEs | 4% (n = 12) | 3% (n = 4) |
| Treatment – related Fatal AEs | n = 4 | n = 0 |
| Discontinuations due to AEs | 15 % | 6 % |

Specific toxicities with an increased incidence compared to placebo included the following:

- Gastrointestinal – diarrhoea, nausea, vomiting, anorexia, abdominal pain;
- Fatigue (19% versus 8%) and asthenia (14% versus 8%);
- Hypertension (40% versus 10%);
- Proteinuria (9% versus 0%);
- Haemorrhagic events (13% versus 5%);
- Elevated TSH (31% versus 5%) and decreased T3 (13% versus 5%);
- Neutropenia (34% versus 6%) and thrombocytopenia (32% versus 5%);
- Hair colour changes (38% versus 3%).

The majority of these events were of grade 1 or 2 in severity.

In the pivotal study, 9 subjects experienced arterial thrombotic adverse events (myocardial ischaemia, MI, CVA or TIA) in the pazopanib arm (3.1%) compared with none in the placebo arm.

Across all studies in RCC, QT prolongation was observed in 1.8% of subjects and 2 cases of Torsades de Pointes were reported. A study of the effects of pazopanib on QT interval is ongoing with results not available until September 2010.

Raised amylase and lipase were reported in the phase 2 studies (amylase and lipase were apparently not measured in the pivotal study, but no cases of pancreatitis were reported).

These toxicities are consistent with those observed with other drugs that target the VEGF pathway.

Hepatotoxicity

In the pivotal study, pazopanib was clearly associated with hepatic enzyme elevations. In addition, there were two deaths involving impaired hepatic function which were considered related to pazopanib.

The FDA has published a guideline[23] on assessing the potential for drugs to cause serious drug-induced liver injury (DILI) – that is, irreversible liver failure that is fatal or requires liver transplantation. The guideline describes "Hy's Law". A patient who:

- develops hepatocellular damage as evidenced by a 3-fold increase above upper limit of normal (ULN) in ALT; and
- has impairment of liver *function* as evidenced by a 2-fold increase above ULN in total bilirubin; and
- has no evidence of cholestasis as evidenced by an increase above ULN in serum ALP; and
- has no other reason to explain these findings;

is referred to as a "Hy's Law case". The expected incidence of severe DILI is approximately 1/10 of the incidence of Hy's law cases.

The FDA guideline states that *"…the finding of two Hy's law cases, and probably even one, is a strong predictor of a significant risk of severe liver injury."* In the submitted studies of pazopanib monotherapy, a total of four such cases were observed in a population of 977 subjects. The predicted incidence of severe DILI in the post-market setting would be approximately 4 in 10,000 subjects. The FDA has approved pazopanib for RCC, but has required a black box warning regarding hepatotoxicity.

Serious DILI was not identified as a risk for sunitinib or sorafenib at the time of their approvals.

**Risk-Benefit Analysis**

1.  Overall risk-benefit
    The pivotal study has demonstrated that pazopanib is effective in the treatment of RCC as assessed by PFS. A benefit in terms of PFS (without a demonstrated benefit on overall survival) has been the basis for approval of several agents in RCC in recent years.

    The pattern of toxicity was generally consistent with that seen for other VEGF pathway inhibitors (sunitinib, sorafenib, bevacizumab). However, pazopanib may have an additional risk of severe DILI. It could be argued that given the availability of other agents that do not appear to be associated with this risk, registration of pazopanib may not be appropriate.

    However, given the terminal nature of the condition being treated and the expected rarity of severe DILI, it could also be argued that the hepatotoxicity risk is not an unacceptable one. On balance, the Delegate concluded that the drug has a favourable risk-benefit ratio and could be approved. It would be appropriate to include in the PI a boxed warning, as implemented in the USA.

The Delegate proposed to approve the application.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission from GlaxoSmithKline Australia Pty Ltd to register a new chemical entity pazopanib hydrochloride (Votrient) tablets 200 mg and 400 mg for the indication:

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[23] "Drug-Induced Liver Injury: Premarketing Clinical Evaluation."
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

*Treatment of advanced and/or metastatic renal cell carcinoma (RCC).*

In making this recommendation the ACPM agreed with the Delegate that the evidence to support a favourable risk benefit ratio for this new chemical entity has been sufficiently demonstrated and noted that while the pattern of toxicity was consistent with other drugs in the class, the risk of severe hepatotoxity warrants additional appropriate management. Therefore the ACPM supported the inclusion of a boxed warning.

The specific conditions of registration should include:

- A requirement to submit for evaluation the final report of the ongoing study of pharmacokinetics in patients with hepatic impairment;
- A requirement to submit for evaluation the final report of the ongoing study comparing pazopanib with sunitinib in subjects with advanced renal cell carcinoma.

Changes to the Product Information which should be made prior to approval include:

- A boxed warning regarding the risk of hepatotoxity.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Votrient, as pazopanib 200 mg and 400 mg film coated tablets in bottles, indicated for:

*"Treatment of advanced and/or metastatic renal cell carcinoma (RCC)."*

With the following specific conditions:

1. The final report of the ongoing study of pharmacokinetics in patients with hepatic impairment must be submitted for evaluation when available.

2. The final report of the ongoing study comparing pazopanib with sunitinib in subjects with advanced renal cell carcinoma must be submitted for evaluation when available.

3. Each batch of pazopanib tablets supplied in Australia must be tested at release and meet the approved finished product specifications.

A boxed warning regarding the risk of hepatotoxity was included in the PI.

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

# PRODUCT INFORMATION

# VOTRIENT® TABLETS

> **Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. [See PRECAUTIONS.]**
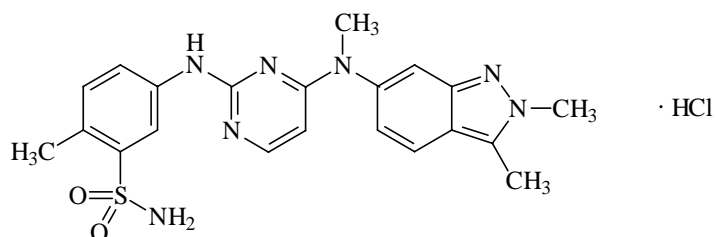
## NAME OF THE MEDICINE

VOTRIENT® (Pazopanib hydrochloride)

## DESCRIPTION

Pazopanib is a member of the tyrosine kinase inhibitor family. It is supplied as the hydrochloride salt, with chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride.

The structural formula is:



Two basic ionisation constants (pKa) of pazopanib free base were determined to be 6.4 and 2.1, and one weakly acidic pKa was determined to be 10.2. The partition coefficient of the free base between octanol and water is 4470 (cLogP = 3.65). The pH of a 0.04% w/v solution of pazopanib hydrochloride in water is about 2.2. Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

Molecular formula: $C_{21}H_{23}N_7O_2S \cdot HCl$
Molecular weight: 473.99 g/mol.
CAS number: 635702-64-6
BCS Classification: Class II (High Permeability, Low Solubility)

Each film-coated tablet contains pazopanib hydrochloride equivalent to either 200 mg or 400 mg of pazopanib free base.

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Each film-coated tablet also contains magnesium stearate, cellulose - microcrystalline, povidone, sodium starch glycollate, hypromellose, macrogol 400, titanium dioxide, polysorbate 80, and iron oxide red CI77491 (200 mg tablet only).


## PHARMACOLOGY

### Mechanism of Action

Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and –β, and stem cell factor receptor (c-KIT), with $IC_{50}$ values of 10, 30, 47, 71, 84 and 74 nM, respectively. Pazopanib also inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR-β receptors in cells *in vitro*. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in mouse models, and the growth of some human tumour xenografts in mice.

### Pharmacokinetics

The pharmacokinetics of pazopanib have been evaluated in 408 subjects. The reported pharmacokinetic parameters such as absolute bioavailability and clearance were obtained from only three subjects.

#### *Absorption*
Pazopanib is absorbed orally with an absolute oral bioavailability of 13.5 – 38.9 % and median time to achieve peak concentrations of 2.0 to 4.0 hours after the dose. Daily dosing results in 1.23- to 4-fold increase in AUC. There was no consistent increase in AUC and $C_{max}$ when the pazopanib dose increased above 800 mg.

Systemic exposure to pazopanib is increased when administered with food. 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 1 hour before or 2 hours after a meal (*see Dosage and Administration*).

Administration of a single pazopanib 400 mg crushed tablet increased $AUC_{(0-72)}$ by 46% and $C_{max}$ by approximately 2 fold and decreased $t_{max}$ by approximately 1.5 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. Therefore, due to this potential for increased exposure, tablets should not be crushed (see Dosage and Administration).

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*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. After 5 mg IV administration, pazopanib displayed a volume of distribution of 9.2 – 13.1 L (< 40 % of total body water). *In vitro* studies suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

*Metabolism*

Results from *in vitro* studies demonstrated that the metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

*Elimination*

Pazopanib is eliminated slowly with mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via faeces with renal elimination accounting for < 4 % of the administered dose. Pazopanib plasma clearance after a 5 mg IV dose ranged from 0.206 to 0.347 L/h (approximately 0.5% of liver blood flow and 5% of glomerular filtration rate).

## CLINICAL TRIALS

The safety and efficacy of VOTRIENT in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-centre study. Patients (N= 435) with locally advanced and/or metastatic RCC were randomized to receive VOTRIENT 800 mg monotherapy once daily or placebo. The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS) and the principle secondary endpoint is overall survival (OS). The other objectives were to evaluate the overall response rate and duration of response.

From the total of 435 patients in this study, 233 patients were treatment naïve and 202 were second line patients who received one prior IL-2 or INFα-based therapy. The performance status (ECOG) was similar between the VOTRIENT and placebo groups (ECOG 0: 42 % vs. 41 %, ECOG 1: 58 % vs. 59 %). All patients had clear cell histology or predominantly clear cell histology. Approximately half of all patients had 3 or more organs involved in their disease and most patients had the lung (74 %), and/or lymph nodes (54 %) as a metastatic location for disease at baseline.

A similar proportion of patients in each arm were treatment-naïve and cytokine-pre-treated (53 % and 47 % in VOTRIENT arm, 54 % and 46 % in placebo arm). In the cytokine-pre-treated subgroup, the majority (75 %) had received interferon based treatment.

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Similar proportions of patients in each arm had prior nephrectomy (89 % and 88 % in the VOTRIENT and placebo arms, respectively) and/or prior radiotherapy (22 % and 15 % in the VOTRIENT and placebo arms, respectively).

The primary analysis of the primary endpoint PFS is based on disease assessment by independent radiological review in the entire study population (first line and second line).

**Table 1. Overall Efficacy Results by Independent Review Committee (IRC)**

| Endpoints/ Study population | VOTRIENT | Placebo | HR (95% CI) | P value |
|---|---|---|---|---|
| **PFS** | **Median (months)** | | | **(one-sided)** |
| Overall ITT | N=290 | N=145 | | |
| | 9.2 | 4.2 | 0.46 (0.34, 0.62) | <0.0000001 |
| Treatment-naïve | N=155 | N=78 | | |
| | 11.1 | 2.8 | 0.40 (0.27, 0.60) | <0.0000001 |
| Cytokine pre-treated | N=135 | N=67 | | |
| | 7.4 | 4.2 | 0.54 (0.35, 0.84) | <0.001 |
| **Response rate** | **% (95% CI)** | | | |
| Overall | N=290 | N=145 | | |
| | 30 (25.1 ,35.6) | 3 (0.5, 6.4) | - | <0.001 |

CI: confidence interval; HR: hazard ratio; ITT: Intent-to-treat; PFS: progression free survival.

**Figure 1    Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Overall Population (Treatment-Naïve and Cytokine Pre-Treated Populations)**



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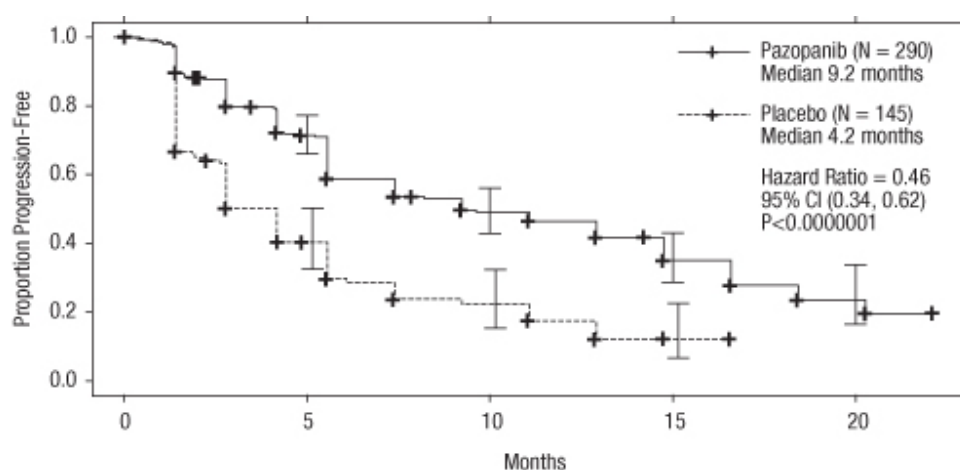
**Figure 2    Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Treatment-Naïve Population**
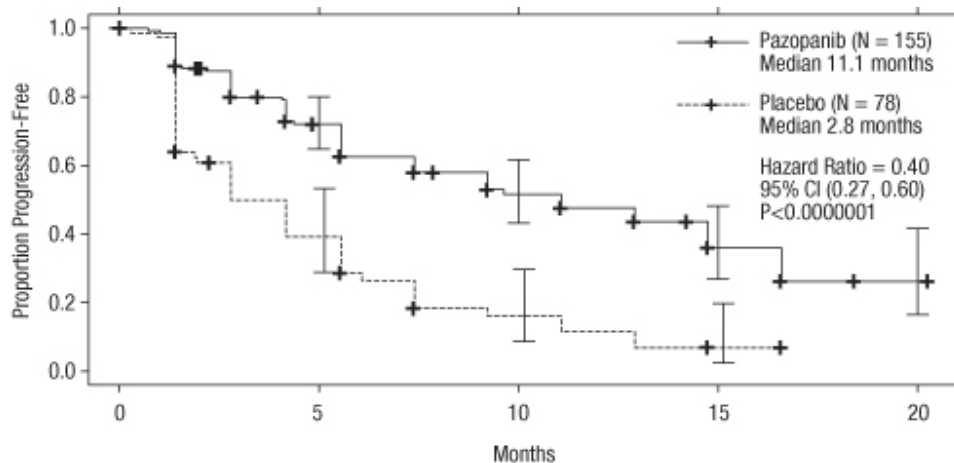


**Figure 3        Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Cytokine Pre-Treated Population**
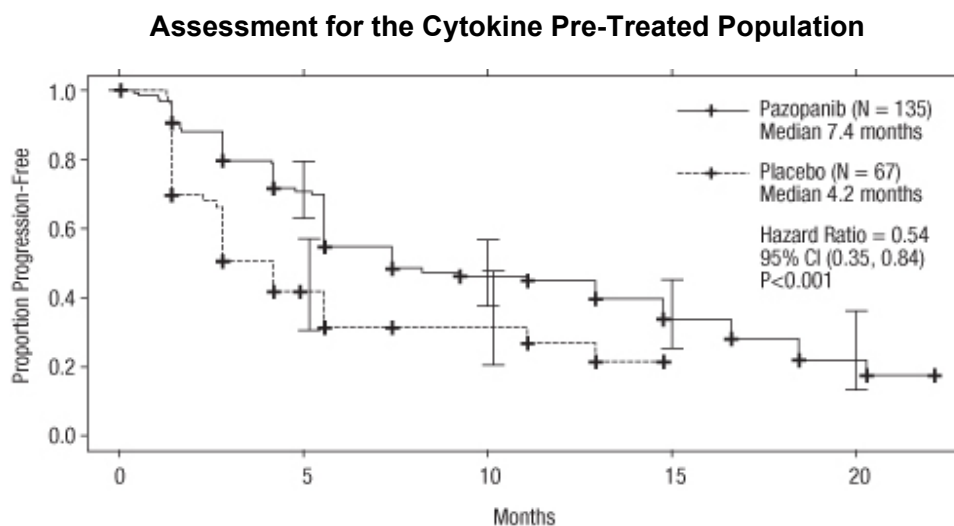


For patients who responded to treatment, the median time to response was 11.9 weeks and the median duration of response was 58.7 weeks as per independent review.

In the pivotal study, the QoL assessments were based on blinded self-reported global scores from two protocol-specified questionnaires, EORTC QLQ-C30 and EuroQoL EQ-5D. Analysis was based on patients who continued on therapy in both arms, prior to progression. The assessments showed no difference between treatment with VOTRIENT or placebo (p > 0.05), indicating no negative impact of VOTRIENT on global quality of life.

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In a Phase 2 study of 225 patients with locally recurrent or metastatic clear cell renal cell carcinoma, objective response rate was 35 % and median duration of response was 68 weeks, as per independent review.  Median PFS was 11.9 months.


## INDICATIONS

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


## CONTRAINDICATIONS

VOTRIENT is contraindicated in patients with hypersensitivity to the active substance pazopanib hydrochloride or to any of the excipients *(see DESCRIPTION).*


## PRECAUTIONS

**Hepatic Effects:**  Cases of hepatic failure (including fatalities) have been reported during use of VOTRIENT.    In clinical trials with VOTRIENT, increase in serum transaminases (ALT, AST) and bilirubin were observed (*see Adverse Events*).   In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin.  The vast majority (92.5%) of all transaminase elevations of any grade occurred in the first 18 weeks.  Grades are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE).

Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment, and as clinically indicated.   Periodic monitoring should then continue after this time period.

The following guidelines are provided for patients with baseline values of total bilirubin ≤ 1.5 x ULN and AST and ALT ≤ 2 x ULN.

- Patients with isolated ALT elevations between 3 x ULN and 8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT returns to Grade 1 (NCI CTCAE) or baseline.

- Patients with ALT of > 8 X ULN should have VOTRIENT interrupted until they return to Grade 1 (NCI CTCAE) or baseline.  If the potential benefit for reinitiating VOTRIENT treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose (400 mg daily) and measure serum liver tests weekly for 8 weeks *(see Dosage and Administration)].*   Following reintroduction of VOTRIENT, if transaminase elevations > 3 X ULN recur, then VOTRIENT should be permanently discontinued.

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- If ALT elevations > 3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 x ULN should be managed as per the recommendations outlined for isolated ALT elevations.

For patients with pre-existing moderate hepatic impairment, VOTRIENT dose modification guidelines (beyond reducing the initial starting dose to 200 mg per day) have not been established (See Dosage and Administration – Populations).

**Hypertension:** Blood pressure should be well controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy (*see Adverse Events*). 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 VOTRIENT dose may be reduced (*see Dosage and Administration*). VOTRIENT should be discontinued if hypertension is severe and persists despite anti-hypertensive therapy and VOTRIENT dose reduction.

**QT Prolongation and Torsade de Pointes:** In clinical studies with VOTRIENT, events of QT prolongation or Torsade de Pointes have occurred (*see Adverse Events*). VOTRIENT should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease. When using VOTRIENT, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

**Arterial Thrombotic Events:** In clinical studies with VOTRIENT, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (*see Adverse Events*). Fatal events have been observed. VOTRIENT should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. VOTRIENT has not been studied in patients who have had an event within the previous 6 months. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

**Haemorrhagic Events:** In clinical studies with VOTRIENT haemorrhagic events have been reported (*see Adverse Events*). Fatal haemorrhagic events have occurred. VOTRIENT has not been studied in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months. VOTRIENT should be used with caution in patients with significant risk of haemorrhage.

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**Gastrointestinal Perforations and Fistula:** In clinical studies with VOTRIENT, events of gastrointestinal (GI) perforation or fistula have occurred (*see Adverse Events*). Fatal perforation events have occurred. VOTRIENT should be used with caution in patients at risk for GI perforation or fistula.

**Wound Healing:** No formal studies on the effect of VOTRIENT on wound healing have been conducted. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical judgement of adequate wound healing. VOTRIENT should be discontinued in patients with wound dehiscence.

**Hypothyroidism:** In clinical studies with VOTRIENT, events of hypothyroidism have occurred (*see Adverse Events*). Proactive monitoring of thyroid function tests is recommended.

**Proteinuria:** In clinical studies with VOTRIENT, proteinuria has been reported (see *Adverse Events*). Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria. VOTRIENT should be discontinued if the patient develops nephrotic syndrome.

**Effects on fertility**

Pazopanib may impair fertility in human males and females. In a female reproductive toxicity study in rats, reduced fertility has been observed. Decreased corpora lutea and increased incidence of ovarian cysts and atrophy have also been noted in rodents. Decreased corpora lutea was also noted in cynomolgus monkeys given 500 mg/kg/day pazopanib (equivalent to the human clinical exposure based on AUC) for up to 34 weeks.

Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations at doses ≥ 100 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC) following 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and epididymal weights at ≥ 30 mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC). Atrophy and degeneration of the testes with aspermia, hypospermia and cribiform change in the epididymis was also observed in male rats given ≥ 30 mg/kg/day in the 26-week toxicity study.

**Use in Pregnancy (Category D)**

There are no adequate data from the use of pazopanib in pregnant women.

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VOTRIENT can cause fetal harm when administered to a pregnant woman. Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below clinical exposure. Effects included cardiovascular malformations, incomplete or absent ossification, increased pre- and post-implantation loss, early resorptions, embryo lethality, and decreased foetal body weight.

VOTRIENT should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

If VOTRIENT is used during pregnancy, or if the patient becomes pregnant while receiving VOTRIENT, the potential hazard to the foetus should be explained to the patient. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with VOTRIENT. Ensure contraceptive cover in women of childbearing potential during use and for four weeks after therapy.

**Use in Lactation**

The safe use of VOTRIENT during lactation has not been established. It is not known whether pazopanib is excreted in human milk. Many drugs are excreted into human milk. VOTRIENT should not be used by breastfeeding women.

**Ability to perform tasks that require judgement, motor or cognitive skills**

There have been no studies to investigate the effect of VOTRIENT on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of VOTRIENT. The clinical status of the patient and the adverse event profile of VOTRIENT should be borne in mind when considering the patient's ability to perform task that require judgment, motor and cognitive skills.

**Genotoxicity**

Pazopanib was negative for genotoxicity in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat micronucleus assay). A synthetic intermediate in the manufacture of pazopanib, which is also present in the final drug substance, was not mutagenic in the Ames assay but was genotoxic in the mouse lymphoma L5178Y TK +/- and micronucleus assays and is controlled to below a daily intake of 0.1 mg.

**Carcinogenicity**

Carcinogenicity studies with pazopanib have not been performed.

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**Interactions with other medicines**

*Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes*

*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 VOTRIENT.

*CYP3A4 Inhibitors*: Concurrent administration of a single dose pazopanib eye drops with the strong CYP3A4 inhibitor, ketoconazole, in healthy volunteers resulted in 220 % and 150 % increases in mean $AUC_{(0-t)}$ and $C_{max}$ values, respectively.

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 may also increase plasma concentrations of pazopanib.

Administration of 1500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, Pgp and 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. Co-administration of pazopanib with a CYP3A4, Pgp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations.

Combination with strong CYP3A4 inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction of pazopanib should be considered when it must be co-administered with strong CYP3A4 inhibitors (*see Dosage and Administration*).

*CYP3A4 Inducers*: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

**Effects of Pazopanib on CYP Substrates**

*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. VOTRIENT 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 dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe

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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 26 % and 31 % in paclitaxel AUC and $C_{max}$, respectively.  Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolised by CYP3A4, CYP2D6, or CYP2C8 is not recommended.  Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

### *Effects of Pazopanib on Transporters*

*In vitro* studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with $IC_{50}$ of 1.2 and 0.79 $\mu$M, respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGT1A1 (e.g. irinotecan) and OATP1B1 (e.g. rosuvastatin).

### *Effect of Food on Pazopanib*

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 1 hour before or 2 hours after a meal (*see Dosage and Administration).*

## ADVERSE EVENTS

### Clinical Trial Data

The safety and efficacy of VOTRIENT in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-centre study.  Patients with locally advanced and/or metastatic RCC were randomized to receive VOTRIENT 800 mg once daily (N=290) or placebo (N=145).  The median duration of treatment was 7.4 months for the VOTRIENT arm and 3.8 months for the placebo arm.

Adverse reactions are listed below by MedDRA body system organ class.

The following convention has been utilised for the classification of frequency:
Very common           $\geq$ 1 in 10
Common                   $\geq$ 1 in 100 and < 1 in 10
Uncommon               $\geq$ 1 in 1,000 and < 1 in 100

Categories have been assigned based on absolute frequencies in the clinical trial data.

### Blood and lymphatic system disorders

*Common*                 Thrombocytopenia
                                 Neutropenia

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**Endocrine disorders**

*Common*                 Hypothyroidism*

**Metabolism and nutrition disorders**

*Very common*      Anorexia

*Common*                 Weight decreased

**Nervous system disorders**

*Very common*      Headache

*Common*                 Transient ischaemic attack*
Dysgeusia

*Uncommon*            Ischaemic stroke*

**Cardiac disorders**

*Common*                 Myocardial ischaemia*
QT prolongation*

*Uncommon*            Torsade de Pointes*
Cardiac Dysfunction (such as reduced ejection fraction and congestive heart failure)

                            Myocardial infarction*

**Vascular disorders**

*Very common*      Hypertension*

**Haemorrhages***

*Common*                 Epistaxis
Haematuria

*Uncommon*            Pulmonary haemorrhage
Gastrointestinal haemorrhage
Cerebral haemorrhage

**Gastrointestinal disorders**

*Very common*      Diarrhoea
Nausea
Vomiting
Abdominal pain

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| *Common* | Dyspepsia |
|---|---|
| *Uncommon* | Gastrointestinal perforation*<br>Gastrointestinal fistula* |

**Hepatobiliary disorders***

| *Very common* | Alanine aminotransferase increased<br>Aspartate aminotransferase increased |
|---|---|
| *Common* | Hepatic function abnormal<br>Hyperbilirubinaemia<br>Lipase elevations |

**Skin and subcutaneous tissue disorders**

| *Very common* | Hair depigmentation |
|---|---|
| *Common* | Rash<br>Alopecia<br>Skin depigmentation<br>Palmar-plantar erythrodysaesthesia syndrome |

**Renal and urinary disorders**

| *Common* | Proteinuria* |
|---|---|

**General disorders and administration site conditions**

| *Very common* | Fatigue<br>Asthenia |
|---|---|
| *Common:* | Chest pain* |

*See *Precautions* for additional information

Table 2 presents the incidence of very common (>10%) treatment-related adverse events for patients receiving VOTRIENT versus those on placebo.

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**Table 2.** **Treatment-related Adverse Events Reported for at least 10% of subjects who received VOTRIENT or Placebo**

| Adverse Event, n (%) | Number (% of subjects) | | | | | |
|---|---|---|---|---|---|---|
| | VOTRIENT (n = 290) | | | Placebo (n = 145) | | |
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| **Any** | 257 (89) | 74 (26) | 11 (4) | 56 (39) | 5 (3) | 1(1) |
| Diarrhoea | 128 (44) | 9 (3) | 2 (<1) | 9 (6) | 1 (1) | 0 |
| Hair colour changes | 107 (37) | 1 (<1) | 0 | 5 (3) | 0 | 0 |
| Hypertension | 106 (37) | 12 (4) | 0 | 13 (9) | 1 (1) | 0 |
| Nausea | 63 (22) | 2 (<1) | 0 | 8 (6) | 0 | 0 |
| Anorexia | 49 (17) | 4 (1) | 0 | 6 (4) | 0 | 0 |
| Vomiting | 48 (17) | 6 (2) | 1 (<1) | 5 (3) | 1 (1) | 0 |
| Fatigue | 46 (16) | 5 (2) | 0 | 2 (1) | 0 | 0 |
| ALT increased | 43 (15) | 15 (5) | 2 (<1) | 3 (2) | 0 | 0 |
| AST increase | 38 (13) | 9 (3) | 1 (<1) | 4 (3) | 0 | 0 |

Table 3 presents laboratory abnormalities occurring in ≥ 15 % of patients who received VOTRIENT.  Grades are based on the NCI CTCAE.

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**Table 3. Selected Laboratory Abnormalities in ≥ 15 % of Patients who Received VOTRIENT and More Commonly than Placebo Arm**

| Parameters | VOTRIENT (N = 290) | | | Placebo (N = 145) | | |
|---|---|---|---|---|---|---|
| | All Grades % | Grade 3 % | Grade 4 % | All Grades % | Grade 3 % | Grade 4 % |
| **Haematologic** | | | | | | |
| Leukopenia | 37 | 0 | 0 | 6 | 0 | 0 |
| Neutropenia | 34 | 1 | <1 | 6 | 0 | 0 |
| Thrombocytopenia | 32 | <1 | <1 | 5 | 0 | <1 |
| Lymphocytopenia | 31 | 4 | <1 | 24 | 1 | 0 |
| **Chemistry** | | | | | | |
| ALT increased | 53 | 10 | 2 | 22 | 1 | 0 |
| AST increased | 53 | 7 | <1 | 19 | <1 | 0 |
| Glucose increased | 41 | <1 | 0 | 33 | 1 | 0 |
| Total Bilirubin increased | 36 | 3 | <1 | 10 | 1 | <1 |
| Phosphorus decreased | 34 | 4 | 0 | 11 | 0 | 0 |
| Calcium decreased | 33 | 1 | 1 | 26 | 1 | <1 |
| Sodium decreased | 31 | 4 | 1 | 24 | 4 | 1 |
| Potassium increased | 27 | 4 | <1 | 23 | 5 | 0 |
| Creatinine increased | 26 | 0 | <1 | 25 | <1 | 0 |
| Magnesium decreased | 26 | <1 | 1 | 14 | 0 | 0 |
| Glucose decreased | 17 | 0 | <1 | 3 | 0 | 0 |

**Lipase Elevations:** In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%).


*Post marketing data*

No post-marketing data are currently available.


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## DOSAGE AND ADMINISTRATION

The recommended dose of VOTRIENT is 800 mg orally once daily.

VOTRIENT should be taken without food (at least one hour before or two hours after a meal) (*see Pharmacokinetics*).

VOTRIENT should be taken whole with water and must not be broken or crushed.

If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

*Dose Modifications*

Initial dose reduction should be from 800 mg to 400 mg daily. Subsequent dose modification, either an increase or decrease in dose, should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of VOTRIENT should not exceed 800 mg.

*CYP3A4 inhibitor*: The concomitant use of strong CYP3A4 inhibitors may increase VOTRIENT concentrations and should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If co-administration of a strong CYP3A4 inhibitor is warranted, a dose reduction to 400 mg of VOTRIENT is recommended based on pharmacokinetic studies. This dose is predicted to adjust the pazopanib AUC to the range observed without inhibitors (*see Interactions with other Medicines*). However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors.


### Populations

Children

The safety and efficacy of VOTRIENT in children have not been established.


Elderly

No alteration of dosage, dosing frequency or route of administration is required in patients over 65 years.


Renal Impairment

There is no experience of VOTRIENT in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis. Renal impairment is unlikely to have a

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clinically relevant effect on VOTRIENT pharmacokinetics given the low renal excretion of pazopanib and metabolites (*see Elimination*).

Hepatic Impairment

The safety and pharmacokinetics of VOTRIENT in patients with pre-existing hepatic impairment have not been fully established (*see Precautions*).  Pharmacokinetic data from patients with normal hepatic function (n = 12) and moderate (n = 7) hepatic impairment indicate that pazopanib clearance was decreased by approximately 50% in those with moderate hepatic impairment [total bilirubin > 1.5 to 3 x Upper Limit of Normal (ULN)].  The dose of VOTRIENT should be reduced to 200 mg per day in patients with moderate hepatic impairment).  There are no data in patients with severe hepatic impairment (total bilirubin > 3 x ULN regardless of any level of ALT); therefore, use of VOTRIENT is not recommended in these patients.  There are no data to support dosing recommendations in patients with mild hepatic impairment.

## OVERDOSAGE

VOTRIENT doses up to 2,000 mg have been evaluated in clinical trials.  Grade 3 fatigue (dose limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2,000 mg and 1,000 mg daily, respectively.

**Symptoms and Signs**

There is currently limited experience with overdosage in VOTRIENT.

**Treatment**

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.  Haemodialysis is not expected to enhance the elimination of VOTRIENT because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

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## PRESENTATION AND STORAGE CONDITIONS

The 200 mg tablets are modified capsule-shaped, pink, film-coated with 'GS JT' debossed on one side.

The 400 mg tablets are modified capsule-shaped, white, film-coated with 'GS UHL' debossed on one side.

### Shelf-Life
24 months.

### Storage
Store below 30°C.

### Nature and Contents of Container
VOTRIENT 200 mg film-coated tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 90 tablets*.

VOTRIENT 400 mg film-coated tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 60 tablets*.

* not all pack sizes may be marketed

## NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

## POISON SCHEDULE OF THE MEDICINE - S4

This document was approved by the Therapeutic Goods Administration on: 22 June 2010

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Version 1.0

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