CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-465

MEDICAL REVIEW(S)

Clinical Review

Application Type	NDA
Submission Number	22-465
Submission Code	None
Letter Date	Dec. 18, 2008
Stamp Date	Dec. 19, 2008
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Clinical Reviewer Name	Yangmin M. Ning M.D., Ph.D.
Clinical Reviewer Name	Ian Waxman M.D.
Clinical Team Leader	V. Ellen Maher, M.D.
Review Completion Date	Oct. 06, 2009
Established Name	Pazopanib
Proposed Trade Name	VOTRIENT®
Therapeutic Class	A Tyrosine Kinase Inhibitor
Applicant	GlaxoSmithKline Research Triangle Park, NC 27709
Priority Designation	Standard Review

Formulation:	Tablets of 200 mg or 400 mg for oral administration
Dosing Regimen:	The recommended pazopanib dosing schedule is 800 mg administered orally once daily without food.
Proposed Indication:	For the treatment of patients with advanced renal cell carcinoma (RCC)
Intended Population:	Adult patients with RCC

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Commonly Used Abbreviations in the Review

Abbreviation	Full Term
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AR	Adverse Reaction
CRF	Case Report Form
DRAR	Drug-Related Adverse Reaction
EKG	Electrocardiogram
LVEF	Left Ventricular Ejection Fraction
OS	Overall Survival
mTOR	Mammalian Target of Rapamycin
PFS	Progression-Free Survival
Pt	Patient
PK	Pharmacokinetics
RCC	Renal Cell Carcinoma
RR	Response Rate
TKI	Tyrosine Kinase Inhibitor
VEGF	Vascular Endothelial Growth Factor
VHL	Von Hippel–Lindau

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This new drug application (NDA 22-465) for pazopanib, submitted by GlaxoSmithKline on December 19th, 2008, seeks marketing approval of pazopanib tablets for the treatment of advanced renal cell carcinoma (RCC). Pazopanib is a new molecular entity, acting as a tyrosine kinase inhibitor.

The reviewers examined the submitted data and study reports and found that the application provided adequate efficacy and safety evidence to support the use of pazopanib in patients with advanced RCC. The reviewers concur with the applicant's conclusions about pazopanib in support of the proposed indication.

The reviewers recommend regular approval of pazopanib at the proposed dosing schedule for the treatment of patients with advanced RCC. This is based on the findings of a robust improvement in progression-free survival (PFS) with pazopanib in a placebo-controlled study and of an acceptable safety profile for pazopanib as demonstrated in the submitted clinical studies of the product.

1.2 Risk Benefit Analysis

The safety and efficacy of pazopanib were evaluated in a randomized, double-blind, placebo-controlled multi-center study of pazopanib compared to placebo in patients with locally advanced and/or metastatic renal cell carcinoma who had received either one or no prior systemic cytokine (IL-2 or INFα) based therapy. The study required clear cell or predominantly clear cell RCC histology. A total of 435 patients were randomized 2:1 to receive either pazopanib 800 mg once daily (N=290) or placebo (N=145). Treatment continued until patients experienced disease progression, death, or unacceptable toxicity. Radiographic assessment of efficacy was performed every 6 weeks and then every 8 weeks after the first 24 weeks.

Of the patients randomized, 53% of patients had received no prior systemic therapy while 47% of patients had received one prior systemic cytokine therapy. The baseline demographic and disease characteristics were well balanced between the two arms. The median duration of exposure to pazopanib was 7.4 months (0.3-23.1) as compared to the median duration of exposure to placebo, 3.8 months (0.3-22.0).

The primary analysis of the study was to compare PFS between the two treatment arms. PFS was defined as the time from randomization to the time of documentation of disease progression or death due to any cause. The primary analysis results, based on efficacy assessments by independent review and conducted in the intent-to-treat (ITT) population, showed a 5.0-month improvement in median PFS with pazopanib. The Kaplan-Meier estimated median PFS was 9.2 months in patients treated with pazopanib as compared to a median PFS of 4.2 months in patients receiving placebo (HR 0.46, $p<0.0000001$). The PFS results remained consistent in subgroup analyses. Sensitivity analyses of the primary endpoint favored the pazopanib arm.

The key secondary endpoints included a comparison of overall survival between the two arms and an estimation of the overall response rate with pazopanib. An interim OS analysis, conducted as planned at the time of the final PFS analysis, suggested a trend in favor of pazopanib. However, there was no statistically significant difference in OS between the arms. The hazard ratio for overall survival was 0.73 (95% CI: 0.53 to 1.00) with a one-sided p-value of 0.02, which did not reach the level, < 0.004, required to demonstrate statistical significance in the interim analysis of OS. The observed overall response rate in the pazopanib arm was 30%, with a median duration of 13.5 months.

The safety analyses showed that adverse reactions, including laboratory abnormalities, were observed more frequently in the pazopanib arm than in the placebo arm. The most commonly observed adverse reactions with a frequency of ≥20% in the pazopanib arm included diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting. Grade 3 or 4 diarrhea and hypertension were observed in approximately 5% of the patients. The important common laboratory abnormalities included elevations in ALT/AST and bilirubin, hypophosphatemia and hypomagnesemia. However, the most important laboratory difference between the two arms was the occurrence of Grade 3/4 ALT elevations, 12% in the pazopanib arm compared to <1% in the placebo arm. This represents the most common pazopanib-associated Grade 3-4 adverse reaction. The majority of the Grade 3-4 ALT elevations were reversible with appropriate dosing modifications. However, severe hepatotoxicity associated with deaths has occurred.

Pazopanib is also linked to important adverse reactions common to other anti-VEGF or anti-VEGF receptor products. The incidence of these important adverse events, including hemorrhage, arterial thrombosis (myocardial or cerebrovascular events), visceral fistula/perforation, and torsarde, was higher in the pazopanib arm when compared to placebo. Some of these events were fatal. QT prolongation (>500 msec) occurred in approximately 1% of patients receiving pazopanib, but

in none of the patients receiving placebo. Similar results were observed in the pooled safety analysis of the three RCC studies.

The hepatic safety of pazopanib was further examined in the pazopanib monotherapy population (approximately 1000 patients). This population included patients with renal cell cancer in addition to patients with a variety of tumor types who had received pazopanib monotherapy. Four Hy's Law cases were identified in this population. These patients had evidence of altered hepatic function, possibly secondary to pazopanib. Two deaths (one of the four Hy's Law cases) associated with hepatic failure may have been related to pazopanib. In addition, one hepatic death that also met the criteria for Hy's Law was identified in a combination study and was considered probably related to pazopanib by the applicant and the reviewers. The causal relationship of this death to pazopanib was supported by autopsy evidence showing extensive hepatocellular necrosis consistent with drug-induced liver injury. All these findings demonstrated that pazopanib can cause severe and fatal hepatotoxicity on the background of marked elevations in ALT.

The estimated rate of death due to the above life-threatening adverse events associated with or possibly related to pazopanib was approximately 2.2% in the three RCC studies of pazopanib. Given that life-threatening and fatal adverse events have been tolerated in oncologic products and that these events are uncommon, the observed incidence of serious toxicities associated with or related to pazopanib appears to be acceptable for the treatment of advanced RCC.

Overall, the efficacy and safety results demonstrated in this NDA submission suggest that pazopanib has a favorable benefit-to-risk profile in the intended patient population. Nevertheless, the risk of developing fatal adverse reactions with the use of the product should not be ignored because of this assessment, but rather be well communicated to patients and health providers who should exercise caution in order to avoid or alleviate the risk.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

Given the life-threatening adverse events or reactions observed with pazopanib in the premarketing clinical studies, the reviewers had the following recommendations that may mitigate the risks associated with the use of this product in routine practice. Note that the applicant has already specified all the important risks as warnings and precautions in the proposed product label for pazopanib.

- Insert a back box warning in the label to describe the risk of severe and fatal hepatic toxicity with pazopanib in order to alert both health care providers and patients.

- Implement a Medication Guide to convey the risks of life-threatening adverse reactions to patients who plan to take or are taking pazopanib for the treatment of advanced RCC. The applicant's proposed Medication Guide is being evaluated for its acceptability.

- Perform post-marketing pharmacovigilance monitoring of hepatotoxicity, especially the occurrence of severe and fatal hepatotoxicity. One post-marketing requirement as described below will be to conduct a study to further evaluate the risk associated with pazopanib re-challenge in patients who have developed hepatotoxicity.

1.4 Recommendations on Post Marketing Requirements/Phase 4 Commitments

- To complete and submit the final study report and datasets for the ongoing trial entitled "VEG108844: A Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma". The specified dates for this requirement are as follows.

  Original Protocol Submission: 05/2008
  Expected Trial Completion Date: 12/2010
  Final Study Report and Dataset Submission: 05/2011

  Study VEG108844 plans to randomize 876 patients 1:1 to receive pazopanib or sunitinib at their proposed or approved marketing dose. The primary endpoint is PFS, and the key secondary endpoints include overall survival and safety. The estimated number of patients in each arm, approximately 440, will be similar to or greater than the number enrolled in their pivotal studies supporting their registration approval. Thus, it is expected that the results of Study VEG108844 will provide adequate efficacy and safety information between the two drugs that may be valuable for both patients and oncologists to make a sound treatment decision. Most importantly, the study assesses changes in left ventricular ejection fraction with both pazopanib and sunitinib. A previous study assessed ejection fraction in patients on pazopanib. However, the median duration of exposure to pazopanib in this study was much shorter than that expected in patients with renal cell cancer. Dates for submission of a protocol, trial completion,

submission of the clinical study report, associated datasets, and any changes in product labeling, if needed, are pending.

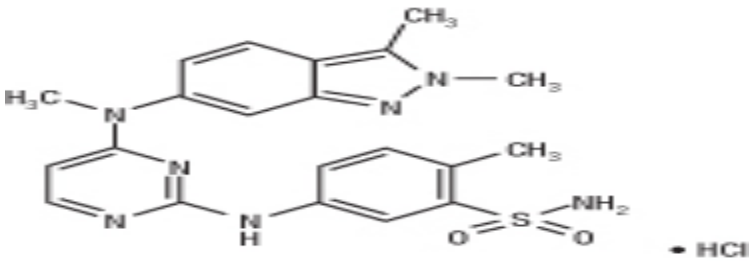
- Conduct a study of at least 1500 patients to assess the safety of the current dose modification plan for pazopanib and the safety of re-challenge with pazopanib following hepatotoxicity. Patients from ongoing studies with pazopanib may be included in this study. Dates for submission of a protocol, trial completion, submission of the clinical study report, associated datasets, and any changes in product labeling, if needed, are pending.

- Submit the final analysis of OS from "VEG105192: A Randomized, Double-Blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

2 Introduction and Regulatory Background

2.1 Product Information

VOTRIENT (pazopanib) is a new tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and-β, and c-kit tyrosine kinases. It is presented as the hydrochloride salt, with the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. Its molecular formula is $C_{21}H_{23}N_7O_2S$•HCl, with a molecular weight of 473.99 daltons and a structural formula as below:



For this NDA, pazopanib will be administered orally at a starting does of 800 mg once daily. To achieve the proposed dose, 400 mg and 200 mg pazopanib tablets are available. Each 200 mg tablet contains 216.7 mg of pazopanib hydrochloride

equivalent to 200 mg pazopanib, and each 400 mg tablet contains 433.4 mg of pazopanib hydrochloride equivalent to 400 mg pazopanib.

The inactive ingredients in the pazopanib tablets include magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate in the core, coated with gray film-coat (200 mg tablet): Hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80, titanium dioxide. Yellow film-coat (400 mg tablet): Hypromellose, iron oxide yellow, macrogol/PEG 400, polysorbate 80, titanium dioxide.

2.2 Tables of Currently Available Treatments for Proposed Indication

Since 2005, five targeted products have received FDA approval for the treatment of advanced RCC. Table 1 summarizes these products with their demonstrated efficacy in the key studies supporting their approval.

Table 1: FDA-Approved Targeted Therapy for Treatment of Renal Cell Carcinoma

Product Name* Approval	Trial Type/ Patient Population	Primary Endpoint	Key Findings
Sorafenib December 2005 Regular Approval	Randomized, double-blind comparison to placebo in patients with advanced RCC after one systemic therapy	PFS	HR: 0.44 (0.35-0.55) Median PFS 167 days vs. 84 days with placebo
Sunitinib January 2006 Accelerated Approval	Two single arm Phase 2 studies in patients with cytokine-refractory RCC	RR	34.0%; 36.5%
February 2007 Regular Approval	Randomized, double-blind comparison to IFNα in patients with treatment-naive advanced RCC	PFS	HR: 0.42 (0.32-0.54) Median PFS 47 weeks vs. 22 weeks with IFNα
Temsirolimus May 2007 Regular Approval	Randomized, open-label comparison to IFNα, in treatment-naive patients with advanced RCC with ≥3 of the 6 negative prognostic risk factors	OS	HR: 0.73 (0.58-0.92) Median OS 10.9 months vs. 7.3 months with IFNα

Everolimus March 2009 Regular Approval	Randomized, double-blind comparison to placebo in patients with RCC whose disease progressed after treatment with sorafenib, sunitinib, or both	PFS	HR: 0.33 (0.25-0.43) Median PFS 4.9 months vs. 1.9 months with placebo
Bevacizumab July 2009 Regular Approval	Randomized, double-blind comparison of bevacizumab + IFNα to IFNα alone in patients with RCC post-nephrectomy	PFS	HR: 0.60 (0.49-0.72) Median PFS 10.2 months vs. 5.4 months with IFNα alone
*All the products received regular approval except for sunitinib, which received accelerated approval in December 2006, followed by the conversion to regular approval in February 2007. PFS: Progression-free survival; RR: Response rate; OS: Overall survival			

2.3 Availability of Proposed Active Ingredient in the United States

Not commercially available at the time of evaluation of this NDA.

2.4 Important Safety Issues With Consideration to Related Drugs

Several life-threatening adverse reactions related to the use of anti-VEGF products have been recognized since the initial approval of bevacizumab in 2003. These adverse reactions include hypertension, hemorrhage, arterial and venous thrombosis, gastrointestinal perforation, impaired wound healing, and proteinuria. These reactions can occur with either a humanized anti-VEGF antibody such as bevacizumab or an inhibitor of VEGF receptor-related tyrosine kinase (TKI) such as sunitinib or sorafenib. This suggests that inhibition of the function of the VEGF signaling pathway may be important for the development of these toxicities. However, differences in toxicity do exist in these products, especially between the two small molecule anti-VEGFR tyrosine kinase inhibitors (TKI). For example, both sunitinib and sorafenib are associated with thyroid dysfunction; however, sunitinib is also associated with decreases in LVEF, prolonged QT intervals and torsade de pointes. These dissimilarities may stem in part from differences between the two drugs in target selectivity or sensitivity, off-target effects, or pharmacokinetics. These observed differences also suggest that anti-VEGF products can differ from each other in toxicity profile despite the common toxicities mentioned above. As such, pazopanib may have a toxicity profile different from sunitinib or sorafenib despite their similar mechanisms of action.

Hepatotoxicity represents a newly recognized toxicity of TKIs. Recent literature reports have revealed cases of sorafenib- or sunitinib-associated hepatic failure and deaths after 3-4 years of marketing.[9-12] This may be suggestive of a class

effect of the anti-VEGF tyrosine kinase inhibitors. Because of the voluntary nature of the reports, it is impossible to estimate the frequency and to reliably establish a causal relationship. However, in their premarketing submissions, no hepatic safety signal was revealed in the reviews of both drugs. [13] Two cases of hepatic failure associated death were described in the review of the patients with GIST treated with sunitinib. The reviewer concluded that there was equivocal evidence of sunitinib induced hepatotoxicity in these two patients. Both patients had liver metastases documented at baseline and a minimal increase in hepatic function tests. Overall, neither sunitinib nor sorafenib disclosed a significant hepatic safety signal in their pre-marketing evaluations. In contrast, pazopanib, as discussed in the safety review of this NDA, has shown ample pre-marketing evidence of hepatotoxicity. This may predict a significant risk of severe hepatotoxicity in a larger post-marketing population. The difference in the incidence of hepatotoxicity in their premarketing settings again highlights the importance of recognizing different toxicity profiles in these products. Therefore, it is essential to label pazopanib for this toxicity to assure optimal use by patients and health care providers.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The pre-submission regulatory activities with the FDA are summarized in Table 2.

Table 2: Regulatory Activities during Pazopanib's Clinical Development for RCC

Milestone	Date	Comments related to clinical perspectives
IND 65747 Submission	September 2002	The product initially used the name GW786034
End-of Phase 1 Meeting	July 2005	Proposed development in patients with advanced RCC using a placebo control in a randomized Phase 3 study. The overall development strategy was based on a study population whose disease has progressed following cytokine-based therapy. Regarding the proposed use of placebo, the Agency responded: "If other drugs are approved and marketed to this population of patients at the time you start your study, a placebo controlled trial may be unethical and you may not be able to accrue patients." Regarding the proposed primary endpoint for demonstration of efficacy, the Agency also stated, "The acceptability of PFS as an endpoint for

		approval depends on the magnitude of the difference, risk benefit ratio and whether any drugs are approved based on survival." The applicant decided to address the concerns through a request for SPA. The proposed randomized discontinuation Phase 2 study was also discussed as supportive of the Phase 3 study.
Special Protocol Assessment	September 2005 through March 2006	No agreement was reached for the proposed Phase 3 study (VEG105192). The applicant later submitted a complete response to initial disapproval, but no agreement letter was issued in response to the revised protocol. A Type A meeting was held on March 10, 2006 to discuss the applicant's proposal to enroll a treatment-naïve patient population outside of the U.S. where recently approved drugs were not available. The Agency stated, "Control patients with no prior therapy should receive either sorafenib, sunitinib, or a cytokine. The use of placebo in a second line patient population will be problematic unless patients have received one of these drugs." The applicant also provided a plan to unblind study treatment at the time of disease progression and to permit patients who are on placebo to receive pazopanib as a treatment option. The agency discouraged the proposal since it may obscure any survival comparison and other therapies may be more appropriate (e.g., sunitinib or sorafenib) to give at the time of progression. No agreement letter was issued on this protocol amendment.
End-of Phase 2 Meeting	July 2007	Overview of the RCC program
Pre-NDA Meeting	June 2008	The applicant specified that three studies, one pivotal study VEG105192 and two supportive studies VEG102616 and VEG107769 were to be submitted for the proposed indication, the use of pazopanib for the treatment of patients with advanced RCC. The applicant's concerns about the submission were addressed.
NDA-submission	December	Regular review designation

	2008	

2.6 Other Relevant Background Information

The approved targeted therapies for RCC belong to two pharmacological classes, anti-VEGF products, including sorafenib, sunitinib, and bevacizumab, and anti-mTOR products, including temsirolimus and everolimus. The effectiveness of the anti-VEGF products in the treatment of RCC (mainly clear cell type) is related to their antagonism of VEGF mediated angiogenesis. Increased VEGF function is a recognized key pathogenetic mechanism in the disease and is derived from the inactivation of the tumor suppressor VHL function either due to mutations of the *VHL* gene itself or to hypermethylation of its promoter region.[1] This is different from the mechanism by which immunomodulatory therapies such as IL-2 or IFNα exert their treatment effect in the disease. Therefore, anti-VEGF based products, including those currently under development, [2, 3] are generally active in patients who are cytokine treatment naive as well as in patients whose disease has progressed following prior immunotherapy. This is implicated by the broad indication statement in the current labels of the three approved anti-VEGF products, "for the treatment of advanced or metastatic RCC". In contrast, the mTOR inhibitor temsirolimus is indicated for the treatment of advanced RCC, whereas everolimus is indicated for advanced RCC after failure of treatment with sunitinib or sorafenib. The effectiveness of an mTOR inhibitor after an anti-VEGF inhibitor reflects the relatively independent mechanisms between the two signal pathways in the disease. Recent evidence also suggests incomplete cross-resistance exists between anti-VEGF products; [2] however, whether the incomplete cross-resistance is clinically beneficial has not been studied in phase 3 trials.

The other important issue is selection of a primary endpoint appropriate for the evaluation of treatment effect or efficacy in RCC. Table 1 shows that the primary endpoints used in the approval of the 5 targeted therapies included PFS and OS. Temsirolimus is the only product for which approval was based on an improvement in OS. All of the others (including everolimus which was approved after temsirolimus) were approved based on a 3-5 month improvement in median PFS. It is important to recognize that there was no effective therapy for renal cell cancer, other than immunotherapy, before the first targeted therapy, sorafenib, was approved on the basis of an improvement in PFS. However, it is essential to realize that PFS has not been well validated as a surrogate for demonstrating clinical benefit of a treatment in the disease.[4] An updated report on the sunitinib study (shown in Table 1) that supported the regular approval of sunitinib based on PFS showed a borderline improvement in OS with sunitinib as compared to IFNα. [5] The correlation between PFS and OS in this case may help establish PFS as a surrogate in the advanced RCC setting. On the other hand, neither sorafenib nor bevacizumab (combined with IFNα) have attained a statistically significant

improvement in OS despite the reported trend in favor of sorafenib or bevacizumab in these analyses. [6-8] These differences in the correlation of PFS with OS or in the improvement in OS *vs.* PFS may relate to variations in study patient population, drug potency and toxicity, and the availability or use of post-study treatments. The heterogeneity of RCC may contribute as well. Most patients enrolled in the sunitinib study had RCC with intermediate prognostic features and, in an exploratory analysis, there appeared to be a survival benefit in those patients. Conversely, patients with either poor or favorable prognostic factors have not shown a survival benefit with sunitinib in the exploratory analyses. [5] Yet with temsirolimus, a survival benefit was demonstrated only in patients with poor prognostic factors. It remains unclear if the survival benefit of temsirolimus can be seen in patients with intermediate or favorable prognostic features. Given the above observations and reasoning, it is important to evaluate PFS and OS in the context of the study patient population, magnitude of improvement, availability of prior effective therapies and/or use of effective therapies after study product. At present, PFS remains a useful surrogate in RCC only if it is reliably assessed in a well-designed, well-conducted study and the magnitude of improvement in median PFS is clinically meaningful.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality and integrity of the submitted data for the proposed indication are found adequate and acceptable. However, numerous issues were identified during the review such as:

- incomplete submission of CRFs in the pivotal study supporting the proposed indication;
- incomplete submission of datasets in non-RCC pazopanib monotherapy studies;
- incomplete information on protocol violations and deviations in the submitted datasets;
- discrepancies in adverse reactions between the datasets and narratives in patients who had SAEs;
- misclassifications of the cause of death such as a death due to a fatal SAE categorized as death due to disease progression; and
- no mention of a SAE in association with a death categorized under disease progression.

All these problems were conveyed to applicant and have been addressed satisfactorily. Details of the correspondences can be found in \\CDSESUB1\EVSPROD\NDA022465\. These problems might affect the safety analyses of the application (see Section 7.1 for reviewers' evaluation and handling

of these issues to ensure the reliability of the safety analyses), but would be unlikely to change the overall efficacy results of the application.

3.2 Compliance with Good Clinical Practices

Since no patients were accrued from the United States, two foreign study sites, as listed in Table 3, were selected for inspection by the Division of Scientific Investigation (DSI) for the pivotal study. The selection of the two sites was based on the analyses of the submitted datasets and study report. The largest enrollment (25%) was from Poland. The selected Polish center had the largest enrollment (6.2%) in the study. It also had high incidences of hepatic dysfunction (6 of the 19 patients assigned to the pazopanib arm had Grade 2, 3, or 4 abnormalities in transaminase). The center in South Korea had a higher response rate (50% in 10 patients that received pazopanib), but a lower estimated HR than the overall population treated with pazopanib. In addition, 3 of the 10 patients in this center had Grade 2 or 3 abnormalities in transaminases. Later, a third center (#33951) in Poland was added based on a recommendation from the DSI. This center (an oncologic center) is in the same city where the other Center (#34145) is located.

Table 3: Sites for DSI Inspection

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Center # 34145: KORALEWSKI, Piotr NZOZ VESALIUS Practice ul. Smolensk 25a m 2, 31-108 Cracow, Poland	VEG105192	**19 patients received pazopanib, 8 patients received placebo**	treatment of patients with advanced renal cell carcinoma
Center # 24756: LEE, Eun-Sik Seoul National University Hospital, 28 Yongon-Dong, Chongno-Ku, Seoul 110744, Korea	VEG105192	**10 patients received pazopanib, 1 patient received placebo**	treatment of patients with advanced renal cell carcinoma
Center # 33951: ROLSKI, Janusz Onkology Centre, Institute by name Maria Sklodowska - Curie, Cracow Department, ul. Garnakarska 11, 31 115, Kracow, Poland	VEG105192	**8 patients received pazopanib, 9 patients received placebo**	treatment of patients with advanced renal cell carcinoma

DSI has completed all planned inspections. Based on the Form FDA 483 and communications with the field investigator and/or participation in the inspection, an inspection summary has been issued. Based on the summary, the two sites in Poland had no regulatory violations. However, the site in South Korea had regulatory violations. These violations, as described in a Form 483, included no source documentation whether study patients received a copy of the signed informed consent document, missing ECOG evaluation in one patient, missing death documentation in three patients, missing CRF reportable entries such as concomitant medications over several months in one patient. The overall DSI assessment was that these violations in the Korean site are unlikely to impact data integrity and that the data from the three sites are acceptable in support of the pending application.

No inspection of the applicant was requested for this NDA.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators who conducted the clinical studies supporting this NDA was submitted in the FDA form 3454. The disclosure was certified by David M. Cocchetto, Ph.D., Vice President, US Regulatory Affairs for the applicant. No investigators in the key study supporting this NDA were found to have financial conflict of interest, either a proprietary interest or significant payments from or equity interest in the applicant.

The independent review of the efficacy assessments in the key study would minimize the potential effects of financial conflicts, if any, on the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewers identified some weakness in the application and were particularly concerned about the lack of data pertaining to the source of the batch-to-batch dissolution variability. The applicant has agreed to an acceptably tight dissolution specification on release (b) (4) . For details, please see the chemistry review.

The CMC reviewers considered that the application is currently approvable pending resolution of an Acceptable Recommendation from the Office of Compliance.

4.2 Product Risk Management Plan (Review of Medication Guide)

The applicant's proposed Medication Guide (MG) was evaluated by reviewers from the Division of Risk Management (DRISK). The DRISK reviewers ensured that the MG is consistent with the product label, removed unnecessary or redundant information, highlighted the major risks associated with the product, ensured that the MG meets the Regulations as specified in 21 CFR 208.20, and ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

For details, please see the DRISK review.

4.3 Preclinical Pharmacology/Toxicology

No significant issues related to pazopanib's clinical safety were identified in the toxicology review. The toxicology review did not reveal a marked hepatic safety signal in the animal studies.

4.4 Clinical Pharmacology

The clinical pharmacology reviewers considered the information contained in this NDA acceptable from a clinical pharmacology perspective. However, the reviewers were concerned that there was insufficient information on drug-drug interaction between pazopanib and a strong CYP3A4 inhibitor (e.g., ketoconazole) and a further drug-drug interaction study was recommended. The reviewers were also concerned about the appropriateness of the proposed dose modifications based on the PK parameters obtained from the chronic dosing studies. (b) (4); however, this does not achieve a meaningful reduction in exposure in the PK parameters. As such, the pharmacology team recommended that the initial dose reduction should be by 400 mg and that subsequent dose reductions should be in 100 mg decrements. The clinical reviewer agreed to the recommendations. However, subsequent dose reductions at present should continue to be in 200 mg decrements since there is no 100 mg tablet formulation available. Therefore, it is important for the applicant to make a 100 mg formulation commercially available in the near future. We note that a 100 mg tablet formulation has been used in a study of pazopanib in patients with impaired hepatic function (NCI8063).

An interim report on study NCI8063 showed that the MTD of pazopanib in patients with moderate hepatic impairment (defined as total bilirubin 1.5-3.0 x ULN regardless of the level of transaminases) was 200 mg once daily. This study also showed that 2 of the 4 evaluable patients with moderate hepatic impairment who received pazopanib 400 mg once daily developed severe hepatic laboratory abnormalities, Grade 3 ALT/Grade 4 AST in one patient, and Grade 4 ALT/Grade 4 AST/Grade 3 hyperbilirubinemia in the other patient. This suggested an increased sensitivity to pazopanib in patients with hepatic impairment at 50% the

recommended dose of pazopanib (800 mg once daily). These observations suggested that the MTD had been exceeded at the 400 mg dose level. Since no DLTs were observed in the 200 mg cohort, it was concluded that the MTD in the moderate hepatic impairment cohort was 200 mg once daily. The pharmacology reviewers agreed with this conclusion and it has been added to pazopanib's label.

Key clinical pharmacology information on the product is summarized as follows.

4.4.1 Mechanism of Action

Pazopanib is a small molecule multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), transmembrane glycoprotein receptor tyrosine kinase (c-Fms), and mitogen-activated protein kinase (P38). *In vivo* animal studies show that pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice.

4.4.2 Pharmacokinetics

Absorption: Following oral administration of pazopanib, the median time to achieve peak serum concentrations is 2.0 to 4.0 hours. Daily dosing at 800 mg results in a geometric mean AUC and C_{max} of 1037 hr*μg/mL and 58.1 μg/mL (equivalent to132 μM/L), respectively. There was no consistent increase in AUC or C_{max} at pazopanib doses above 800 mg.

Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with a high-fat or low-fat meal resulted 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.

Distribution: Binding of pazopanib to human plasma protein in vivo was greater than 99% and was not concentration dependent over the range of 10 to 100 μg/mL.

Metabolism: In vitro studies demonstrated that pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8.

In vitro studies suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP). Other *in vitro* studies show that pazopanib is a potent inhibitor of UGT1A1 enzymatic activity with an IC_{50} of 1.2 μM. This may be relevant to the low grade increases in serum total bilirubin levels seen with pazopanib.

Excretion: Pazopanib has a mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via feces with renal elimination accounting for <4% of the administered dose.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The three clinical studies that support the proposed indication for the treatment of advanced RCC are listed in Table 4. In addition, Table 5 lists studies that used pazopanib monotherapy in non-RCC malignancies or during early development. These studies are included in the evaluation of hepatotoxicity in this review. Studies that are ongoing or combine pazopanib with other antitumor products are not included in this review unless specific safety signals were revealed that can help us understand the safety profile of pazopanib as a single agent. One ongoing Phase 3 study compares pazopanib with sunitinib in patients with advanced RCC. This is listed in Table 6 for information only, since no data are available for review at the time of this NDA submission. In the future, this study may provide important efficacy and safe information between the two drugs.

Table 4: Clinical Studies in Support of Pazopanib for the Treatment of RCC

Study Number	Study Design	Primary Endpoint	Dose Group	Status at Submission
VEG105192 (Key Study)	Randomized, double-blind, placebo-controlled, Phase 3 (N=435)	Progression-free survival	Pazopanib 800 mg vs. Placebo, once daily	Complete (120–day safety update submitted; follow-up for survival)
VEG102616 (Supportive)	Double-blind, placebo-controlled, randomized discontinuation design (Revised to single arm after the initial phase) (N=225)	Response Rate	Pazopanib 800 mg vs. Placebo (Revised from a discontinuation design to single arm pazopanib 800 mg after the first 60 patients)	Primary analysis complete (follow-up for safety)
VEG107769 (Supportive)	A cross-over single-arm study of patients (placebo) previously enrolled in VEG105192 (N=71)	Safety Evaluation	Pazopanib 800 mg	Primary analysis complete (study ongoing)

Table 5: Clinical Studies in non-RCC Malignancies that Used Pazopanib Monotherapy

Phase	Study ID (time)	Study Population	Key Study Objectives	Key Design Elements	Major Findings
Phase 1	VEG10003 (12/2002-09/2006)	Patients with solid tumors refractory to standard therapy, or for whom no standard therapy exists (N=63)	Dose finding; Safety and tolerability; PK/PD analyses	Open-label, dose-escalation (50-2000 mg at three different schedules, qd, bid, or three times weekly) in 16 cohorts	The MTD was not determined in this study. However, a dose of 800 mg once daily was selected for evaluation in Phase 2 studies based on a manageable safety profile and the PK data. Safety signals: Hypertension and GI symptoms. No Grade 3 ALT observed.
	VEG10004 (07/07-07/08)	Patients with solid tumor malignancies (N=10)	PK and metabolites of pazopanib with a single [14C] labeled dose of pazopanib	Open label, with a single dose of [14C] labeled pazopanib at 400 mg on day 1 followed by daily pazopanib at 800 mg starting on Day 8 for up to 7 weeks.	Fecal excretion was the predominant route of elimination. Less than 4% of the orally administered dose was excreted in the urine. Incomplete oral absorption with observed absolute bioavailability of 14%, 21% and 39% in patients with evaluable data
	VEG10005 (09/06-08/07)	Patients with cancer (N=35)	Evaluation of the effect of a low- or high-fat meal on the PK of pazopanib	Open-label randomized study: Part 1 Randomized food effect: 1 dose of 800 mg fasting, and 1 dose of 800 mg with a high-fat meal or 800 mg low-fat meal; Part 2 Pazopanib 800 mg PO, once daily (continued through week 12 if stable disease achieved)	Administration of pazopanib 800 mg with food increased AUC; 2.3-fold with a high-fat meal and 1.9-fold with a low-fat meal. Cmax was also increased approximately 2-fold with food. The half-life was not influenced by food. Safety signals: hypertension and bleeding
	VEG10007 (07/06-02/08)	Patients with solid tumors (N=24)	Drug interaction profiling: Cytochrome P450	Open-labeled, multi-drug probe interaction study. The probes used included	(see details in the clinical pharmacology review)

Phase	Study ID (time)	Study Population	Key Study Objectives	Key Design Elements	Major Findings
			enzyme probes, PK	midazolam, flumazenil, caffeine, omeprazole, dextromethorphan, warfarin, vitamin K (cocktail= CKT). Pazopanib (800 mg) continued through week 12 if stable disease achieved.	Safety signals: hypertension and hepatobiliary events
Phase 2	VEG104450 (03/06-04/08)	Patients with ovarian cancer (N=36)	Activity of pazopanib in ovarian cancer	Open-label, single arm; dosing pazopanib at 800 mg once daily.	Overall response rate was about 18-21%. Safety signals: common adverse reactions (≥25%): diarrhea, fatigue, nausea, abdominal pain, hypertension, elevated ALT/AST. The most common AEs leading to pazopanib discontinuation were ALT/AST elevations.
	VEG105281 (11/06-ongoing)	Patients with advanced cervical cancer (N=74 in the pazopanib monotherapy group, 77 each in the lapatinib monotherapy group or in the combination group)	Activity and safety of pazopanib as monotherapy or in combination with lapatinib	Randomized, open-label, three arms; once daily dose of pazopanib (800 mg) , lapatinib (1500 mg), or pazopanib with lapatinib (note that the combination arm was terminated because it crossed a futility boundary at the interim analysis Of the 74 patients treated with pazopanib, 70 stopped the treatment as of July 2008.	No efficacy reported. Safety signals: Preliminary results were similar to those observed in VEG104450. However, an imbalance in toxicity was observed in the combination group compared to the monotherapy groups, with a few patients having fatal SAEs. Changes in LVEF were monitored in the study and the interim data will be analyzed in the safety review.
	VEG20002 (11/05-ongoing)	Patients with advanced and/or	Activity and safety of pazopanib in	Open-label, single arm with pazopanib at 800	Overall response rate was 7% (PR only). The most common

Phase	Study ID (time)	Study Population	Key Study Objectives	Key Design Elements	Major Findings
		metastatic soft tissue sarcoma (N=142)	the study disease	mg once daily.	AEs included fatigue nausea, diarrhea, hypertension, anorexia, hypopigmentation, vomiting and weight loss; 16% of patients had ALT elevations of Grade 2 or greater. Fatal SAEs related to pazopanib included one case of intestinal perforation and one case of DIC.
	VEG20006 (01/05-12/05)	Patients with recurrent or refractory Multiple Myeloma (N=21)	Activity and safety of pazopanib in multiple myeloma	Open-label, single arm study of pazopanib at 800 mg once daily.	Study terminated early due to lack of clinical efficacy. The safety results showed the following common adverse reactions: fatigue, nausea, diarrhea, muscle spasms, hypertension, and arthralgia. Hepatotoxicity was observed as well.
All the above listed studies are irrelevant to the efficacy claim for pazopanib in the current application (see *5.3*). Their hepatic safety data were screened to identify Hy's Law cases in the pazopanib monotherapy population					

Table 6: Clinical Study of Pazopanib in Comparison of Sunitinib in Patients with Advanced RCC

Phase	Study ID (time)	Study Population	Key Objectives	Key Design Elements	Major Findings
Phase 3	VEG108844 (ongoing)	Patients with locally advanced and/or metastatic renal cell carcinoma (N=876 planned)	Efficacy and safety of pazopanib compared to sunitinib	Randomized, open-label, active-controlled study of pazopanib 800 mg once daily dosed continuously or sunitinib 50 mg PO once daily in 6-week cycles of dosing - 4 weeks of treatment, followed by 2 weeks without treatment.	N/A

5.2 Review Strategy

The reviewers examined the submitted data by comparing information in various relevant datasets, assessing accuracy and consistency of the information contained in the datasets against information described in case narratives and/or case report forms, investigating causality of life-threatening adverse reactions (whenever indicated) with information across all relevant datasets, and conducting independent analyses of efficacy and safety. Identified discrepancies or issues during the review were conveyed to the applicant for further clarification or correction. Newly submitted information or data during the review were also checked against that originally submitted, if applicable, to determine their consistency and reliability. In addition, the reviewers evaluated consistency in efficacy and safety results of the three clinical studies in RCC. Special attention was paid to evaluation of the hepatotoxicity of pazopanib in both the RCC patient population and the pazopanib monotherapy population.

5.3 Discussion of Individual Studies

Three studies, as listed in Table 4, support the efficacy and safety claims of pazopanib for the treatment of patients with advanced RCC. Their major features are as summarized in the table. The key study is VEG105192 because it was a randomized, placebo-controlled trial in which the primary endpoint, progression-free survival, was assessed by independent review. Thus, review of this study, as shown in Sections 6 and 7, constitutes the basis for regulatory decision making. The other two studies VEG102616 and VEG107769 were single-arm Phase 2 trials, with response rate and safety as their primary endpoint, respectively. Their results are supportive in this NDA. The demonstrated response rates in either of the studies were similar to those observed in the key study. In addition, adverse reactions reported from the two studies were pooled with those from the key study for the safety overview analyses.

The 4 Phase 1 studies as listed in Table 5 provided information on the general tolerability, PK and pharmacodynamic (PD) parameters of pazopanib. Their results helped establish or supported the pazopanib dosing schedule used in the RCC studies, which is 800 mg once daily administered orally. For details of the PK and PD information, please see the clinical pharmacology review of this NDA.

The 4 Phase 2 studies listed in Table 5 are not relevant to the proposed indication in this NDA. However, these studies increase the number of study patients using pazopanib monotherapy and are therefore helpful in evaluation of toxicities such as hepatotoxicity, which, as summarized in the last column of the table, was also observed in these non-RCC studies.

6 Review of Efficacy

6.1 Indication

The proposed product label in the NDA submission for pazopanib had the following statement: VOTRIENT is a tyrosine kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma. (b) (4)

Reviewer's Comments: *The proposed indication is similar to the five other approved products for the disease. However, everolimus is indicated in patients who have received prior sunitinib or sorafenib. Since pazopanib's anti-RCC mechanism of action is similar to sunitinib, sorafenib, and bevacizumab, use of pazopanib or other anti-VEGF pathway products after failure of treatment with any one of them has not been established to be clinically beneficial. Therefore, it is not recommended to use pazopanib after treatment failure with the other VEGF signaling inhibitors. Likewise, use of the other VEGF signaling inhibitors after treatment failure with pazopanib is not recommended.*

6.1.1 Methods

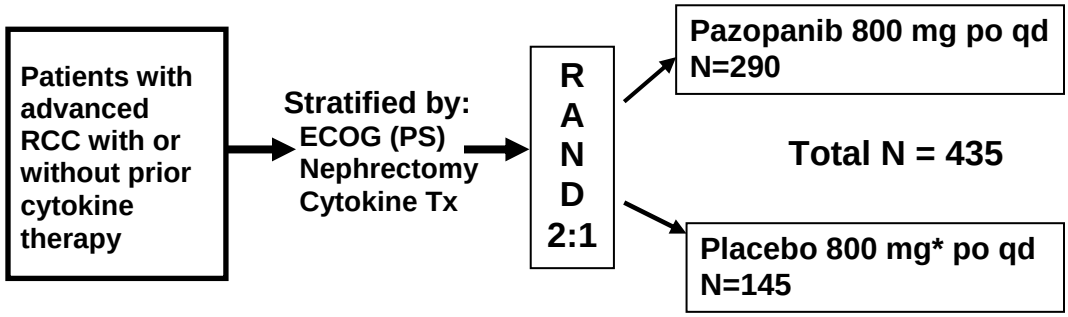
The review focused on the efficacy of pazopanib demonstrated in the placebo-controlled study VEG105192. Efficacy evidence from the 2 supportive studies was also reviewed to examine consistency and reliability, specifically in response rates across the three studies. The reviewers evaluated the original protocols and follow-up amendments in relation to the FDA recommendations associated with the key study. Efficacy endpoints were evaluated by verifying the accuracy of documented tumor lesions between CRFs and relevant datasets and by examining the completeness of the datasets based on independent review. With the statistical reviewers' help, discrepancies in evaluation of tumor lesions between the independent review and investigator were also inspected. Factors that might affect efficacy analyses such as withdrawal, intolerable toxicities, and missing or imbalanced efficacy assessment visits were considered and evaluated as appropriate based on the protocols and amendments. Statistical analyses were performed by the statistical reviewers and were compared to the applicant's study reports. Sensitivity analyses were conducted when indicated to assess the reliability of the results and conclusions. Importance and implications of the efficacy results were also discussed accordingly.

Protocol Review for Study VEG105192

Study Design

VEG105192 was a Phase 3, randomized, double-blind, placebo-controlled multi-center study of pazopanib compared to placebo in patients with locally advanced and/or metastatic renal cell carcinoma who had received either one or no prior systemic cytokine (IL-2 or INFα) based therapy. Clear cell or predominantly clear cell RCC histology was required for study entry. Patients with no prior therapy were eligible for the study only if they were from countries or regions where no standard first-line therapy was available or where systemic cytokine therapy was not recognized as standard therapy for RCC. Patients, who had received prior anti-VEGF therapy including sorafenib and sunitinib, were excluded. Eligible patients were stratified and randomized in a 2:1 ratio to receive either pazopanib or placebo as shown in Figure 1. Treatment continued until patients experienced disease progression, death, or unacceptable toxicity. Efficacy assessment was conducted every 6 weeks and then every 8 weeks after the first 24 weeks.

Figure 1: Design of the Key Study VEG105192



*tablets matching the pazopanib tablets

Protocol Amendments

The original protocol was developed in November, 2005. Since then, there were 5 protocol amendments, two prior to the protocol initiation, and three after the initiation. Major modifications and other significant protocol events are summarized in Table 7. Relevant background information can be seen in Table 2 of the review.

Among these amendments, the modification of the guidelines for hepatic toxicity represents a major modification to the protocol. These guidelines were based on updated safety information from VEG102616. The modified guidelines started one year after protocol initiation.

Table 7: Protocol Milestones of VEG105192

Milestone	Date	Major Changes or Comments
Original Protocol	11/21/2005	
Amendments 1-2	1/31/2006 3/22/2006	• Updated on treatment options for RCC and study rationale based on the FDA's approval of sorafenib and sunitinib for advanced RCC in the United States; • Exclusion of symptomatic progression as a measure for determining a PD event, per FDA comments; • Clarification of dosing of study product in relation to meals; • Reduced the interval of disease assessment from every 8 weeks to every 6 weeks for the first 24 weeks in order to capture early disease progression from both treatment arms.
Initiation of Protocol	04/18/2006	First patient
Amendment 3	05/09/2006	• Inclusion of treatment-naïve subjects in countries where cytokine, sunitinib or sorafenib were not approved or not readily available; • Deletion of the description of study patient populations related to the approval of sorafenib or sunitinib; • Ethical justification: inclusion of pazopanib as a treatment option for patients who progressed from the placebo arm via an open label extension study, VEG107769; • Specification of a minimum enrollment target for each treatment-naïve and cytokine-pretreated subgroup (≥150) and for the entire study (350-400); • Expansion of the secondary endpoints to evaluate PFS in two subpopulations: the first-line population and second-line population; • Revisions to the interim analysis to incorporate the changes described above
Amendment 4	08/07/2006	• Inclusion of treatment-naïve patients

Milestone	Date	Major Changes or Comments
		from countries where cytokines were approved but were not considered an effective therapy for advanced RCC; • Specification of agents targeting the angiogenesis pathways as an exclusion criterion. The protocol said "the preference is to offer patients a clinical trial that involves an anti-angiogenic agent with a mechanism similar to sunitinib and sorefanib".
Amendment 5	05/23/2007	• Update on the safety data from the Phase 2 study VEG102616; • Addition of detailed guidelines for dose modification for liver toxicity; • Addition of fractionated bilirubin levels if total bilirubin is ≥ 1.5 x ULN; • Introduction of specific recommendations regarding oral hypoglycemics and the possible risk of hypoglycemia in combination with calcium blockers in the setting of decreased cardiac conduction and contractility;
Data Cut-Off for Efficacy Analyses	05/23/2008	
NDA-submission	12/19/2008	• Regular Review designated

Objectives

Primary:

- To compare PFS of patients treated with pazopanib to those treated with placebo.

Secondary:

- To compare overall survival (OS) of patients treated with pazopanib to those treated with placebo.
- To evaluate PFS in two subpopulations: the population that has received no prior systemic treatment for locally advanced or metastatic RCC (first-line population), and the population that has received one prior cytokine-based systemic treatment for locally advanced or metastatic RCC (second-line population).
- To compare overall response rate [ORR = complete response (CR) + partial response (PR)] in patients treated with pazopanib to those treated with placebo.

- To assess the incidence, severity and causality of all adverse events (AE), serious adverse events (SAEs) and other safety parameters in patients treated with pazopanib and placebo.

Key Inclusion Criteria

- Patients with a diagnosis of clear cell RCC or RCC of predominantly clear cell histology (Patients with non-clear cell RCC were ineligible.)
- With locally advanced RCC (defined as disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to Stage IV RCC according to AJCC staging)
- The disease had to be measurable at baseline per the RECIST criteria, defined as a lesion that could be accurately measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques, or ≥ 10 mm with spiral CT scan. Baseline head, chest, abdominal and pelvic CT or MRI scans must be performed within 2 weeks prior to the first dose of study medication; baseline bone scan must be performed within 3 weeks of the first dose of study medication.
- Patients had received only one prior systemic cytokine based treatment [interleukin-2 (IL-2) or interferon-α (INFα)] for locally advanced or metastatic RCC with documented disease progression or documented treatment discontinuation due to unacceptable toxicity.
- Patients who had no prior systemic therapy for advanced/metastatic RCC must live in countries or regions where standard first-line therapy for advanced/metastatic RCC was not established or recognized, or where the established therapies such as sunitinib, sorafenib, IFNα or IL-2 were not available.
- Adequate baseline organ function: Hepatic function test parameters; total bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 2 x ULN
- At least 4 weeks from the last surgery and 2 weeks from radiotherapy or the last systemic cytokine therapy; complete recovery from prior surgery, and/or reduction of all AEs to Grade 1 from prior systemic therapy or radiotherapy
- Performance score of < 2, assessed by the Eastern Cooperative Oncology Group (ECOG) criteria
- Age 18 years or older
- Had offered written informed consent

Exclusion criteria

- Had received any prior products that target VEGF or VEGF receptors regardless of treatment setting (adjuvant, neo-adjuvant, or metastatic).
- History or presence of central nervous system (CNS) metastasis or leptomeningeal tumors as documented by CT or MRI scan, analysis of cerebrospinal fluid or neurological exam
- Baseline corrected QT interval (QTc) prolongation defined as QTc interval > 470 msecs.
- With any of the following cardiac or cardiovascular disorders:

  - History of Class III or IV congestive heart failure
  - History of cardiac angioplasty or stenting, myocardial infarction, or unstable angina within the previous 6 months
  - History of cerebrovascular accident within the previous 6 months
  - History of untreated deep venous thrombosis (DVT) within the previous 6 months
  - Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140mmHg, or diastolic blood pressure (DBP) of ≥ 90mmHg]
- Evidence of bleeding diathesis or coagulopathy
- Active GI disorders: peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to beginning study treatment; malabsorption syndrome or disease that could significantly affect gastrointestinal function, or major resection of the stomach or small bowel that could affect the absorption of pazopanib; unable to swallow and retain orally administered medication
- Had other clinically significant disorders or condition that could interfere with patient's safety, obtaining informed consent or compliance to the study (*e.g.*, active infections, including HIV).
- Current or prior use of an investigational anti-cancer drug within 4 weeks of start of study

Reviewer's Comments: *The eligibility criteria considered the known toxicities associated with anti-VEGF pathway products. On the other hand, the exclusion of patients with the medical conditions listed above makes it difficult to assess whether pazopanib could be safely used in those patients or whether they would have a similar treatment benefit if used with caution. Before further evidence is obtained to establish the risk-to benefit profile in patients with medical conditions excluded from participation, use of pazopanib in those patients should be discouraged. This is especially important for patients who have received one of the other with anti-VEGF pathway products and who have had disease progression or intolerable toxicity, since pazopanib uses the same antitumor mechanism as do the other anti-VEGF pathway products.*

Study Conduct

Upon completion of all the required baseline assessments, eligible patients were registered into the applicant's Registration and Medication Ordering System by the investigator or authorized site staff for stratification and central randomization. The three stratification factors were ECOG PS (0 vs. 1), prior nephrectomy (yes vs. no), and one prior cytokine-based systemic treatment for advanced RCC (yes vs. no). The 2:1 randomization was based on the

applicant's randomization schedule and the blinded treatment assignment was sent back through a fax to the study site.

Treatment assignment remained blinded throughout the period of treatment administration or until there was objective evidence of disease progression.

Treatment Plan

Randomized patients received study product, either pazopanib or placebo, at 800 mg (2 X 400 mg tablets) administered once daily by mouth, starting on Day 1. Pazopanib tablets were provided as 200 mg and 400 mg tablets and placebo tablets matching the 200 mg and 400 mg pazopanib tablets were used as control. The 200 mg tablets were used only for dose modification as indicated. Study product had to be taken 1 hour before or 2 hours after meals.

Dose delay and/or dose modification were based on toxicity types and severity. In general, for Grade 2 or 3 toxicities, patients should interrupt study treatment until toxicity resolves to ≤ Grade 1, and then restart study treatment at 400 mg. If the toxicity reoccurred, patients should discontinue study treatment and be followed up per protocol. For Grade 4 toxicities, patients should discontinue study treatment and be followed up per protocol. In addition, the applicant had specific guidelines for treatment-related adverse events such as hypertension, proteinuria, hemorrhage, and hepatic toxicity. Relevant to concerns about the hepatic safety of pazopanib, Table 8 lists the detailed plans used for managing hepatic function test abnormalities during the study.

If dose reduction was indicated, the dose should be reduced to 400 mg and the patient should be monitored for 10 to 14 days. If toxicity did not recur, the dose could be increased to 600 mg with continued monitoring for an additional 10-14 days. The dose could be further increased to 800 mg if there was no further recurrence or worsening of the toxicity. If the toxicity did not lessen after the initial dose-reduction to 400 mg, the investigator might further reduce the dose of the study medication to 200 mg and monitor the patient for 10-14 days. If the toxicity did not recur or worsen, the dose could then be increased step-wise back to 400 mg, 600 mg and 800 mg, if toxicity did not recur or worsen, after monitoring for 10-14 days at each step.

Table 8: Dose Modification Guidelines for Hepatic Function Test Abnormalities in VEG105192 (adopted from the applicant's protocol)

Note: As many patients are taking multiple concurrent medications it is critical to do a thorough evaluation of the patient's concurrent medications, identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary.	
(A). ALT of ≤ 3.0 x ULN	Continue study treatment at 800mg with full panel liver function tests (LFTs)[1] monitored as per protocol.
(B). ALT > 3.0 x ULN to ≤ 8.0 x ULN **without** bilirubin elevation (defined as total bilirubin < 2.0 x ULN or direct bilirubin ≤ 35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	1. Continue study treatment at 800mg. 2. Perform the following assessments for excluding hypersensitivity and other contributing factors: • Eosinophil count • Viral serology for hepatitis A, B and C • Liver imaging 3. Monitor patient closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST reduced to Grade 1. 4. If the patient is withdrawn from study treatment, follow up per protocol.
(C). ALT > 3.0 x ULN **with** concomitant elevation in bilirubin (defined as total bilirubin ≥ 2.0 x ULN; **with** direct bilirubin > 35%) or **with** hypersensitivity symptoms (e.g., fever, rash). (D). ALT > 8.0 x ULN	1. Interrupt study treatment immediately 2. Consult a hepatologist and perform the following assessments to identify co-contributing factors: • Eosinophil count • Viral serology for hepatitis A, B, C and E, cytomegalovirus (CMV), Epstein-Barr virus (EBV IgM antibody, or heterophile antibody, or monospot testing) • Anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti-mitochondrial antibody • Serum creatinine phosphokinase (CPK) for possible muscle injury caused LFT elevation • Liver imaging (ultrasound or CT scan) 3. Monitor patient closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until LFTs reduced to Grade 1. Note: If the patient is benefiting from the study treatment, contact GSK medical monitor for possible re-challenge. Re-treatment may be considered if **ALL** following criteria are met: • ALT/AST reduced to Grade 1 • Total bilirubin < 1.5 x ULN or direct bilirubin ≤ 35% • No hypersensitivity signs or symptoms • Patient is benefiting from therapy. GSK Medical Monitor will consult the Chairman of the GSK Safety Board regarding the individual patient. If approval for retreatment is granted, the patient must be reconsented (with new informed consent specific to hepatotoxicity).

1. Full panel LFTs include: AST, ALT, alkaline phosphatase, γ-GT and total bilirubin. If at any time the total bilirubin is > 1.5 x ULN, perform bilirubin fractionation for direct and indirect bilirubin.

Prohibited medicines during the study: Numerous medicines were prohibited within 14 days prior to the first dose of study drug until discontinuation of study treatment. These included the following:

- **Anticoagulants:** warfarin at therapeutic doses
- **Oral hypoglycemics:** tolbutamide, chlorpropamide
- **Erectile dysfunction agents:** sildenafil, tadalafil, vardenafil
- **Ergot derivatives:** dihydroergotamine, ergonovine, ergotamine, methylergonovine.
- **Neuroleptics:** pimozide.
- **Antiarrhythmics:** bepridil, flecainide, lidocaine, mexilitine, amiodarone, quinidine, propafenone.
- **Immune modulators:** cyclosporine, tacrolimus, sirolimus.
- **Miscellaneous:** theophylline, quetiapine, risperidone, tacrine, clozapine, atomoxetine, tizanidine

Investigational products other than the study product were not allowed. Once another anti-cancer therapy had been initiated, the patient should stop treatment with the study product and be followed up per the protocol.

Reviewer's Comments: *The numerous prohibited medicines during the study may represent a challenge for both patients and health care providers after pazopanib becomes commercially available, since the safety of pazopanib in the presence of these medicines remains unknown. Some of these medicines, e.g., chlorpropamide or theophylline, are less likely to be used in clinical practice. However, many of them are commonly used, e.g. the drugs for erectile dysfunction and arrhythmias.*

Efficacy Assessments

Primary Endpoint
The primary objective of the study was to evaluate and compare PFS between the two treatment arms. PFS was defined as the time from randomization to the time of documentation of disease progression or death due to any cause, as evaluated by an independent review committee (IRC).

As shown in Table 9, efficacy assessments by CT or MRI were obtained at baseline, every 6 weeks and then every 8 weeks after the first 24 weeks. Bone scan was also performed as scheduled to help evaluate disease response or progression. Disease progression was based on radiographic assessments of target and non-target lesions using the RECIST criteria.

Secondary Endpoints
Two key secondary efficacy endpoints were to assess overall survival and overall response rates between the two treatments. To assess overall survival, defined as the time interval from randomization to death, all patients were continued in the study and followed until death, if possible, after disease progression or withdrawal for any reason. To evaluate the overall tumor response rate, defined as

the percentage of patients achieving a complete or partial tumor response per RECIST criteria, the best confirmed response result of a patient, determined by the independent review, was used for calculation.

Safety Assessments

Clinical assessments for safety were conducted at baseline, on day 8, every 3 weeks within the first 24 weeks and every 4 weeks after Week 24 until 28 days following treatment discontinuation. Safety assessments included physical examinations, vital signs, clinical laboratory evaluations, ECG, ECOG PS, AE/SAE assessments and pregnancy status in female subjects with child-bearing potential. Elements of the assessments varied with the time of visits or assessments. The detailed plan for the assessments is shown in Table 9.

An adverse event (AE) was defined as any untoward medical occurrence that was temporally associated with the use of study product, whether or not considered related to the product. A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death, disability or incapacity, was life-threatening, required hospitalization or prolonged existing hospitalization, or represented an event that required intervention to prevent the listed negative outcomes (e.g., development of malignancies). All toxicities including laboratory abnormalities and AEs were graded according to NCI-CTC, Version 3.0.

Table 9: Study Procedures in VEG105192 (Adopted from the original protocol)

Assessments/ Procedures	Screening[1] Baseline	D 1 Pre-Dose	Study Treatment Period[2]							Treatment Discontinuation Visit	PD-FU[5]	Survival FU[6] Every 3 months
			Day 1 to Week 24				Week 24 to treatment discontinuation					
			D 8[3]	Q 3 Wks[4]	Q 6 Wks	Q 12 Wks	Q 4 Wks[4]	Q 8 Wks	Q 12 Wks			
Informed consent	♦											
Eligibility	♦----------♦											
Demography & medical history[7]	♦											
Physical examination	♦	♦		♦			♦			♦[12]		
Vital signs, BP	♦	♦	BP only	♦			♦			♦[12]		
ECOG PS	♦			♦			♦			♦[12]	♦	
Randomization code		♦										
ECG	♦			Wk 3 only		♦			♦	♦[13]		
Clinical chemistry[8]	♦		AST & ALT only	♦			♦			♦[12]		
Hematology[8]	♦			♦			♦			♦[12]		
Coagulation tests[8]	♦			♦			♦			♦[12]		
Urinalysis[8]	♦		♦	♦			♦			♦[12]		
Thyroid function tests[8]	♦					♦			♦	♦[13]		
Serum pregnancy test	♦		---------- As clinically indicated ----------									
Disease assessments[9]	♦				♦			♦		♦[14]	♦	
QoL questionnaires	♦		Week 6, 12, 18, 24, 48 only							♦[15]		
PGx[10]	♦											
Obtain archived tumor tissues	♦											
Blood sampling for proteomics	♦											
Population PK samplings[11]		Pre- & post-dose		Wk 3 only								
Record concomitant medication	♦	♦	♦	♦			♦			♦		
Record post-treatment medication												
Dispense study medication		♦		♦			♦					
AE/SAE assessments		♦	♦	♦			♦			♦	♦[16]	♦[16]
Survival assessment			♦	♦			♦				♦	♦[17]

1. All Screening/Baseline procedures must be completed within 3 weeks prior to randomization/first dose. However, disease assessments using CT, MRI or chest X-ray, and serum pregnancy test for women with child-bearing potential must be performed within 2 weeks from the 1st dose.
2. Study Treatment Period is from the first dose of study medication until a patient experiences one of the following: progressive disease (PD), unacceptable AE/SAE, death during treatment, or withdrawal of consent for any reason.
3. The visit window is ± 1 day.
4. The visit window for clinic visit (Q3 Wk until Week 24 and Q4 week thereafter) is ± 3 days
5. PD FU (progressive disease follow-up) is for patients who stopped study treatment due to unacceptable AE/SAE, or discontinued for other reason without PD. These patients should be followed every 6 weeks until Week 24 or every 8 weeks thereafter until PD, initiating another anti-cancer treatment or death which ever occurs first.
6. Survival FU is from PD or initiation of another anti-cancer treatment until death due to any cause.
7. Including cancer history, prior anti-cancer therapies.
8. Specified individual parameters included in these clinical laboratory assessments.
9. Refer to disease efficacy assessments and windows for assessments.
10. Patients must sign the PGx informed consent prior to blood sampling.
11. On PK sampling days, patients must be dosed at clinic as blood draw occurs before and after dosing.
12. Only perform these tests if the last ones are performed ≥ 3 weeks.
13. Only perform these tests if the last ones are performed within ≥ 12 weeks.
14. Only perform if the last disease assessments have not shown progressive disease and have been performed ≥ 7 weeks and the patient is not followed for PD.
15. Only perform the quality of life assessment if the last one is assessed within ≥ 8 weeks.
16. To follow-up unresolved AEs/SAEs that are treatment-related until they are resolved or the patient dies.
17. Patients are followed by phone contact or clinic visit until death.
18. Abbreviations: BP = blood pressure, D = day; Q = every, for example: Q 3 Wks = every 3 weeks.

Statistical Methods

The primary efficacy analysis of PFS was conducted in the Intent-to-Treat (ITT) population, summarized using the Kaplan-Meier method, and compared between treatment arms at the final analysis using a stratified log-rank test. For the details, please see the statistical review for the NDA.

The time interval from randomization to disease progression or death was used in the analysis for patients who had an event. Censoring was performed in patients who had not had a PFS event or who had other situations that prevented the applicant from defining a PFS interval. The detailed censoring rules for the primary analysis are shown in Table 10.

Table 10: Assignments for Progression and Censoring dates for the Primary Analysis (adopted from the protocol)

Situation	Date of Progression or Censoring	Outcome
No baseline assessment	Randomization	Censored
Progression documented between scheduled visits	Next scheduled visit	Progressed
No progression	Date of last visit with adequate disease assessment	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate disease assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate disease assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate disease assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between visits with adequate disease assessment	Date of death	Progressed
Death or progression after an extended lost-to-follow-up time (greater than 12 weeks)	Date of last visit with adequate disease assessment	Censored

An adequate disease assessment comprises imaging assessment of the target tumor lesion(s) and non-target tumor lesion(s)/site(s) using CT and/or MRI of the chest, abdomen and pelvis with a schedule of every 6 weeks until Week 24 and every 8 weeks thereafter (± 7 days). In addition, an adequate disease assessment includes a bone scan every 24 weeks. A patient may have a bone scan prior to the scheduled bone scan to confirm a CR/PR. After the confirmatory assessment, the subsequent bone scans will be performed every 24 weeks or sooner if clinically indicated.

PFS analyses in subpopulations of interest, including first-line and second-line populations, were planned to explore any differences in efficacy between the two groups.

For the key secondary efficacy endpoint, overall survival, Kaplan-Meier survival curves were planned to summarize the differences between the treatment arms and a stratified log-rank test was used to test this difference. Patients who were alive at the time of the analysis were censored at the time of last contact. Response rate was another important secondary endpoint. It was calculated based on the independent review of best response with confirmed results of PR and CR. Patients with an unknown or missing response were to be treated as non-responders. Response rates were compared between treatment arms using a Fisher's exact test. Approximate 95% confidence limits for the difference in response rates were also calculated.

6.1.2 Demographics

A total of 435 patients were randomized (2:1) in Study VEG105192, 290 to the pazopanib arm and 145 to the placebo arm. They were distributed in 80 study centers from 23 countries, as shown in Table 11. Half of the patients, 215 of the

435 (49%), were from Eastern Europe and Russia; whereas no patients were from the United States.

All the patients were included in the ITT population for planned efficacy analyses. Since all the patients received at least one dose of study product, the safety population was identical to the ITT population.

Table 11: Geographic Distribution of the Patients in Study VEG105192

Country	Placebo N=145	Pazopanib N=290	Total N=435
Poland	36	72	108 (25%)
Russian	10	22	32 (7%)
UK - CMD	6	22	28 (6%)
Argentina	11	14	25 (6%)
Tunisia* (France)	12	10	22 (5%)
Korea	8	14	22 (5%)
Chile	8	13	21 (5%)
Lithuania	8	11	19 (4%)
Slovakia	4	14	18 (4%)
Italy	4	12	16 (4%)
Pakistan	4	11	15 (3%)
Eleven countries with less than 15 of patient enrollments were the Czech Republic (14), Australia (13), Ukraine (13), India (13), Austria (12), New Zealand (12), Brazil (11), Estonia (9), China [9, Hong Kong (3)], Latvia (2), and Ireland (1). **Note the applicant labeled Tunisia as France in the data collection because the French LOC covers Tunisia.*			

Demographic and baseline disease characteristics of the ITT population were examined and the results are shown by treatment arm in Tables 12 and 13. Overall, the characteristics were balanced between the arms.

Table 12: Baseline Demographics of the Patients in VEG105192

Parameter	Placebo N = 145	Pazopanib N = 290
Sex		
Male, n (%)	109 (75%)	198 (68%)
Female	36 (25%)	92 (32%)
Age		
Median (range)	60 years (25-81)	59 years (28-85)
Race		
Caucasian	122 (84%)	252 (87%)

Asian	23 (16%)	36 (12%)
Other	0	2 (1%)
Performance Status		
0	60 (41%)	123 (42%)
1	85 (59%)	167 (58%)

Table 13: Disease Characteristics of the Patients in VEG105192

Parameter	**Placebo N = 145**	**Pazopanib N = 290**
Histology		
Clear Cell	129 (89%)	264 (91%)
Predominately Clear Cell	16 (11%)	25 (9%)
Prior Surgery		
Nephrectomy	127 (88%)	258 (89%)
Other	14 (10%)	20 (7%)
Time from Initial Diagnosis (mos)		
Median (range)	13.8 (1-152)	15.7 (0-184)
Unknown n (%)	15 (10%)	29 (10%)
Disease Involvement at Baseline		
Lung	106 (73%)	214 (74%)
Lymph Nodes	86 (59%)	157 (54%)
Bone	38 (26%)	81 (28%)
Liver	32 (22%)	75 (26%)
Prior Therapy		
Cytokine	67 (46%)	135 (47%)
None (treatment-naïve)	78 (54%)	155 (53%)
MSKCC Risk Factors*		
0 (Favorable)	57 (39%)	113 (39%)
1-2 (Intermediate)	77 (53%)	159 (55%)
≥3 (Poor)	5 (3%)	9 (3%)
* The 5 risk factors are a poor performance status (ECOG >1), a low serum hemoglobin level, an elevated serum LDH level, an elevated corrected serum calcium, and no prior nephrectomy. (Note: "no prior nephrectomy" was used instead of the conventional "a time interval of <1 year from diagnosis to treatment").		

No patients were found to have received antiangiogenic products prior to enrollment. For the patients who had one prior systemic cytokine-based therapy, their treatments are summarized in Table 14. The types of treatment were generally balanced between the arms.

Table 14: Prior Cytokine Treatments in Patients in VEG105192

Parameter	**Placebo N = 67 (of 145)**	**Pazopanib N =135 (of 290)**
Prior Cytokine for Metastatic Disease		
IFNα	45 (67%)	101 (75%)
IL-2	8 (12%)	11 (8%)
IFNα + IL-2	13 (19%)	23 (17%)

Reviewer Comments:
All the listed characteristics appear balanced between the two treatment arms. Prognosis of the study disease has been known to be heterogeneous despite clear cell histology. Several risk factors have been identified to predict the patient's outcome. The common model used is the MSKCC classification. In this application, the applicant substituted one of the 5 MSKCC factors "a time interval of <1 year from diagnosis to systemic treatment" with "absence of prior nephrectomy". The significance of the substitution remains unclear in the prognosis of the disease.

6.1.3 Patient Disposition

Overall patient disposition at the time of the efficacy analyses was examined and the results are shown in Table 15. The majority of the patients came off the study because of disease progression. Relative to placebo, more patients discontinued pazopanib due to adverse events and withdrawal.

Table 15: Patients Disposition in VEG105192

	Placebo N = 145	**Pazopanib N = 290**
Enrolled	145	290
Treated		
On Treatment	14 (10%)	63 (22%)
Off Treatment*	131 (90%)	227 (78%)
Progressive Disease	112	147
Death	9	11
Adverse Events	5	41
Lost to Follow Up	1	3
Withdrawal	2	14
Other	1	11

*Reasons for study discontinuation were based on investigator's assessments (stopdrug dataset). Few patients withdrew voluntarily but were classified as "Other". The information shown above reflects adjusted tabulations of the reasons for "off treatment".

Major protocol violations and/or deviations that may have an important impact on the efficacy evaluation of pazopanib were investigated and the major findings are summarized in Table 16. These included inadequate efficacy assessment, missing scheduled efficacy assessment, and absence of baseline scans or measurable disease. Note that the initial NDA submission provided only the eligibility violations but did not provide any information on violations or deviations during study conduct. The applicant later summarized the conduct violations and deviations based on the review of the CRFs. Therefore, it is likely that the information shown here may under-represent the real protocol violations and deviations, which, in general, should be reported and collected during the study period.

Table 16: Major Protocol Violations/Deviations with Likely Impact on Assessment of the Primary Endpoint

	Placebo N=145	Pazopanib N=290
Eligibility Criteria Unmet	**1 (<1%)**	**3 (1%)**
Hepatic lab abnormality	0	1
No measurable disease	0	1
>1 prior systemic therapy	1	0
QTc >470	0	1
Inadequate Efficacy Assessment	**5 (3%)**	**26* (9%)**
Missed Efficacy Assessment	**3 (2%)**	**15* (5%)**

* Six patients had both inadequate and missed assessments

Reviewer Comments:
A sensitivity analysis of the impact of the violations was performed based on the independent review of the key study.

6.1.4 Analysis of Primary Endpoint(s)

Analysis of Primary Endpoint

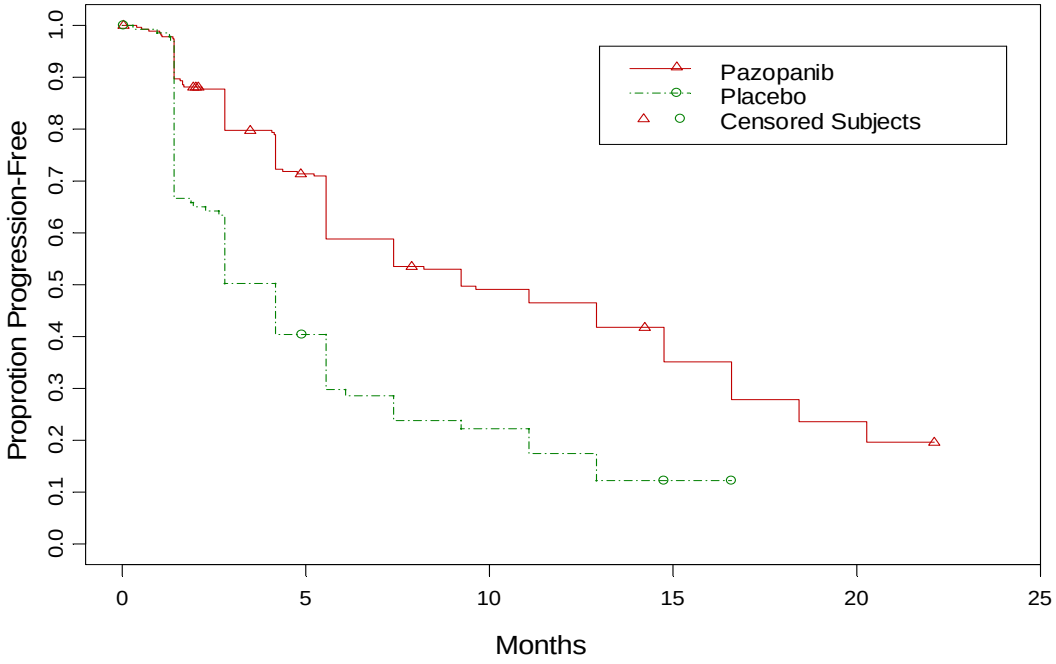
The primary endpoint, progression free survival (PFS), was evaluated based on the independent review of radiographic assessments of disease progression. The data cut off for the analysis was on May 23, 2008.

In the ITT population, the Kaplan-Meier estimate of median PFS in patients from the pazopanib arm was 9.2 months as compared to a median PFS of 4.2 months in patients from the placebo arm. The hazard ratio for disease progression or death in the pazopanib arm compared to the placebo arm was 0.46 (95% C.I. 0.34 to 0.62, p-value < 0.0000001). These results are shown in Table 17 and the Kaplan-Meier curves for the analysis were presented in Figure 2.

Table 17: Primary Endpoint Analysis Results by Independent Assessment

	Placebo N = 145	**Pazopanib N = 290**
Status		
Progressed or Died	98 (68%)	148 (51%)
Censored	47 (32%)	142 (49%)
Progression Free Survival		
Median (95% CI)	4.2 mo (2.8, 4.2)	9.2 mo (7.4, 12.9)
Adjusted Hazard Ratio (95% CI)	0.46 (0.34, 0.62)	
Stratified Log-rank p value	< 0.0000001	

Figure 2: K-M Curves for PFS Based on the Assessments by Independent Review



Sensitivity Analyses of the Primary Endpoint

As discussed in the protocol violations, more patients in the pazopanib arm than in the placebo arm had protocol violations/deviations in the efficacy assessment, 14% vs. 6%, as shown in Table 16. To explore whether these violations/deviations affected the PFS results seen in the ITT population, a sensitivity analysis was conducted which excluded the patients who had the violations/deviations. Its results are shown in Table 18.

Table 18: Sensitivity Analysis of the Impact of the Protocol Violations/Deviations on Efficacy Assessments of PFS by Independent Review

	Placebo N = 145	Pazopanib N = 290
With Violations	8 (6%)	35 (14%)
Without Violations	137 (92%)	255 (86%)
Progression Free Survival		
Adjusted Hazard Ratio (95% CI)	0.457 (0.347, 0.603)	
Stratified Log-rank p value	< 0.0001	

To examine the robustness of the primary analysis results, a sensitivity analysis was also conducted based on investigator's assessments of disease progression and death. As shown in Table 19, the results in the ITT population were consistent with those in the primary analysis based on the independent review. The Kaplan-Meier estimated median PFS was 9 months (95% CI: 7.4 to 10.9) in the pazopanib arm and 3 months (95% CI: 2.8- 4.2) in the placebo arm. The hazard ratio was also similar, 0.44 with 95% CI: 0.34 to 0.57, p-value < 0.0000001).

Table 19: Sensitivity Analysis of the PFS by Investigator Assessments

	Placebo N = 145	Pazopanib N = 290
Status		
Progressed or Died	126 (87%)	178 (61%)
Censored	19 (13%)	112 (39%)
Progression Free Survival		
Median (95% CI)	3.0 mo (2.8, 4.2)	9.0 mo (7.4, 10.9)
Adjusted Hazard Ratio (95% CI)	0.44 (0.34, 0.57)	
Stratified Log-rank p value	< 0.0000001	

Reviewer's Comments

The primary endpoint analysis results demonstrate that pazopanib statistically prolonged PFS. A 5-month improvement in median PFS was seen when compared to placebo. This magnitude of improvement seems comparable to the other products approved for the treatment of patients with advanced RCC. The results are also vigorous despite the protocol violations and the differences in assessments between the independent review and investigator's evaluation. Based on the statistical review, the overall disagreement between the independent and investigator's reviews of disease progression and censoring was approximately 32% in both arms.

6.1.5 Analysis of Secondary Endpoints(s)

The first secondary endpoint was a comparison of differences in overall survival between the two treatment arms. An interim OS analysis was conducted as planned at the time of the final PFS analysis. The interim analysis showed that there was no statistically significant difference in OS despite a trend in favor of pazopanib. The results of the analysis are shown in Table 20 and the Kaplan-Meier curves in Figure 3. The hazard ratio for overall survival was 0.73 (95% CI: 0.53 to 1.00) with a one-sided p-value of 0.02, which did not reach the level, $p < 0.004$, required to demonstrate statistical significance for this interim analysis of OS. At the time of analysis, 176 deaths (61% of the required 287 deaths for the final survival analysis) had occurred. However, since 70 patients from the placebo arm had crossed over to receive pazopanib in the extension study at the time of the interim analysis, longer follow up may not be able to demonstrate a statistically significant difference between the arms in survival. The final OS analysis was planned when 287 deaths had occurred. This is projected to be early in 2010.

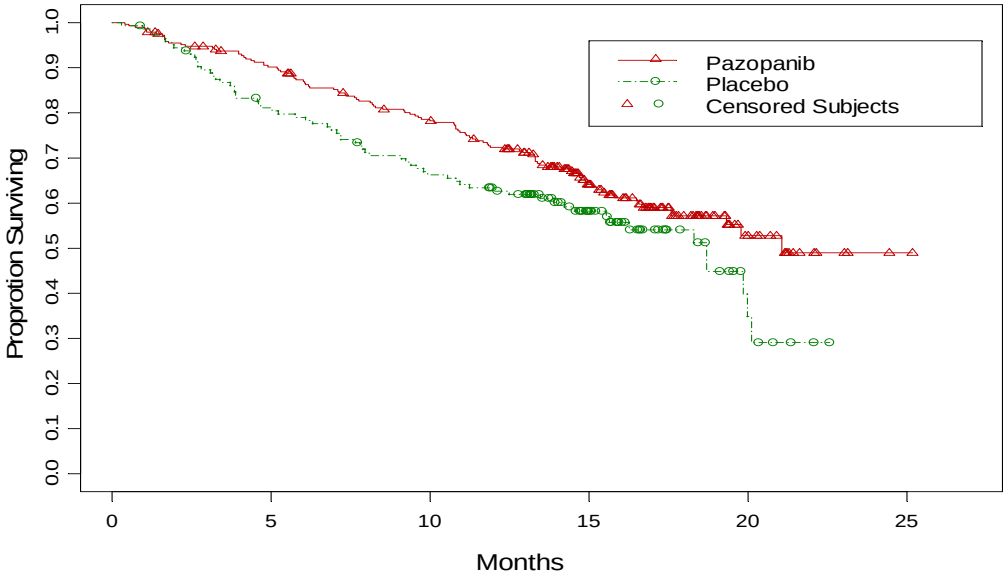
Table 20: Kaplan-Meier Estimates of Overall Survival (An Interim Analysis)

	Placebo (N=145)	Pazopanib (N=290)
Number (%) of Subjects		
Died (event)	67 (46)	109 (38)
Censored	78 (54)	181 (63)
Estimates for overall survival (months)		
1st Quartile (95% CI)	7.2 (4.7, 9.8)	11.1 (9.4, 13.3)
Median (95% CI)	18.7 (14.6, 20.1)	21.1 (19.3, NC[1])
3rd Quartile (95% CI)	NC[1] (20.0, NC[1])	NC[1] (NC[1], NC[1])
Adjusted Hazard Ratio (95% CI)	0.73 (0.53, 1.00)	
Stratified Log-Rank P-Value	0.020	
Unadjusted Hazard Ratio (95% CI)	0.020	
Unstratified Log-Rank P-Value	0.73 (0.54, 0.99)	

[1]: NC: not calculable

Adopted from the applicant study report following FDA statistical verification of the data and results

Figure 3: Kaplan-Meier Curves for Overall Survival (An Interim Analysis)



The other key secondary endpoint was overall response rate. The results of the analysis based on the independent review are shown in Table 21. The response rate demonstrated with pazopanib in the placebo-controlled study is similar to that observed in Studies VEG102616 and VEG107769.

Table 21: Overall Response Rates in VEG105192

	Placebo N=145	**Pazopanib N=290**
Overall RR (CR+PR) N (%) (95% CI)	5 (3%) (0.5%, 6.4%)	88 (30%) (25.1%, 35.6%)
CR: N (%)	0 (0%)	1 (<1%)
PR: N (%)	5 (3%)	87 (30%)
Duration of Response Median (95% CI)	--*	58.7 weeks (52.1, 68.1)
RR in Treatment- Naïve Group (95% CI)	4% (0, 8.1%)	32% (24.3%, 38.9%)
RR in Cytokine Pretreated Group (95% CI)	3% (0, 7.1%)	29% (21.2%, 36.5%)

*The number of patients is too small to provide a meaningful estimate of the duration of response.

Reviewer's Comments
The secondary endpoint analyses support the PFS results. The interim analysis results for OS suggested a trend, consistent with the observed prolongation in PFS with pazopanib. Although the tumor response to pazopanib was basically limited to a partial response, these responses appear to form an important basis for the observed delay in disease progression as reflected by the prolongation in PFS.

6.1.6 Subpopulations

The protocol planned to evaluate PFS in two subpopulations: the population that has received no prior systemic treatment for locally advanced or metastatic RCC (treatment-naïve subgroup) and the population that has received one prior cytokine-based systemic treatment for locally advanced or metastatic RCC (cytokine-pretreated subgroup). As shown in Table 22 for the treatment-naïve subgroup and in Table 23 for the cytokine-pretreated subgroup, PFS was prolonged with pazopanib in both subgroups as compared with placebo. However, the prolongation in the treatment-naïve subgroup appeared greater than that in the cytokine-pretreated subgroup.

Table 22: PFS in the Treatment-naïve Subgroup

	Placebo	**Pazopanib**
	(N=78)	**(N=155)**
Number (%) of Subjects		
Progressed or Died (event)	57 (73)	73 (47)
Censored	21 (27)	82 (53)
Kaplan-Meier Estimates for PFS (months) Median (95% CI)	**2.8 (1.9, 5.6)**	**11.1 (7.4, 14.8)**
Unadjusted Hazard Ratio		
Estimate (95% CI)	0.40 (0.27, 0.60)	

Adopted from the applicant study report after FDA statistical verification

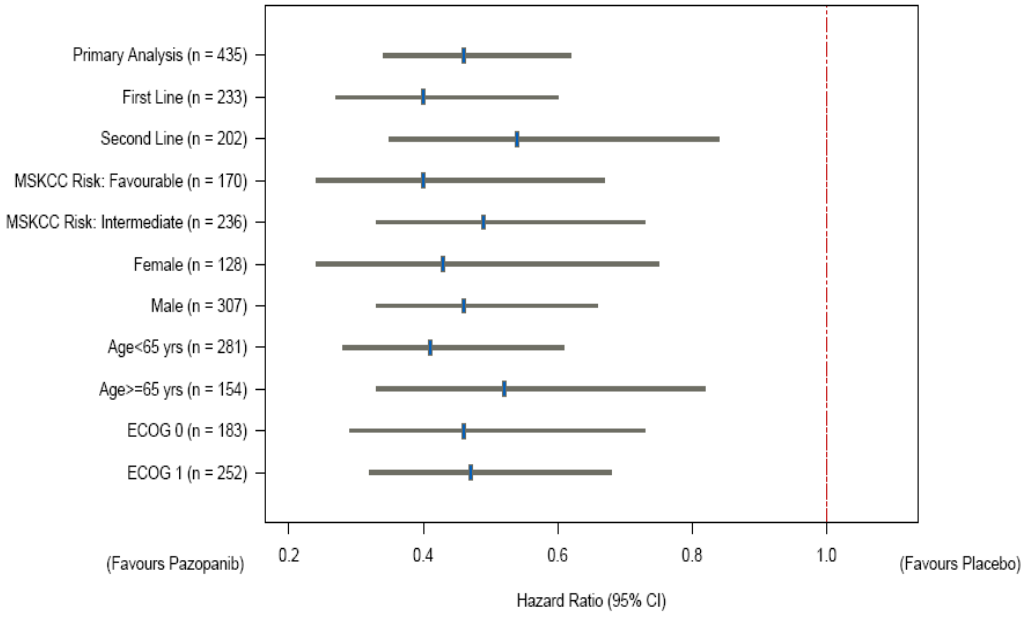
Table 23: PFS in the Cytokine-Pretreated Subgroup

	Placebo	**Pazopanib**
	(N=67)	**(N=135)**
Number (%) of Subjects		
Progressed or Died (event)	41 (61)	75 (56)
Censored	26 (38)	60 (45)
Estimates for progression free survival (months) Median (95% CI)	**4.2 (2.8, 5.6)**	**7.4 (5.6, 12.9)**
Unadjusted Hazard Ratio		
Estimate (95% CI)	0.54 (0.35, 0.84)	

Adopted form the applicant study report after FDA statistical verification

Other subgroup analyses of PFS by gender, age, performance status, and the modified MSKCC risk classification were also examined and the results, as shown in Figure 4, were generally consistent with the primary analysis results.

Figure 4: Subgroup Analyses of PFS



PFS differences by region were also investigated. As shown in Section 6.1.2, 49% of the patients were from the Eastern Europe-Russia region. It would be appealing to see if there were any differences in PFS between patients from that region and patients from other regions. As shown in Table 24, patients from both regions had an improvement in median PFS with pazopanib; however, the PFS improvement in patients from the Eastern Europe-Russia region appeared to be less than that in patients from other regions. The reasons for this difference remain unclear.

Table 24: Progression-Free Survival by Region in ITT Population

	Placebo	**Pazopanib**
Eastern Europe-Russia		
Number of Subjects	**(N=69)**	**(N=146)**
Progressed or Died (event)	47	80
Censored	22	66
Estimates for progression free survival (months)		
Median (95% CI)[1]	**4.2 (2.8, 5.6)**	**7.4 (5.6, 11.1)**
Unadjusted Hazard Ratio[2] (95% CI)	0.46 (0.32, 0.67)	
Other		
Number of Subjects	**(N=76)**	**(N=144)**
Progressed or Died (event)	51	68
Censored	25	76
Estimates for progression free survival (months)		
Median (95% CI)[1]	**2.8 (2.6, 5.6)**	**12.9 (7.4, 16.6)**
Unadjusted Hazard Ratio[2] (95% CI)	0.42 (0.29, 0.61)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable. One dose schedule has been developed for pazopanib since the conclusion of study VEG10003.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The majority of the patients in the study came off the study because of disease progression. Thus, the study findings are unlikely to underestimate or overestimate the persistence of efficacy with pazopanib. The median duration of response observed in patients who achieved partial or complete RECIST response was about 58.7 weeks (equivalent to 13.8 months). This suggests that pazopanib was able to maintain efficacy for a prolonged period in patients who were initially sensitive to the product.

6.1.9 Additional Efficacy Issues/Analyses

No patients in the placebo-controlled study were from the United States. Yet, 62 patients in the Phase 2 study VEG102616 were from the United States. To estimate if the efficacy of pazopanib demonstrated in the patients from the US was similar to that observed in the key study, an inter-study comparison of response rates was conducted. PFS was not used for the comparison since VEG102616 was a single arm study. Table 25 shows the results of overall response rates based on the independent review. Given the over response rate of 34.7% in the Phase 2 study, the response rate observed in patients from the US was similar to that in non-US patients in the Phase 2 study and was also comparable to that in the placebo-controlled study. These observations suggest that there was a similarity between patients from US and non-US regions in their response to pazopanib.

Table 25: An Inter-Study Comparison of Response Rate between the USA and non-USA Patients

	Phase 2 Study of Pazopanib		**Phase 3 Study**
	Patients from the USA N=63	**Patients NOT from the USA N=162**	**Pazopanib N=290**
Overall RR (CR+PR) N (%) (95% CI)	 20 (32%) (20.3%, 43.2%)	 58 (36%) (28.4%, 43.2%)	 88 (30%) (25.1%, 35.6%)
The overall response rates in the Phase 2 study was 34.7% (78 of the 225)			

Reviewer's Comments
The baseline characteristics were also found to be comparable between the patients from the US and the patients from non-US regions. Despite this and

the above similarity in response rates, it would be difficult to make a conclusive assessment given the small sample size of the patients from the US.

7 Review of Safety

7.1 Methods

The safety of pazopanib in patients with advanced RCC was evaluated by examining the submitted datasets, case report forms (CRFs), and narratives. Internal consistency in these different information sources was assessed. This mainly includes evaluation of complete documentation of adverse reactions, accuracy of grading toxicity, and attribution to life-threatening adverse reactions. Fatal SAEs and deaths during the study were scrutinized for causality with respect to study product, with special attention to whether there were misclassifications of these events as disease progression. For important cases, additional information was requested from the applicant to understand clinical scenarios and to better define causality. Safety results obtained from the applicant's datasets were compared to those described in the applicant's study report.

Non-RCC pazopanib monotherapy studies were utilized for investigation of any safety signals from the RCC clinical studies or safety concerns raised by products similar to pazopanib. This included the examination of Hy's Law cases in the pazopanib monotherapy population, assessment of changes in LVEF, and inspection of additional events of interest such as gastrointestinal perforation and torsade.

In addition, differences in adverse reactions between the original submitted datasets and the 120-day safety update datasets were also checked for any new safety signals. For this review, the 120-day safety update datasets were used to generate pazopanib's profile of AEs and laboratory abnormalities in RCC.

Adverse events or reactions coded under Medical Dictionary for Regulatory Activities (MedDRA)-preferred terms were analyzed based on the submitted datasets. Due to considerable variations in describing the same or a similar event, different preferred terms were combined whenever medically indicated during the review. Adverse events or reactions were based on investigator's reports during the study. Adverse events reported at screening were not included in the review. A drug-related adverse reaction (DRAR) was defined as any adverse event considered to be related to the drug by the investigators. In the placebo-controlled key study, classifying DRARs may be less important since the control arm provided a valuable background for understanding the safety profile of pazopanib. Therefore, DRARs will not be analyzed specifically in this review.

7.1.1 Clinical Studies Used to Evaluate Safety

The assessment of the safety and tolerability of pazopanib was based mainly on the placebo-controlled Phase 3 study, VEG105192. For the pooled safety analyses, the safety data from the two supportive RCC studies were used, as shown in Table 26. Eight additional studies that used pazopanib monotherapy were explored for hepatic safety information, focusing mainly on cases that met Hy's Law criteria. All patients included in the safety analyses received at least one dose of pazopanib.

Table 26: Clinical Studies Used for the Safety Analyses of Pazopanib

	Study ID	Number of Patients Treated with Pazopanib	Total Number of Patients		
Key Data Source	**VEG105192**	290 (pazopanib) 145 (placebo)	435	593 (pooled RCC)	990 (mono)
Studies used in the pooled safety analyses with the key study	**VEG102616**	225			
	VEG107769	78			
Non-RCC studies used for hepatic safety screening in the pazopanib monotherapy population in addition to the three RCC studies	**VEG10003**	63			
	VEG10004	10			
	VEG10005	35			
	VEG10007	24			
	VEG104450	36			
	VEG105281	74			
	VEG20002	142			
	VEG20006	21			

7.1.2 Adequacy of Data

The submitted datasets were examined for their integrity, content and type. All the 112 narratives in the key study were evaluated against the corresponding datasets and CRFs. Forty six patients had no CRFs in the initial submission. These were submitted later by the applicant after a notification from the Agency. Discrepancies or deficiencies in reporting AEs such as inaccurate grading of toxicity, inappropriate classification of causality were found in some patients and the findings were conveyed to the applicant. Having considered the total number of reported AEs, the reviewers estimated that the discrepancies including the AEs without grading may account for a 1.5% to ~2.9% of the AEs reported. This would not generate important effects on the overall safety analysis results. In

addition, physical, laboratory, and EKG examination information was included in the submission. A total of 593 patients with RCC received pazopanib and approximately 1000 patients with a variety of tumor types have received pazopanib monotherapy. Thus, the overall safety data is adequate to assess the safety and tolerability of pazopanib in patients with RCC.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Pooled analyses of adverse events associated with pazopanib were performed based on the 120-day safety data from the 593 patients with RCC. The median duration of exposure to pazopanib was 7.7 months (range 0.1-38.6) in this population. Adverse events were reported in 566 (95%) patients and 21 (4%) had fatal serious adverse events (SAEs) during the studies. The fatal SAEs occurring in 2 or more patients included hemorrhage (6), cardiac or cardiovascular events (3), sudden death (3), colonic perforation (2) and hepatic failure (2). The remainder of the fatal SAEs included infection and renal failure or were unknown. The details of these SAEs are listed in Table 27.

Table 27: Fatal SAEs Reported in the Three RCC Clinical Studies of Pazopanib

Study ID	Patient ID	SAE(s)	*Reviewer's Comments*
VEG102616	40	Large intestine perforation	
VEG102616	233	Hepatic failure	
VEG102616	228	Dyspnea	*Uncertain of the cause per the narrative*
VEG102616	648	Renal failure acute	
VEG102616	365	Thrombocytopenia, Subdural hemorrhage	
VEG102616	318	Fatigue, Dyspnea	*(uncharacterized)*
VEG105192	160	Rectal hemorrhage with hepatic function abnormal	*Hepatic dysfunction might not have contributed significantly to the death. It would be clearer if there was information on coagulation parameters at the time of death.*
VEG105192	912	Hepatic function abnormal	
VEG105192	463	Cardiac failure	*Acute cardiovascular event not ruled out.*
VEG105192	571	Pleural effusion	*Died* (b) (6)*, but pleural effusion resolved on 07/16/07 per the narrative*
VEG105192	830	Dyspnea	*Sudden death with sudden dyspnea*
VEG105192	170	Hemoptysis	
VEG105192	1075	Bronchopneumonia	
VEG105192	444	Hemoptysis	
VEG105192	398	Peritonitis	
VEG105192	77	Ischemic stroke	

VEG105192	705	Myocardial ischemia	
VEG105192	954	Gastric hemorrhage	
VEG107769	117	Sudden death	
VEG107769	114	Sudden death	*(3 days after the last dose, found dead in AM)*
VEG107769	92	Upper gastrointestinal hemorrhage	

The most commonly reported adverse events with a frequency of >20% and the most commonly detected laboratory abnormalities are listed in Table 28. These included diarrhea (55%), hypertension (41%), hair color changes (40%), nausea (32%), fatigue (29%), anorexia (24%), and vomiting (20%). Most of these events were Grade 1-2, but grade 3 events included hypertension (6%), diarrhea (4%), and fatigue (4%). The common laboratory abnormalities, as listed, were increases in ALT, AST and serum glucose. Although approximately 50% of patients in the pooled analysis were from the key study, there seem to be no important differences between the pooled analysis results and the safety results of the key study. This suggests that the pazopanib's safety profile, as determined by the key study, is representative of its safety profile in patients with advanced RCC.

Table 28: Adverse Events or Laboratory Abnormalities in ≥20% of Patients in the RCC Studies (A Pooled Exploratory Analysis)

Clinical Parameter	**Pazopanib N=593**		
	All Grades	**Grade 3**	**Grade 4**
Adverse Event			
Diarrhea	55%	4%	<1%
Hypertension	41%	6%	0
Hair Color Change	40%	<1%	0
Nausea	32%	<1%	0
Fatigue	29%	4%	0
Anorexia	24%	2%	0
Vomiting	21%	2%	<1%
Laboratory Test			
ALT	52%	9%	1%
AST	54%	6%	<1%
Hyperglycemia	48%	2%	0
Bilirubin (total)	36%	2%	<1%
Hypophosphatemia	36%	4%	0
Hyponatremia	35%	6%	<1%
Hypocalcemia	34%	1%	<1%
Increase in Creatinine	29%	0	<1%
Alk Phosphatase Increase	27%	2%	<1%
Hyperkalemia	27%	5%	<1%

7.2 Adequacy of Safety Assessments

As discussed above, the safety data sources appear adequate for registration purposes. To further evaluate the adequacy of the safety assessments, the reviewers considered the design of the key study, the use of a placebo control, the duration of exposure to treatment, measured or monitored clinical safety parameters, and the known toxicities of products in this class. The reviewers paid special attention to any new safety signals revealed in the intended patient population. Based on the safety review findings described below and given the estimated median overall survival for patients with advanced RCC, the reviewers considered the safety assessments to be adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The median duration of exposure of patients to pazopanib in the three RCC studies (N=593) was 7.7 months (range 0.1-38.6). This pooled duration of exposure is similar to that observed in the placebo-controlled study, which is shown in Table 29. However, this controlled study revealed that patients treated with pazopanib had a high incidence of dose delay and reduction when compared to placebo. While the mean dose in the pazopanib arm was reduced from 800 to 700 mg, the median dose remained at 800 mg. This suggests that, although the incidences of dose delay and reduction were high compared to placebo, most patients in the study tolerated the planned dose of pazopanib. This can also be seen by noting that 37% of patients had dose reductions during the study.

Table 29: Extent of Exposure to Pazopanib in VEG105192

	Placebo (N=145)	**Pazopanib (N=290)**
Duration of Exposure (months) Median (range)	3.8 (0.3-22.0)	7.4 (0.3-23.1)
Daily dose (mg) Median (range)	800* (380-832)	800 (217-800)
Mean (SD)	787 (51)	700 (148)
Dose Delay (days)		
Number of Patients **(%)**	14 (10%)	124 (43%)
Median Duration (range)	12 (1-21)	7 (1-137)
Dose Reduction		
Number of Patients **(%)**	9 (6%)	106 (37%)
Median (range)	400 (200-400)	400 (200-600)
Placebo tablets matching the pazopanib tablets		

The demographics of the patients pooled from the three RCC studies are shown in Table 30. The demographics of patients treated with pazopanib in the key study, as shown previously in Table 12, are listed for reference only. The comparison suggests that the pooled RCC population was similar to the pazopanib patient population in the placebo-controlled study.

Table 30 Demographic Information on Patients in the RCC Population Relative to that in VEG105192

	Patients Treated with Pazopanib in the Three RCC Studies N=586*	**Patients in the Pazopanib Arm (VEG105192) N=290**
Age (yrs) Median (Range)	59 (25-85)	59 (28-85)
Sex n (%) Male Female	407 (69%) 179 (31%)	198 (68%) 92 (32%)
Race n (%) White Asian Black/other	489 (83%) 89 (15%) 8 (2%)	252 (87%) 36 (12%) 2 (1%)
* Does not include the 7 patients mentioned in the 120 day safety update who crossed over to VEG107769 after the initial data cut-off for the NDA submission.		

7.2.2 Explorations for Dose Response

There was only one planned dose of pazopanib, administered at 800 mg once daily, in the RCC studies. Although approximately one third of patients had a dose reduction, their safety data is inadequate to fully address whether a reduced dose would result in a reduction in a given toxicity.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to the RCC studies.

7.2.4 Routine Clinical Testing

All patients enrolled in the key study had physical and laboratory examinations at screening, every 3 or 4 weeks, and at study discontinuation. These examinations, as shown in the Study Procedures (Table 9) provided sufficient information to assess what tests were needed for safe use of pazopanib after marketing. With the safety results obtained from the key study and the pooled RCC studies, the

reviewers found that it is important to monitor blood pressure, ECG, hepatic function tests, thyroid function, and any clinical symptoms that may suggest thrombosis, visceral perforation or bleeding while pazopanib is used.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific metabolic parameters were monitored in the studies in support of the proposed indication as there was no evidence in the early clinical studies suggesting specific metabolic changes. No PK studies of drug interaction were performed in the studies involving patients with RCC. However, no clinical safety information revealed specific drug-drug interaction with pazopanib in the RCC studies. The applicant did conduct studies evaluating the effect of pazopanib on CYP probe substrates and the effect of CYP3A4 inducers and inhibitors on pazopanib. Details can be found in the clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events of Similar Drugs in Drug Class

Life-threatening adverse reactions associated with the use of anti-VEGF or anti-VEGFR products include hemorrhage, arterial and venous thrombosis, gastrointestinal perforation, decreases in LVEF, prolonged QT intervals and torsade de pointes. Therefore, special attention was paid to those adverse reactions and their association with pazopanib. Table 31 shows the incidence of some of these adverse events in the RCC program. Since the information was pooled, their attribution to pazopanib may be difficult to determine. However, the results from the placebo-controlled study as shown in the next section suggest the possible relationship of these events to pazopanib.

Table 31: Important Life-Threatening Adverse Events in the RCC Studies

Adverse Event n (%)	**Pazopanib N=593**	
Grade	**≥ Grade 3**	**Deaths***
Hemorrhage	14 (2%)	6 (1%)
Arterial Thrombotic Events	14 (2%)	3 (<1%)
Perforation/Fistula	5 (1%)	2 (<1%)
Torsade de Pointes	2 (<1%)	0

*Deaths related to the adverse events listed.
Note that two deaths associated with hepatic failure were identified as well. Taken together, the estimated rate of deaths associated with these life-threatening events is approximately 2.2% in the RCC studies of pazopanib.

` ***Reviewer's Comments***

The exposure information based on the placebo-controlled study and the pooled RCC studies seems adequate for the intended population. This is consistent with what has been observed with other TKIs that have been approved for the treatment of advanced RCC [see Drugs@FDA]. The occurrence of the important, life-threatening adverse events recognized in other anti-VEGF products in the RCC studies of pazopanib suggests that these products share a similar adverse reaction profile. The estimated rate of death related to these events and to hepatotoxicity (discussed in Section 7.3.3) is about 2.2% for pazopanib. Therefore, warnings concerning these serious risks must be communicated effectively to both patients and heath care providers who consider using pazopanib.

7.3 Major Safety Results

The results described in this section were basically based on the datasets of the randomized placebo-controlled study VEG105192. For the review of significant adverse events, information from the two other RCC studies was also used as appropriate for better understanding of pazopanib's safety profile. The 120-day safety update datasets were used for the analyses of adverse events, deaths, and laboratory abnormalities. All randomized patients received at least one dose of study drug or placebo and thus all were included in the analyses described below.

7.3.1 Deaths and Serious Adverse Events

Based on the 120-day safety update, there were 223 patient deaths reported as of January 9, 2009. As shown in Table 32, the majority of patients died of disease progression. The number of patients who died of other causes was similar between the arms, about 7% each. The causes of death, other than disease progression, are listed in Table 33. The identification number of patients who died due to fatal SAEs is bolded. Since some of the deaths occurred > 28 days after treatment discontinuation, these are not equal to the number of the deaths due to a serious adverse reactions, which are listed in Table 34. Although the percentages of SAEs in the two arms appear similar, disease entities related to the fatal SAEs, as shown in Table 33, are noticeably different. Fatal SAEs in the pazopanib arm were due to bleeding (4), cardiac/cardiovascular events (3), hepatic failure (1), and gastrointestinal perforation (1).

The four patients (one in the placebo and three in the pazopanib arm) who died within 28 days after the first dose of study treatment were examined closely and no evidence was found to suggest that the cause of the death was associated with an acute toxicity.

Table 32: Deaths in VEG105192

	Placebo N=145	Pazopanib N=290
Death (%)	76 (52%)	147 (51%)
≤28 days from First Dose	1 (<1%)	3 (1%)
≤28 days from Last Dose	13 (9%)	32 (10%)
>28 days from Last Dose	63 (43%)	115 (39%)
Cause of Death		
Disease Progression	66 (46%)	127 (44%)
Cardiovascular	1	5
Sudden Death	2	2
Bleeding	0	4
Hepatic	1	1
Other *	6	8

*included infections, pulmonary edema, gastrointestinal perforation, and unknown or unspecified.
Based on the 120 day update data with incorporation of fatal SAE identified in the AE dataset.

Table 33: Deaths Not Due to Disease Progression (Including Fatal SAEs) in VEG105192

Placebo N=10/145 (7%)			Pazopanib N=20/290 (7%)		
Subject ID	**Category of Death in the Dataset**	**Cause of Death**	**Subject ID**	**Category of Death in the Dataset**	**Cause of Death**
588	Other, specify	Aspiration pneumonia	**160**	Non-Hematologic toxicity	*Rectal Bleeding* (additional hepatic dysfunction)
507	Other, specify	Respiratory insuficiency for progression disease	911	Other, specify	CVA
			912	Non-Hematologic toxicity	*Hepatic failure*
69	Other, specify	Sudden death			
453	Other, specify	*Acute pulmonary edema*	**463**	Non-Haematologic toxicity	*Cardiac failure*
920	Non-Hematologic toxicity		**571**	Other, specify	SAE *(pleural effusion)*
537	Other, specify	*Sudden death*	62	Other, specify	unknown
639	Other, specify	Renal Cell Carcinoma with chronic liver disease.			
850	Other, specify	*Chest infection*			

766	Other, specify	Cardio-respiratory failure due to pulmonary metastatic deposits	**830**	Other, specify	*Sudden death:* patient developed sudden SOB, was taken to the local hospital but died on the way; consider PE, acute MI
91*	*Under disease progression*	*Weakness*			
			170	Other, specify	*Hemoptysis*
			1073	Non-Hematologic toxicity	Unknown
			1075	Non-Hematologic toxicity	*Pneumonia*
			757	Other, specify	Unknown
			152	Other, specify	Gastric cancer
			354	Other, specify	Stroke
			23	Other, specify	Unknown
			398	Other, specify	*Peritonitis secondary to bowel perforation*
			77	Other, specify	*Acute ischemic cerebral stroke*
			300	Other, specify	*Gastric Carcinoma*
			705	Non-Hematologic toxicity	*MI*
			954*	*(under "Disease progression")*	*Gastric hemorrhage*
			444*	*(under Disease progression)*	*Hemoptysis*

*Patients who had a fatal SAE but were not listed under deaths in the 120 day safety update dataset.

Patients with fatal SAE(s) are labeled with underlining and bolding their ID number.

Missing information in the category "other" was filled in by the reviewer based on the information specified in another column of the dataset and is labeled in italic.

Table 34: Overview of Adverse Reactions, Serious Adverse Events in VEG105192

	Placebo (N=145)	Pazopanib (N=290)
All Grade Adverse Events (%)	107 (74%)	271 (93%)
SAEs (%) Fatal (%) Non-Fatal (%)	28 (20%) 4 (3%) 24 (17%)	74 (26%) 13 (4%) 61 (22%)

Reviewer's Comments
Discrepancies were found in the classification of the cause of death in a few patients. Some of the discrepancies are listed in Table 33. In addition, patients with a SAE were found classified as disease progression without mention of the SAE in the death dataset: e.g., patient 386 was categorized as death due to disease progression. However, the hepatic failure associated with or related to pazopanib appeared to be a more important and immediate cause of death in this patient. The reviewers would believe that these discrepancies relate to different understandings of the clinical manifestations of those cases and/or different medical judgment.

7.3.2 Dropouts and/or Discontinuations

Table 35 listed the reasons for discontinuation of study treatment at the time of the data cut-off for the efficacy analyses. The percentage of patients who discontinued due to disease progression was higher in the placebo than in the pazopanib arm. In contrast, more patients in the pazopanib arm discontinued because of adverse events, withdrawal, and other reasons. The primary reason for adverse event-related discontinuations, as shown in Table 36, was an abnormal hepatic function test. The second most common reason was a cardiovascular event.

Table 35: Discontinuation of Treatment in VEG105192

	Placebo N=145	Pazopanib N=290
Treatment Discontinued	**131 (90%)**	**227 (78%)**
Disease Progression	112 (77%)	147 (51%)
Death*	9 (6%)	11 (4%)
Adverse Events	5 (3%)	41 (14%)
Lost to Follow-up	1 (1%)	3 (1%)
Withdrawal	2 (1%)	14 (5%)
Other**	2 (1%)	11 (4%)

*Not including death after disease progression
**Including investigator decision, protocol violation, and noncompliance.

Table 36: Adverse Events Leading to Discontinuation in VEG105192

	Placebo N=145	Pazopanib N=290
Treatment Discontinued due to AEs	**7 (5%)**	**46 (16%)**
Hepatic abnormalities	**1**	11
Cardiovascular events	0	6
Fatigue	1	5
GI disturbance	0	7
Proteinuria	0	3
Hypertension	0	2
Hemorrhage	0	2
Other	5	12

Hepatic abnormalities: increases in ALT, AST, or bilirubin
Cardiac events: myocardial infarction, ischemic cerebral stroke, transient ischemic attack.
GI disturbance: diarrhea, anorexia, vomiting,
Other includes: confusion, infection, hand-foot syndrome, edema, dehydration, anemia, anxiety, convulsion, atrial fibrillation, etc.
Based on the 120-day safety AE dataset.

Table 37 shows the major reasons for dose reductions, which included hypertension, gastrointestinal disturbance, hepatic laboratory abnormalities, fatigue, hematologic toxicities, rash, and proteinuria. Clearly, more patients from the pazopanib arm required does interruption and/or dose reductions as compared to placebo.

Table 37: Dose Interruption and Dose Reductions in VEG105192

	Placebo N=145	Pazopanib N=290
Patients with Dose Interruption	**14 (10%)**	**100 (35%)**
Patients with Dose Reduction	**5 (4%)**	**72 (25%)**
Common Reasons:		
Hypertension	2	20
GI disturbance	0	17
Hepatic abnormalities	1	16
Fatigue	1	10
Hematologic toxicities	0	4
Rash	0	5
Proteinuria	0	5

Patients could have > 1 dose reductions because of the same or different adverse events. Based on the initial exposure dataset.		

Reviewer's Comments
The above information on the reasons for discontinuation and dose reductions strongly suggest that pazopanib's tolerability is linked to hypertension, cardiovascular conditions, constitutional reactions such as fatigue, gastrointestinal reactions, and abnormal hepatic function test results.

7.3.3 Significant Adverse Events

Based on the findings of the above pooled safety analyses from the three RCC studies and the known toxicities of other approved anti-VEGF products used for the treatment of RCC and other malignancies, important adverse events such as hemorrhage, arterial and venous thrombosis and visceral fistula or perforation were investigated vigilantly and compared to placebo in VEG105192. As shown in Table 38, all the listed events except for venous thrombosis occurred more frequently with pazopanib than with placebo. Of these events, all severe and life-threatening events as evidenced by ≥Grade 3 toxicity occurred only with pazopanib, but not with placebo, indicating that pazopanib was likely related to the occurrence of these events. Therefore, these events represent important safety warnings and precautions for pazopanib.

Table 38: Important Adverse Events Observed in VEG105192

Adverse Event	Placebo N=145		Pazopanib N=290	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hemorrhage	8 (6%)	0	32 (11%)	7 (2%)
Myocardial Infarction/Ischemia	0	0	8 (3%)	6 (2%)
Stroke/TIA	0	0	5 (2%)	3 (1%)
Venous Thrombosis*	2 (1%)	1 (<1%)	3 (1%)	2 (1%)
Fistula/Perforation	0	0	3 (1%)	2 (1%)
*Includes vena cava thrombosis, renal vein thrombosis, and splenic vein thrombosis.				

Torsade is another significant adverse event associated with pazopanib. As shown in 7.2.6, there were two cases of torsade observed in the RCC studies. One of the two was from the pazopanib arm of the placebo-controlled study. Torsade was not observed with placebo. The relatively detailed information on this case and the other case from VEG102616 is summarized in Table 39. For the case in VEG105192, the attribution to pazopanib could not be ruled out despite the

alternative explanations provided by the investigator and/or the applicant. Since pazopanib was associated with a prolonged QT interval in some patients in the placebo-controlled study, the reviewers remain concerned that pazopanib may be causally related to torsade de pointes in these pazopanib-treated patients *[see Section 7.4.4 for details concerning QT prolongation]*. Also, it remains unclear whether torsade was involved in the three sudden deaths observed with pazopanib in the RCC studies.

Table 39: Patients with Torsade in the Studies of Pazopanib in RCC

Patient # (Study ID)	Case Description
Subject 804 (VEG105192)	This patient was a 51-year-old female with a history of Grave's disease who had cardiac arrest due to ventricular tachycardia. This occurred after 78 days of treatment with pazopanib 800 mg once daily. The patient developed severe atrial fibrillation one day prior to the cardiac arrest. Because of the atrial fibrillation, pazopanib was interrupted, and a dose of amiodarone and metoprolol were used and the fibrillation/flutter resolved back to sinus rhythm. The ECG obtained one day prior the cardiac arrest indicated a *normal QT/QTc of 338/481 ms, but her post-arrest ECG showed a QT/QTc of 546/581 ms. Both serum potassium and magnesium levels were normal. The patient was resuscitated and was diagnosed with dilated cardiomyopathy with severe systolic dysfunction. The investigator stated that there was a reasonable possibility that the atrial fibrillation and cardiac arrest may have been caused by the investigational product. Later, the investigator no longer considered the atrial fibrillation to be life-threatening, but considered the dilated cardiomyopathy a "consequence of cardiac arrest and electrical discharge".
Subject 644 (VEG102616)	This 66-year-old male patient with a medical history of hypertension and radiation to the left leg developed grade 4 ventricular fibrillation 345 days after the start of pazopanib. The ventricle fibrillation resolved with defibrillation. A cardiology consultation diagnosed *"polymorphic ventricular tachycardia with prolonged QT-torsades de pointes and PVC with couple intervals that initiated polymorphic ventricular tachycardia, possibly caused by pazopanib"*. Other workup results were unremarkable except for the ECHO finding of moderate to severe concentric left ventricular hypertrophy with diastolic dysfunction. One week prior to the ventricular fibrillation, the patient had a bleed in the spine from demyelination (related to hemangioblastoma of the spine per the investigator).

**The narrative did not specify whether that ECG was obtained with uncontrolled atrial fibrillation.*

One distinctive significant adverse reaction revealed in the pazopanib application is hepatotoxicity, the most common adverse reaction of Grade 3 and greater. The review of laboratory abnormalities as shown in Section 7.4.2 indicates that pazopanib was associated with hepatic injury, evidenced by an excess incidence of moderate to marked ALT elevations compared to placebo. As such, deaths related to or associated with hepatic failure or with unresolved hepatic injury at the time of death were also examined carefully in this placebo-controlled study. Four cases of severe or fatal hepatotoxicity were identified in the pazopanib arm, but none in the placebo arm. Key clinical information and the assessment of the information are listed in Table 40. Despite differences in their clinical scenarios, the evidence from the four cases suggests that pazopanib-induced hepatic injury can be severe and life-threatening and that the occurrence of pazopanib-associated fatal hepatotoxicity appears unpredictable.

Table 40: Patients Died with Severe or Unresolved Hepatotoxicity in VEG105192

Study Arm/ Patient ID	Cause of Death (in dataset)	Hepatotoxicity and Severity	Key Confounding Factor(s)	Assessment of the death
Placebo/None				
Pazopanib/ Patient 386*	Disease progression with hepatic failure	Unresolved and severe	Questionable pulmonary infection	Possibly related to pazopanib
Pazopanib/ Patient 912	Rapid disease progression	Unresolved and severe, with diffuse hepatic necrosis on autopsy	Tumor in the liver	The acute clinical course suggests that pazopanib may have contributed to the hepatic failure.
Pazopanib/ Patient 170**	Hemoptysis	Recurrent hepatotoxicity with drug rechallenge; Unresolved and severe	Tumor in the lungs	Unresolved hepatotoxicity probably related to pazopanib Unkown whether this contributed to the hemoptysis
Pazopanib/ Patient 160**	Rectal Bleeding	Resolving hepatotoxicity	Bleeding from other organs, the lungs and esophagus	Resolving hepatotoxicity possibly related to pazopanib Unknown whether this contributed to the bleeding

*Details in Table 41
** Further information in Section 7.5.1

To further illustrate the course of hepatotoxicity, more detailed information from patient 386 is presented in Table 41.

Table 41: Patient Death with Severe Hepatotoxicity in VEG105192

Subject 386 (VEG105192): A 60 year-old male with RCC metastatic to the lungs (no hepatic metastasis) and with normal liver function at baseline started pazopanib on Oct. 19, 2006. He complained of severe nausea and sleepiness on Nov. 14, 2006 and was admitted on (b) (6) with shortness of breath. Physical examination showed hepatosplenomegaly on admission. Pazopanib was discontinued on Nov. 16, 2006 due to an elevation in bilirubin. The patient died on (b) (6) No autopsy was performed. Relevant lab and vital signs are listed below. The patient did not have a history of Gilbert's disease or hyperbilirubinemia. The investigator considered the hepatic injury as possibly related to pazopanib and ascribed the death as due to disease progression in the lungs. GSK concluded that the hepatic injury was related to liver ischemia as a terminal event secondary to respiratory and cardiac compromise.

Date	Oct. 19	Nov 9	Nov 15	Nov 16	Nov 17*
Pazopanib	800 mg once daily			Stopped	Palliative care initiated
Vital sign	T 36.5 BP 106/60 HR 105 RR not/ found (n/f)	T 37.0 BP 128/96 HR 103 RR (n/f)	T (n/a) BP 128/105 HR 126 RR 16 Pox 94% (RA)	T 37.0 BP 110/60 HR 98 RR (n/f) Pox 94% (RA)	Not found (n/f)
T. bilirubin (5-17 uM) **[D bili<10]**	11 n/a	30 n/a	40 **[9]**	n/f	62 **[17]**
ALT (12-41 IU/L)	12	19	15	n/f	1517
Alkaline Phosphate (44-132 IU/L)	141	124	116	n/f	147
Albumin (g/L)	31	29	27	n/f	24
Hemoglobin (g/dL)	11.9	13.7	13.2	n/f	11.9

*AST and LDH were not reported on that day.
The report of the CXR (Nov 15) stated that there were extensive pulmonary metastasis, with signs of edema in the lungs.

FDA Assessment of Subject 386: Attribution of the hepatic injury and death to pazopanib can not be ruled out. The reviewers agree with the investigator's assessment of the hepatotoxicity. No evidence in the medical record shows prolonged hypotension, hypoxia and signs of acute heart failure that could support the possibility of ischemic hepatic injury in this case. The patient had at least one week of hyperbilirubinemia (1.8-2.4 x ULN, > 1.5 x ULN) prior to the onset of severe hepatic injury while continuing pazopanib at 800 mg once daily. This dosing schedule could impose a significant risk of hepatotoxicity to the patient since, as shown in

Section 4.4 of the review, patients with moderate hepatic impairment had a MTD of 200 mg and could develop severe hepatic injury when receiving pazopanib at 400 mg once daily. Therefore, it is possible that the continuation of pazopanib at 800 mg once daily in the face of hepatic impairment elicited the severe hepatic injury in this patient.

(Note this patient was not included in the list of patients with fatal SAEs, but rather in the list of patients who died due to disease progression.)

Tables 42 and 43 provide data from two additional patients from other studies who died with hepatic failure. The case shown in Table 43 occurred in a patient from a study that used daily pazopanib in combination with two doses of topotecan on Days 1 and 15 only. This patient died of fulminant hepatic failure for which the autopsy evidence revealed hepatocellular necrosis, consistent with drug-induced hepatic injury. This evidence strongly implicates the role of pazopanib in this patient's hepatic failure and death.

Table 42: Patient Death with Severe Hepatotoxicity in VEG102616

Subject # (Study)	Brief History	LFT (Day)	Confounding Factors	Investigator's and Applicant's Assessment
Subject 233 (VEG102616)	71 year-old female with **normal hepatic function** and **no liver metastasis** at baseline (KPS 80%) developed hyperbilirubinemia 9 days after pazopanib was initiated. She was hospitalized on day 9 (with BP 120/80 mmHg-HR 80) and pazopanib was discontinued. The patient died on day 13 "*due to hepatic insufficiency with multiorgan failure*". No autopsy was performed.	ALT (< 63 IU/L) 17 (baseline) **24 (day 9)** 1086 (day 12) AST(< 33 IU/L) 48 (baseline) **77 (day 9)** 5796 (day 12) Bilirubin(total <1.2 mg/dl/ direct <0.2 mg/dL) total/direct 0.5/0.1 (baseline) **2.3/0.5 (day 9)** nf /2.5 (day12) Alk Phos (< 94 IU/L) 62 (baseline) **109 (day 9)** 182 (day 12) LDH(< 192 IU/L) 197 (baseline) **1316 (day 9)** 9256 (day 12)	Large tumor at right kidney (97x67); peritoneal carcinomatosis ; pulmonary metastases; Co-med: acetaminophen Morphine UGT1A1 genotype: TA6TA7 (associated with decreased expression of UGT1A1)	There was no reasonable possibility that the hepatic failure and death were related to study drug, but rather to terminal disease progression and liver ischemia.
FDA Assessment of Subject 233: Attribution of the hepatic injury and death to pazopanib can				

not be ruled out given the acute clinical course and the patient's good performance status at the beginning of the study (only 9 days ago). The reviewers agree with the investigator's assessment of the death as due to hepatic insufficiency with multiorgan failure, but consider that the hepatotoxicity may have been related to pazopanib. It is unclear whether the patient may have developed hepatic ischemia since no vital signs were found in her medical records during hospitalization. Therefore, no evidence supports the possibility of ischemic hepatic injury in this case. Compared to the levels of ALT, this patient did have concurrent large magnitude elevations in LDH and AST, suggestive of an involvement of other organs and tumor in the pathological process. Although it is unclear whether the hepatotoxicity, as evidenced by the elevation in ALT, was part of the multiple organ failure, the hyperbilirubinemia (1.9 x ULN, > 1.5 x ULN) prior to the onset of severe hepatic injury suggests that the patient could be at risk given that the half-life of pazopanib of about 31 hours. As shown in Section 4.4 of the review, patients with moderate hepatic impairment had a MTD of 200 mg and could develop severe hepatic injury when receiving pazopanib at 400 mg once daily. Therefore, it is possible that the severe hepatic injury observed in this patient may have been related to pazopanib despite the listed confounding factors.

Table 43: Patient Death with Pazopanib-Related Fulminant Hepatic Failure

Subject 121 (HYT109091): A 37 year-old female with advanced sarcoma who had no hepatic metastasis and normal hepatic function at enrollment received daily pazopanib (800 mg) plus topotecan on days 1 and 15 only. On Day 33, pazopanib was discontinued due to fatigue, anorexia, diarrhea, and transaminase elevations. On Day 36, she was admitted for similar symptoms and was found to have a Grade 4 ALT elevation. On day 40, she died of hepatic failure. Key laboratory and clinical information is listed below. The investigator considered the hepatic failure to be possibly related to study drug, but not to concomitant medicines that included domperidone, oxazepam, loperamide, odansetron, and acetaminophen PRN. Hepatitis serology and other viral test results were negative. An autopsy showed hepatocellular necrosis and the hospital pathologist stated that this was consistent with drug-induced hepatic injury. The sponsor concluded that drug-induced liver injury cannot be ruled out in this case, but proposed that the injury may be due to ischemia. There was one recording of BP 115/80, HR 113 and Pox 99% **5 days after study initiation.** The vital signs during hospitalization are shown below.

Date	Day 1	Day 15	Day 33	Day 36	Day 37	Day 39*
Vital signs	n/f	n/f	T (n/f) BP 105/78 HR 109 RR (n/f) Pox 99%	n/f	T 37.5 BP 95/65 HR 103 RR (n/f) Pox 100% (O2 1L/min))	n/f
ALT (0-35 IU/L)	20	28	92	1934	2552	2800
T. bilirubin (3-21 μM)	11	9	16	n/f	43	43
Alkaline Phosphate (0-120 IU/L)	54	57	62	84	91	86
Creatinine (50-105 μM)	73	62	87	128	143	200

Acetaminophen (mg/L)	n/f	10.9	8.2	n/f	n/f	n/f
*On Day 39, PT was 47.9 (normal 11.5-14.5) and PTT 61 (normal 29-39)						
FDA Assessment of Subject 121: The hepatic injury and death were considered probably related to pazopanib and this is supported by the pathological evidence. This assessment is consistent with the applicant's assessment. The attribution of hepatic failure to topotecan was considered unlikely because the last dose of topotecan was 18 days prior to the onset of hepatic laboratory abnormalities. The attribution of the hepatic failure to acetaminophen was considered unlikely because the serum acetaminophen levels were very low (A level below 15 mg/L at any time within 24 hours after ingestion is very unlikely to be associated with hepatotoxicity, Harrison's Principles of Internal Medicine, 16th Edition, 2005). Further, the vital signs in this case, as listed above, do not show any sign of prolonged hypotension or hypoxia to support the possibility of ischemic hepatic injury. Thus, this case demonstrates that pazopanib-induced hepatotoxicity can be fatal in some patients.						

Reviewer's Comments
The significant adverse events above outline the major risks associated with pazopanib in patients with RCC. These adverse events appear to be similar to those found with other anti-VEGF products (see drugs@fda for sunitinib, sorafenib, and bevacizumab), but differences do exist among the products. For example, severe and fatal hepatotoxicity was found with pazopanib, but was not found with these other agents in the premarketing setting. There were other risk factors or confounding factors involved in the events described (e.g., underlying atherosclerosis). However, it is unknown if those factors would be sufficient to elicit the adverse events in the absence of pazopanib. It is possible that pazopanib interacts with another factor or that pazopanib itself precipitated these occurrences. Since the study excluded patients with a variety of comorbid medical conditions, the safety of pazopanib in patients who have had such a history (e.g., bleeding or cardiovascular events) within the previous 6 months remains unknown. Pazopanib should only be used in those patients after a careful evaluation of the risk-to-benefit in the individual.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly observed adverse events with an incidence rate of 10% or more in the pazopanib arm, regardless of causality, are shown in Table 44. Compared to placebo, the incidences of all the listed events, except for asthenia,

are much higher with pazopanib. This is suggestive of a causal relationship to pazopanib.

Table 44: Common Adverse Events (>10%) Observed with Pazopanib in VEG105192

Adverse Event	Placebo N=145		Pazopanib N=290	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Diarrhea	13 (9%)	1 (<1%)	152 (52%)	13 (5%)
Hypertension	16 (11%)	1 (<1%)	116 (40%)	14 (5%)
Hair Color Change	5 (3%)	0	109 (38%)	1 (<1%)
Nausea/Vomiting	23 (16%)	3 (2%)	104 (36%)	8 (3%)
Abdominal Pain/Discomfort*	12 (9%)	2 (1%)	63 (21%)	9 (3%)
Fatigue	13 (9%)	4 (2%)	57 (20%)	7 (2%)
Asthenia	12 (9%)	1 (<1%)	35 (12%)	8 (3%)
Rash	7(5%)	0	30 (10%)	1(<1%)
Proteinuria	0	0	29 (10%)	6 (2%)

* Contained the terms abdominal pain, abdominal distension, abdominal discomfort
Note that adverse events related to laboratory abnormalities are not included in the above tabulation.

Adverse events with a frequency of ≥5% but <10% are shown in Table 45. Compared to placebo, several events such as dysguesia, chest pain, and hand-foot syndrome also appeared more frequently with pazopanib. Events with similar incidence rates between the arms included cough, constipation, dyspnea, and pyrexia. These likely represent nonspecific adverse events or adverse events related to the underlying disease.

Table 45: Common Important Adverse Events (≥5%-10%) Observed with Pazopanib in VEG105192

Adverse Event	Placebo N=145		Pazopanib N=290	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Weight Loss	5 (3%)	1 (<1%)	28 (10%)	2 (1%)
Dysguesia	1 (<1%)	0	25 (8%)	0
Alopecia	1 (<1%)	0	24 (8%)	0

Adverse Event	Placebo N=145		Pazopanib N=290	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Cough	15 (10%)	0	23 (7%)	0
Constipation	9 (6%)	0	19 (7%)	1 (<1%)
Dyspnea	10 (7%)	1 (<1%)	18 (6%)	5 (2%)
Chest Pain	2 (1%)	0	18 (6%)	0
Hand-Foot Syndrome	1 (<1%)	0	16 (5%)	2 (1%)
Pyrexia	10 (7%)	0	15(5%)	0

7.4.2 Laboratory Findings

The common laboratory abnormalities during study were examined and the major findings are shown in Table 46. The remarkable laboratory difference between the two arms was in the frequency of Grade 3/4 elevations in ALT/AST, 14% in the pazopanib arm compared to 1% with placebo. As such, hepatic laboratory abnormalities were further examined and the results are shown in Table 47. ALT, which is more specific than AST for reflecting hepatocellular injury, was elevated more frequently with pazopanib than with placebo. The rate of ≥ Grade 2 ALT elevation, defined as > 2.5xULN, was 23% in the pazopanib arm compared to 3% in the placebo arm while the rate of ≥ Grade 3 ALT elevation (defined as > 5.0xULN) was 12% in the pazopanib arm versus <1% in the placebo arm. Similarly, elevations in total bilirubin were seen more commonly in the pazopanib arm than in the placebo arm, but appeared primarily as Grade 1-2 abnormalities.

Table 46: Commonly Detected Laboratory Abnormalities in VEG105192

Test	Placebo N=145			Pazopanib N=290		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
ALT/AST	47 (32%)	2 (1%)	0	195 (67%)	36 (12%)	5 (2%)
Hyponatremia	43 (30%)	8 (4%)	0	105 (36%)	14 (5%)	4 (2%)
Hypophosphatemia	24 (16%)	2 (1%)	0	103 (36%)	13 (5%)	0
Hypomagnesemia	37 (25%)	0	0	88 (30%)	2 (1%)	4 (2%)
Hypoglycemia	4 (3%)	0	0	49 (17%)	0	1 (<1%)
Anemia	88 (26%)	2 (1%)	1 (<1%)	156 (55%)	5 (2%)	2 (1%)
Neutropenia	13 (9%)	0	0	105 (36%)	4 (2%)	1 (<1%)
Thrombocytopenia	13 (9%)	0	1 (<1%)	103 (35%)	4 (2%)	1 (<1%)

Table 47: Abnormalities in Hepatic Laboratory Tests in VEG105192

Test	Placebo N=145					Pazopanib N=290				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
ALT	37 (26%)	32 (22%)	3 (2%)	1 (1%)	0	172 (59%)	107 (37%)	29 (10%)	31 (11%)	5 (2%)
AST	31 (22%)	26 (18%)	4 (2%)	1 (1%)	0	168 (58%)	118 (41%)	27 (9%)	21 (7%)	2 (1%)
Bilirubin (total)	20 (14%)	13 (9%)	4 (2%)	2 (1%)	1 (1%)	108 (37%)	60 (20%)	39 (13%)	7 (2%)	2 (1%)
ALT elevations > 3xULN: 3% with placebo vs. 19% with pazopanib										

Since many patients had tumor involvement of the liver, association of the frequent ALT elevations with tumor metastases was investigated. As shown in Table 48, the high incidence of ALT elevation in the pazopanib arm does not appear to be related to the presence or absence of hepatic metastases.

Table 48: Differences in ALT and Bilirubin between Patients with and without Hepatic Metastases in the Pazopanib Arm of VEG105192

Test	Pazopanib N=290									
	Patients with Hepatic Lesions* N=93					Patients without Hepatic Lesions** N=197				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
ALT	50 (54%)	34 (37%)	9 (10%)	5 (5%)	2 (2%)	122 (62%)	73 (37%)	20 (10%)	26 (13%)	3 (2%)
Bilirubin (total)	41 (44%)	26 (28%)	11 (12%)	3 (3%)	1 (1%)	67 (37%)	34 (17%)	28 (14%)	4 (2%)	1 (1%)

Based on the independent review of RCC lesions.
*Patients with any hepatic lesions (target, non-target, and new lesions) during study
**Including Subject 440 whose lesions were not documented in the independent review. The subject's baseline scans did not meet the protocol requirements.

Furthermore, Table 49 shows that the majority of these Grade 3 and 4 ALT elevations were found to be reversible with either dose modifications (interruption and/or dose reduction) or treatment continuation with no dose modifications. However, two patients did have an irreversible ALT abnormality and died with hepatic failure (*see Section 7.3.3*) in the key study. This evidence indicates that hepatic injury occurs in approximately 10% of the patients treated with pazopanib and that the injury can be irreversible and fatal in some patients.

Table 49: Outcome of the Grade 3 or 4 ALT abnormalities in VEG105192

Parameter	**Grade 3/4 ALT N=36 of 290 on Pazopanib**
Timing of Occurrence	
≤6 weeks after treatment initiation	72%
>6 weeks after treatment initiation	28%
Dose Modification	
Interruption	55%
Reduction	55%
Neither	39%
Discontinuation	19%
Recovery (Grade 0-2)	92%
Deaths Associated with Hepatic Insufficiency	2 patients

Reviewer's Comments

Because of the excess and marked ALT elevations in the pazopanib arm compared to placebo, the reviewers were motivated to compare the incidence of abnormalities in ALT and bilirubin in the key studies supporting the three TKIs for the treatment of RCC. The following table shows that in a premarketing setting, pazopanib appears to have the highest incidence rate of Grade 3/4 ALT abnormalities. Both pazopanib and sunitinib had higher incidences of bilirubin elevations compared to their control. Note that the rates shown in the table should not be compared directly to each other because of the inherent problems with cross-study comparisons.

	The Sorafenib Study*		**The Sunitinib Study****		**The Pazopanib Study**	
	Sorafenib N=384	Placebo N=384	Sunitinib N=375	IFNα N=360	Pazopanib N=290	Placebo N=145
ALT						
Any Grade	24%	19%	46%	39%	59%	26%
Grade 3/4	0	<1%	3%	2%	**13%**	**<1%**
Bilirubin						
Any Grade	8%	6%	19%	2%	37%	14%
Grade 3/4	n/f	n/f	1%	0	3%	2%

*Based on the initial medical review of sorafenib for treatment of RCC, accessed through Drugs@fda.
** Based on the review of sunitinib for RCC, accessed through Drugs@fda.

Additional important laboratory findings were thyroid function test abnormalities. Table 50 shows the incidence rates of such abnormalities. More patients in the pazopanib arm had TSH elevations (33% vs. 8%). The percentage of patients who met the criteria for hypothyroidism was 5% with pazopanib compared to <1% with placebo, suggesting that pazopanib was associated with the development of hypothyroidism. Hyperthyroidism also appeared more commonly with pazopanib. Overall, thyroid dysfunction has occurred with pazopanib and periodic monitoring of thyroid function during treatment with pazopanib is therefore needed.

Table 50: Abnormalities in Thyroid Function Test in VEG105192

Thyroid Test (%)	**Placebo (N=145)**	**Pazopanib (N=290)**
Baseline TSH >5 mU/L	14 (10%)	24 (8%)
TSH **>5 mU/L** >5 but ≤10 mU/L >10 mU/L	 12 (8%) 9 (6%) 3 (2%)	 96 (33%) 54 (19%) 42 (14%)
Free T4<LLN and TSH>5 mU/L	1 (<1%)	14 (5%)
Free T4>ULN and TSH<0.3 mU/L	1 (<1%)	6 (2%)

7.4.3 Vital Signs

In the placebo-controlled study, more patients treated with pazopanib when compared to patients receiving placebo, had increases in their blood pressure or decreases in their weight. The differences in these percentages can be seen in Tables 44-45. No important differences were found for heart rate and temperature between the arms.

7.4.4 Electrocardiograms (ECGs)

In VEG105192, ECGs were obtained at Screening, Week 3, Week 12 and every 12 weeks thereafter until the end of study. They were read locally and QTc measurements were calculated using Bazett's formula.

The submitted ECGs have been evaluated by the Interdisciplinary Review Team for QT studies. It was found that the submitted ECG data did not reliably support the applicant's concentration-QTc analysis that showed no exposure-response relationship. Nevertheless, the reviewers found 3 patients in the pazopanib arm

whose QTc was prolonged >500 msec during the study, but none in the placebo arm. In addition, one patient had a QTc of 499.7 msec, as shown in Table 51. The finding of QTc prolongation of >500 mesc only in the pazopanib arm suggests that pazopanib prolongs the QT interval in some patients. Monitoring of ECGs during treatment with pazopanib should be performed. The applicant is currently conducting a dedicated QT study to further evaluate the effect of pazopanib on QT interval.

Table 51: Patients with QTc Prolongation with Pazopanib in VEG105192

Patient ID	Detection Time during Study	QTc Value
VEG105192.0000386	WEEK 3	505
VEG105192.0000999	WEEK 3	503
VEG105192.0000062	WEEK 12	499.7
VEG105192.0000782	WEEK 3	506

7.4.5 Special Safety Studies

Declines in left ventricular ejection fraction (LVEF) have been reported with other tyrosine kinase inhibitors. In VEG105192, LVEF was not monitored during the study since the preclinical and early clinical studies did not suggest that a decline in LVEF was an important safety signal for pazopanib. Recently, changes in LVEF were monitored in a three-arm Phase 2 study (VEG105281) of pazopanib, lapatinib, and pazopanib plus lapatinib in patients with advanced cervical cancer. LVEF was measured at baseline, week 3, and then every 9 weeks. A total of 226 patients were enrolled in the study, and 74 patients received pazopanib monotherapy. With a median treatment exposure of 2.9 months (0.2-15.3) in the 74 patients, no patients had a LVEF <40%. However, one patient had a 10% decrease in LVEF to a level below the institute lower limit of normal. One additional patient had a decline from baseline LVEF of 55% to 45% and pazopanib was discontinued by the investigator. None of the patients had clinical symptoms suggestive of cardiac insufficiency. These two cases suggested that pazopanib may decrease LVEF in some patients. Clinical monitoring of cardiac dysfunction should be performed with pazopanib.

Reviewer's Comments

The median duration of exposure in this study is much shorter than that in patients from the pazopanib arm of VEG105192. It remains unclear if longer exposure may be associated with a significant risk of decreasing LVEF with pazopanib. The applicant is currently conducting a study (VEG108844) comparing pazopanib with sunitinib in patients with advanced RCC, in which LVEF is being monitored after 3 cycles of treatment and then as clinically indicated. Since sunitinib has been known for its depressive effect on LVEF, it

would serve as a positive control in this study for monitoring changes in LVEF. Therefore, this study will provide valuable safety information between the two drugs. Differences in cardiac and hepatic safety would be important for appropriate clinical use of the two drugs. Therefore, completion of the study should be one of the post-marketing requirements.

7.4.6 Immunogenicity

Pazopanib is a small molecule. Monitoring antibodies against pazopanib is unnecessary.

7.5 Other Safety Explorations

7.5.1 Evaluation of Hepatotoxity in the Monotherapy Population

Given the increased incidence of elevations in ALT and bilirubin with pazopanib and the observed deaths with severe hepatotoxicity and hepatic failure (*see Section 7.3.3*), the presence of Hy's Law cases was investigated in the pazopanib monotherapy population of approximately 1000 patients (*see Section 7.1.1*).

Hy's Law serves as an ominous indicator of the potential for a drug to cause serious and severe hepatic injury. In non-oncologic settings, if 2 or more patients in 1000 meet the criteria for Hy's Law, hepatic failure or death is likely to be seen in at least 2 patients in 10,000. This ratio is not fixed and may vary from drug to drug. Despite that, such estimation has been observed with several non-oncologic drugs that were either withdrawn from marketing or not approved. This included troglitazone, bromfenac, ximelagatran, and dilevalol (*see Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation (drafted in October, 2007, and finalized in July, 2009*).

Hy's Law is defined as a concurrent elevation in ALT > 3xULN and total bilirubin > 2xULN with no evidence of biliary obstruction or of other causes that can reasonably explain the elevation. Alkaline phosphatase should not be substantially elevated (a < 3 xULN elevation can be seen in almost any type of liver disease according to Harrison's Principles of Internal Medicine, 16th edition). Therefore, it is critical to rule out an obstructive basis for the elevated bilirubin and to rule out other causes of hepatic injury (e.g., liver metastases, other drugs or viral hepatitis) in defining a Hy's Law case. Medications which are able to cause an elevation in ALT (hepatic injury) along with a reduction in the synthesis and transportation of bilirubin (injury that interferes with normal liver function) are more likely to be associated with a significant risk of severe hepatotoxicity. After screening the pazopanib monotherapy population, four

cases that met the Hy's Law criteria were identified. As shown in Table 52, all four patients (Patients 152, 170, 386, and 410) were from the RCC studies (N=593), three in VEG105192 and one in VEG107769. All had concurrent elevations of ALT > 3xULN and total bilirubin > 2xULN, but with either normal alkaline phosphatase or a value < 3xULN.

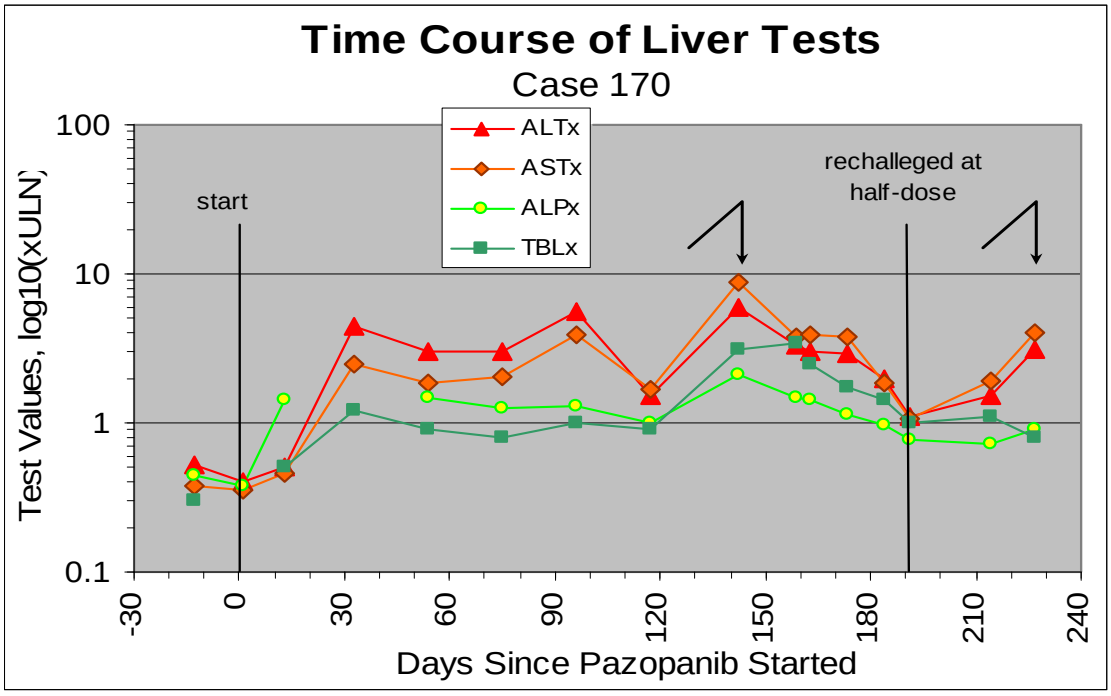
The time course of the hepatic tests in three of the four patients is shown in Figures 5-7. For patient 386, see Table 41 for the changes in ALT and bilirubin. None of the four patients had evidence of other factors that could contribute to the hepatic abnormalities, such as liver metastases. Patient 170 took both acetaminophen as needed (approximately 1600 mg daily) and pazopanib prior to the first elevation in ALT to > 3xULN and total bilirubin to > 2xULN. The ALT and bilirubin abnormalities returned to normal levels after discontinuation of the two drugs. However, hepatocellular injury recurred within a week after the patient was rechallenged with pazopanib (at a 50% dose) in the absence of acetaminophen or other confounding factors. The patient developed icterus (no bilirubin levels were reported after the recurrence of hepatic injury with the rechallenge) and pazopanib was discontinued. Three weeks later, the patient died of hemoptysis. The hepatic toxicity remained unresolved at the time of death. No clinical information was available to verify if the hemoptysis was related to a coagulopathy secondary to the hepatotoxicity. In the other two patients, no confounding factors or reasons other than pazopanib were found to adequately explain the concurrent elevations of ALT and bilirubin. Patient 152 had fractionations of total bilirubin measurements and the results showed that the direct bilirubin to total bilirubin ratios ranged from 44% to 52% for 2 weeks. These high ratios (>30%) strongly suggest that the pazopanib-induced hepatic injury resulted in compromised hepatic function. Further, the patient had a recovery to normal transaminases and bilirubin levels 4 weeks after discontinuation of pazopanib. In contrast, Patient 410 had resolution of the hepatic abnormalities while continuing treatment with no dose modification, suggestive of adaption to pazopanib.

The estimated rate of Hy's Law cases in the pazopanib monotherapy population is about 4 patients per 1000. Because all the patients were found in the RCC studies that had 593 patients, one could also use 593 as a denominator, which would result in an estimated rate of 7 patients per 1000.

Table 52: Patients Meeting the Hy's Law's Criteria in the Pazopanib Monotherapy Population

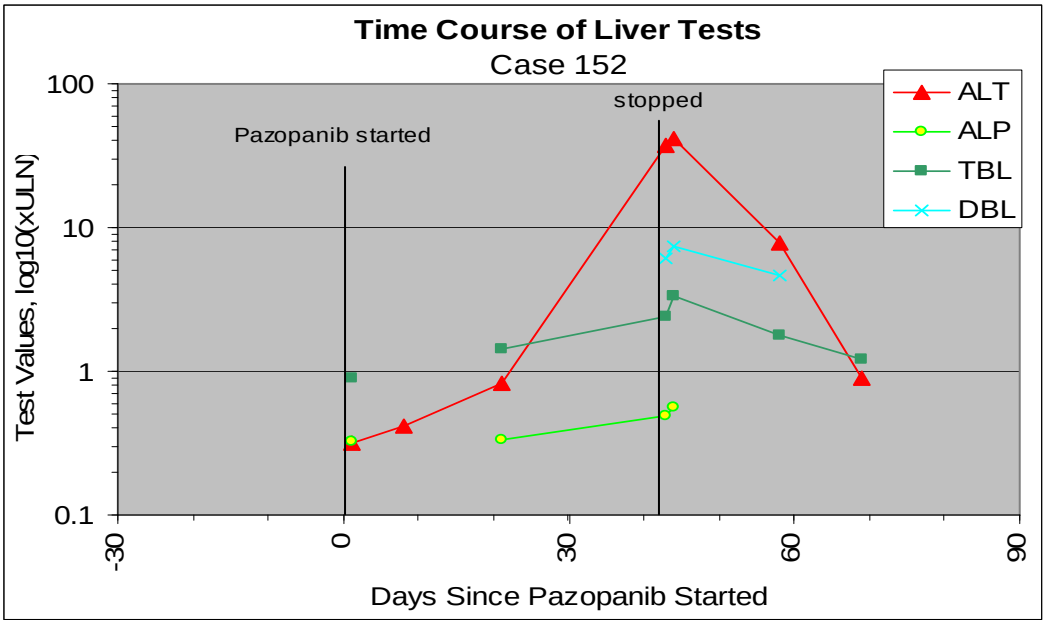
Patient ID	Recovery	Occurrence of Severe Hepatic Injury	Applicant's Assessment	FDA's Assessment
Pt 170 (VEG105192)	No	Death with Hepatic Injury	Included	Probably Related
Pt 386 (VEG105192)	No	Death	Not Excluded	Possibly Related
Pt 410 (VEG105192)	Yes	No (discontinued)	Included	Probably Related
Pt 152 (VEG107769)	Yes	No (adapted)	Included	Probably Related

Figure 5: Time-Course of Hepatic Function Tests in Relation with Pazopanib in Patient 170 from VEG105192



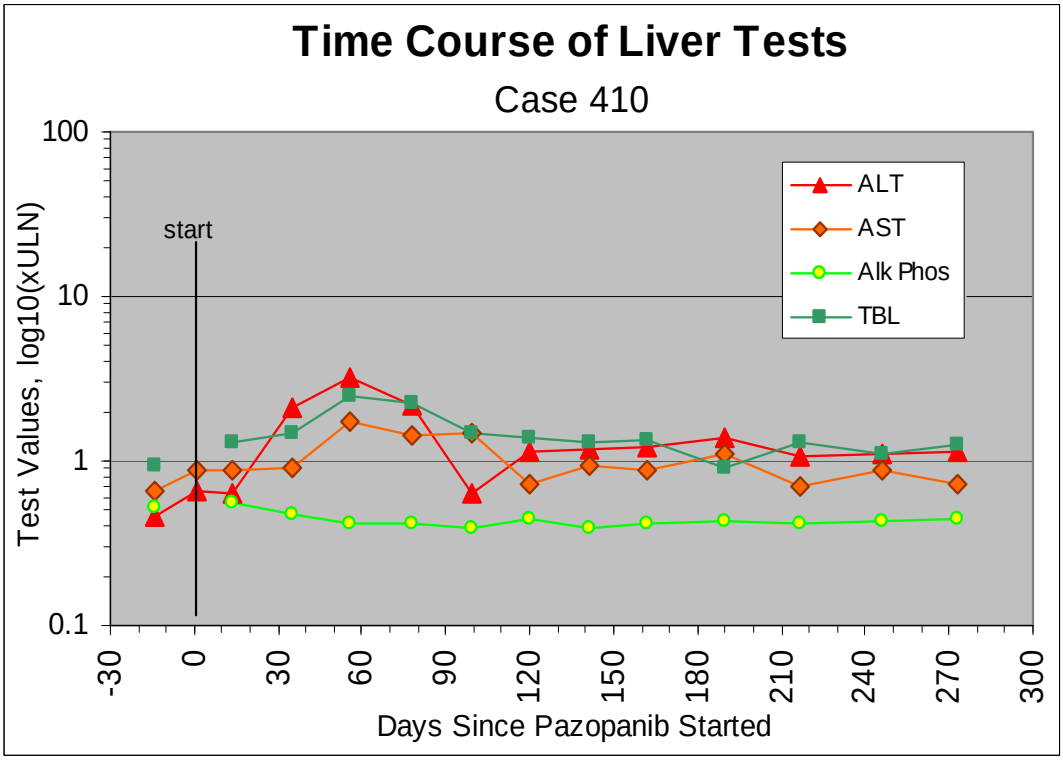
No bilirubin fractionation performed for the total bilirubin in Patient 170

Figure 6: Time-Course of Hepatic Function Tests in Relation with Pazopanib in Patient 152 from VEG105192



DBL shown in the above figure denotes direct bilirubin. The direct bilirubin/total bilirubin ratios at the three time points from the left to right were 51%, 44%, and 52%, respectively.

Figure 7: Time-Course of Hepatic Function Tests in Relation with Pazopanib in Patient 410 from VEG107769



No bilirubin fractionation performed for the total bilirubin in Patient 140

The above estimated rates of Hy's Law case may be underestimated since several possible patients were eliminated due to the presence of a confounding factor such as moderately elevated alkaline phosphatase, a reported history of cholecystitis, or use of acetaminophen or herbs. Such cases are shown in Table 53 to illustrate the difficulty in identifying Hy's Law cases. It is critical to point out that a confounding factor does not necessarily act as an excluding factor. The reviewers considered the confounding factors listed for each case in Table 53 less likely to be responsible for the observed concurrent elevations in ALT and bilirubin. In two cases, patient 160 and patient 618, the concurrent elevations were associated with a direct/total bilirubin ratio of >50%, suggestive of decreased bilirubin excretion or backward leakage of bilirubin secondary to damaged hepatocytes or bile system. Nevertheless, the reviewers excluded them in the above estimation of the rate of Hy's Law cases in the monotherapy population.

Table 53: Potential Hy's Law Cases Excluded with Presence of Confounding Factor(s)

Patient ID	Recovery	Investigator's Causality Assessment and/or Outcome	Major Laboratory Findings	Reason(s) for Elimination in Hy's Law Analysis
Pt 160 (VEG105192)	Recovering	Possibly related to study drug; the patient died with rectal bleeding	ALT 2.8xULN /AST 5.4xULN; total bilirubin 6.7xULN; a direct/total bilirubin ratio of up to 80%; INR up to 1.82	Bone metastases with ALP 7.2x ULN, but no biliary obstruction as evidenced by an ultrasound. While ALT normalized with AST 2.7xULN, ALP 5.4xULN. Hepatitis C RNA negative but with a positive test (titer 2.2, normal <1.0) for HVC antibody.
Pt 618 (VEG102616)	Yes	Possibly related to both study drug and herbs, confirmed by an independent reviewer	ALT 4.2xULN /AST 2.2xULN; total bilirubin 2.2xULN; a direct/total bilirubin ratio of up to 63%; normal ALP levels	Concurrent with the use of herbs
Pt 321 (VEG105192)	Yes	Not assessed	ALT 3.7xULN; total bilirubin 2.5xULN; no direct bilirubin level; normal ALP levels	A reported history of cholecystitis in the CRF
Pt 412 (VEG105192)	Yes	Adapted with 50% dose	**At baseline:** Normal hepatic laboratory results;	One tumor lesion of 1.5 mm in the liver at baseline and week 6 assessments; concurrent use of acetaminophen after the hepatic

		reduction after the Grade 3 hepatic laboratory abnormalities	**At week 9:** ALT 6xULN; total bilirubin 8.2xULN; no direct bilirubin level; ALP 3.7 x ULN **At week 12:** ALT x 3.7 ULN; total bilirubin 2.0x ULN; no direct bilirubin level; ALP 2.2xULN; After week 12 to week 18 and discontinuation : basically normalized	laboratory abnormalities occurred

Reviewer's Comments

The evidence shown in this section demonstrates that pazopanib-induced hepatic injury can fulfill Hy's Law criteria and can compromise hepatic function as reflected by a ratio of direct bilirubin to total bilirubin above 40%. This further attests that pazopanib-related excess and marked elevations in ALT and AST are not simple hepatic leaks of transaminases, but may have severe functional consequences in some patients. Together with the evidence of fatal hepatotoxicity as described in Section 7.3.3, these Hy's Law cases may predict a significant risk of severe hepatic injury with pazopanib [according to the Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation (drafted in October, 2007, and finalized in July, 2009)].

7.5.2 Time Dependency for Adverse Events

The evidence shown in Section 7.4.2 suggests that majority of marked ALT elevations occurred within 6 weeks after the initiation of pazopanib in the placebo-controlled study. Differences in the incidence of all-grade ALT abnormalities were examined against different treatment periods in all the patients from the three RCC studies. As shown in Table 54, ALT elevations appeared in 40% of the patients within the first 6 weeks. Having considered the overall ALT elevation rate of 52% (*shown in Table 28*) in this population, one can extrapolate that the majority of patients with ALT elevations had the problem detected within the first 1-2 months following treatment. The incidence of ALT elevations remained similar within the first 24 weeks (close to 6 months), but came down after 24 weeks, suggesting that patients might have developed adaptation to the treatment with time. This is likely as the liver is a very regenerative organ. Of the common adverse events, hypertension also appeared within the first 24 weeks of treatment.

Table 54: Rates of Elevations in ALT and Bilirubin with Time in the RCC Studies

Adverse Event	Pazopanib N=593		
	<6 weeks	>6-24 weeks	>24 weeks
ALT	231/572 (40%)	230/511 (45%)	99/331 (30%)
Bilirubin	131/572 (23%)	152/511 (30%)	87/331 (26%)
Not including patients with unscheduled visit All the analyses excluded the information at baseline and Day 1 Scheduled laboratory tests varied with studies			

7.5.3 Drug-Demographic Interactions

Differences in overall adverse reactions with respect to age, gender, and region were explored in the RCC patient population. The results are shown in Tables 55-57. Selected common adverse reactions or events listed in the tables were examined. Table 55 shows that patients with advanced age, compared to younger patients, had a higher incidence of severe adverse events. However, of the three common adverse events only fatigue was elevated in the older age group.

Table 55: Exploratory Safety Analyses by Age Groups

	Pazopanib N=593			
	Age <65 (N=392)		Age ≥65 (N=201)	
Any Adverse Events	373 (95%)		191 (95%)	
Serious Adverse Events	100 (26%)		72 (36%)	
Adverse Event	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	224 (57%)	17 (4%)	102 (50%)	7 (3%)
Hypertension	162 (41%)	26 (7%)	83 (41%)	12 (6%)
Fatigue	103 (26%)	11 (3%)	69 (34%)	10 (5%)
Laboratory Test				
ALT	218 (56%)	32 (8%)	118 (58%)	31 (15%)
Bilirubin	135 (34%)	7 (2%)	80 (40%)	7 (3%)
Excluding adverse events and abnormalities at baseline or screening				

Table 56 shows that the safety profiles between male and female patients were comparable with a slight increase in all adverse events and in severe events in female patients. Note that males were more likely to have an elevation in bilirubin than female patients.

Table 56: Exploratory Safety Analyses by Gender

	Pazopanib N=593			
	Male Patients (N=414)		Female Patients (N=179)	
Any Adverse Events	391 (94%)		173 (97%)	
Serious Adverse Events	115 (28%)		57 (32%)	
Adverse Event	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	235 (57%)	15 (4%)	91 (51%)	9 (5%)
Hypertension	170 (41%)	25 (6%)	75 (42%)	13 (7%)
Fatigue	114 (28%)	14 (3%)	58 (32%)	7 (4%)
Laboratory Test				
ALT	234 (56%)	42 (10%)	105 (58%)	22 (12%)
Bilirubin	164 (40%)	10 (2%)	51 (28%)	4 (2%)
Excluding adverse events and abnormalities at baseline or screening				

The analyses shown in Table 57 were intended to investigate whether the safety profile in the 63 patients enrolled from the USA was similar to that of patients enrolled outside the USA. Although the overall AE and SAE rates as well as the rate of ALT abnormalities were similar between the two groups, the US patients seemed to have higher incidences of all-grade diarrhea and fatigue relative the non-US patients. Also, the rate of Grade 3 hypertension was higher in the US patients while grade 1-4 hypertension was similar between the two groups. It is unclear whether these differences are representative of patients from the United States. Regardless, the small sample size of the US patient population in the RCC studies limits the interpretation of the exploratory results as shown in Table 57.

Table 57: Exploratory Safety Analyses between Patients from the USA and Other

	Pazopanib N=593			
	Patients from the USA (N=63)		Patients from Other Countries (N=530)	
Any Adverse Events	63 (100%)		501 (95%)	
Serious Adverse Events	19 (30%)		153 (29%)	
Adverse Event	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	49 (78%)	1 (2%)	277 (52%)	23 (4%)
Hypertension	29 (46%)	11 (17%)	216 (40%)	27 (5%)
Fatigue	45 (71%)	3 (5%)	127 (24%)	18 (3%)

Laboratory Test				
ALT	38 (60%)	10 (16%)	298 (56%)	53 (10%)
Bilirubin	14 (22%)	0	201 (38%)	14 (3%)
Excluding adverse events and abnormalities at baseline or screening				

7.5.4 Drug-Disease Interactions

Not implicated with the evidence available.

7.5.5 Drug-Drug Interactions

Not planned in the RCC studies.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No preclinical data is suggestive of the potential carcinogenicity of pazopanib.

In the placebo controlled study, 4 patients were found to have other cancers, 1 in the placebo arm (unspecified tumor (Grade 3) of the left foot) and 3 in the pazopanib arm (1 with squamous cell carcinoma of the right ear lobe, 2 with gastric cancer). The clinical significance of these observations is unclear. Monitoring for neoplasms such as gastric cancer in a post-marketing setting would be important for further understanding of whether the oral formulation of pazopanib has any association with gastric cancer.

7.6.2 Human Reproduction and Pregnancy Data

No reports of pregnancy were found in the clinical studies of pazopanib.

7.6.3 Pediatrics and Effect on Growth

Not applicable for the NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses were reported in the studies. However, the safety information from the Phase 1 study VEG10003 may help understand the toxicities associated with doses higher than the recommended dose of 800 mg once daily. In that study, 3 patients in each cohort of 1000 mg, 1400 mg, or 2000 mg received treatment for at least 3 weeks. Two of the nine patients developed a Grade 3 adverse event: one in the 2000 mg cohort had Grade 3 fatigue and the

other in the 1000 mg cohort had Grade 3 hypertension along with Grade 2 bradycardia (the patient was on concurrent atenolol). Both resolved with discontinuation or dose reduction.

The drug has no potential for being abused in the population intended.

8 Postmarketing Experience

None

9 Appendices

9.1 Literature Review/References

1 Brugarolas J. Renal-cell carcinoma — Molecular pathways and therapies. *N Engl. J Med.* 2007; 356:185-7
2 Chung EK and Stadler WM. Vascular endothelial growth factor pathway-Targeted therapy as initial systemic treatment of patients with renal cancer. *Clin. Genitourinary Cancer* 2008; 6: S22-28.
3 Molina AM and Motzer RJ. Current algorithms and prognostic factors in the treatment of metastatic renal cell carcinoma. *Clin. Genitourinary Cancer* 2008; 6: S7-23.
4 Stadler WM. Effective therapy for metastatic renal cell cancer, whither to now. *J. Clin. Oncol.* 2009; 27: 3573-3574.
5 Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 2009; 27: 3584-3590.
6 Kane RC, Farrell AT, Saber H, et al. Sorafenib for the treatment of advanced renal cell carcinoma. *Clin. Cancer Res.* 2006; 12: 7271-8.
7 Rini BI, Halabi S, Rosenberg J, et al. Bevacizumab plus interferon-alpha versus interferon-alpha monotherapy in patients with metastatic renal cell carcinoma: Results of overall survival for CALGB 90206. *J Clin. Oncol.* 2009; 27:18s, abs# 5019.
8 Escudier BJ. Bellmunt J, Negrier S, et al: Final results of the phase III, randomized, double-blind AVOREN trial of first-line bevacizumab (BEV) + interferon-α2a (IFN) in metastatic renal cell carcinoma (mRCC). *J Clin. Oncol.* 2009; 27:15s, abs# 5020.
9 Taran A, Ignatov A, Smith B, et al. Acute hepatic failure following monotherapy with sunitinib for ovarian cancer. *Cancer Chemother Pharmacol* 2009; 63:971–972
10 Mueller EW, Rockey ML, and Rashkin MC. Sunitinib-related fulminant hepatic failure: Case report and review of the literature. *Pharmacotherapy* 2008; 28:1066–1070
11 Weise AM, Liu CY, and Shields AF. Fatal liver failure in a patient on acetaminophen treated with sunitinib malate and levothyroxine. *Ann Pharmacother* 2009; 43:761-6.
12 Schramm C, Schuch G, and Lohse AW. Sorafenib-induced liver failure. *Am J Gastroenterol*. 2008;103:2162-3
13 *Drugs@fda*, medical review of sunitinib or sorafenib.

9.2 Labeling Recommendations

Based on the clinical and statistical reviews, numerous recommendations were made to improve the applicant's initial label in Sections highlights, safety, and efficacy. This was done to assure information accuracy and product safety. A black box warning was added to alert physicians to the risk of severe and fatal hepatic toxicity based on the premarketing clinical data. To show major clinical recommendations effectively, the areas changed in the label or modified with the recommendations are highlighted in yellow as attached on the following pages. Since the label has not been finalized, the changes shown in the attached version may not represent the final label to be associated with approval of the product. In addition, rearrangements of adverse events or reactions were made as appropriate to reflect their clinical importance.

11 Pages Withheld as Draft Labeling b(4)

9.3 Advisory Committee Meeting

This application was referred to the Oncologic Drugs Advisory Committee (ODAC) for review because of the considerable evidence of hepatotoxicity in the premarketing setting and because of its status as a new molecular entity. The overall benefit-to-risk profile of pazopanib was assessed for the use of pazopanib in patients with advanced RCC. The ODAC meeting was held on October 5, 2009. After the presentations from both applicant and FDA review teams, the committee discussed the benefit and risks associated with the drug in the intended patient population. The product background information was summarized to the committee as follows:

The randomized, placebo-controlled Phase 3 trial of pazopanib in advanced RCC showed a 5 month improvement in median PFS (HR 0.46 (0.34-0.62)), without a statistically significant improvement in OS. The safety results showed an excess incidence of hepatotoxicity in addition to the occurrence of important adverse reactions known to VEGF inhibitors, including hypertension, hemorrhage, arterial thromboembolic events, and gastrointestinal perforation. It is also associated with torsade de pointes and a prolonged QTc interval.

The voting question to the committee was "Is the benefit-to-risk profile demonstrated for pazopanib acceptable for the treatment of patients with advanced RCC?" The vote results showed: ***Yes=10, No = 0, Abstain = 0.***

Overall, committee members considered that pazopanib was efficacious but toxic. The committee members noted that the serious toxicity of pazopanib appears comparable to other drugs used for the same indication. The committee members expressed concerns about the potential liver toxicity signal and strongly recommended post-market monitoring of this possible signal if approved.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22465	ORIG-1	GLAXO WELLCOME MANUFACTURING PTE LTD DBA GLAXOSMITHKLINE	VOTRIENT TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANGMIN NING
10/14/2009

VIRGINIA E MAHER
10/15/2009

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-465 **Applicant:** GlaxoSmithKline **Stamp Date:** Dec. 19, 2008

Drug Name: VOTRIENT ®
pazopanib **NDA/BLA Type:** NME

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			x	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: VEG10003 Study Title: A Phase I, Open-Label, Multiple Dose, Dose Escalation Study of GW786034 in Patients with Solid Tumors. Sample Size: 63 Arms: single Location in submission: M5	x			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 VEG105192 A Randomized, Double-blind, Placebo-controlled, Multi-center Phase 3 Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma Indication: adults with advanced renal cell carcinoma --- Supportive Study #1 VEG102616 A Phase II Study of GW786034 Using a Randomized Discontinuation Design in Subjects with Locally Recurrent or Metastatic Clear-Cell Renal Cell Carcinoma Indication: same as the above				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Not clearly stated, a request will be sent. Regardless, the study disease has no important differences in diagnosis, treatment, and prognosis from countries to countries.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Adequate in patients with advanced renal cell carcinoma.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			The sponsor had specified more datasets to be submitted in March 2009.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report			X	May be indicated

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				during review
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Clinical reviewers found that the Integrated Summary of Safety included in the application did not include safety data from all of the pazopanib monotherapy studies. However, these data are important for understanding the overall safety profile of pazopanib in all of patients treated with the drug. This concern was conveyed to the sponsor on Feb 9, 2009. The sponsor responded on Feb 13, 2009 with the proposals to address the concern. After reviewing these proposals, the reviewers had the following comments (as listed in the table below) for the sponsor to consider in preparation of the proposed submission.

Study ID	Number of Patients in the Current ISS Dataset	Number of Patients Reported in the Overview of Pazopanib Clinical Program	Difference in the Number of Patients	Issues To Be Addressed in your Proposed Submission
VEG 20002	138	142	4	Ensure that all patients are included your submission
VEG 105290	0	35	N/A	Include all patients enrolled
VEG 105430	0	36 (41 in your response)	N/A	Include all patients enrolled.
VEG 105281	60	119	59	Ensure that all patients are included in your submission
VEG 107200	0	22	N/A	Include all patients enrolled
VEG 109609	0	6 (15 in your response)	N/A	FDA notes that the study was terminated for reasons unrelated to safety and that no datasets will be submitted. Please submit narratives for

				patient deaths, discontinuations and SAEs.
VEG 109693	0	11	N/A	Include all patients enrolled
Study NCI8063	n/a	(27 in your response)	N/A	FDA reviewers note that data from this study of patients with mild-moderate hepatic dysfunction will be available in July, 2009.

YangMin (Max) Ning, MD, PhD — Mar. 5, 2009

Reviewing Medical Officer — Date
Ellen Maher, MD

Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yang-Min Ning
3/26/2009 04:15:56 PM
MEDICAL OFFICER

Virginia E Maher
3/26/2009 04:49:01 PM
MEDICAL OFFICER