CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-465

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES– TEAM LEADER'S MEMO

NDA /Serial Number:	22-465
Drug Name:	Votrient (Pazopanib, GW786034 – VEGF Tyrosine Kinase Inhibitor)
Applicant:	GlaxoSmithKline
Indication(s):	Treatment of Patients with Locally Advanced and /or Metastatic Renal Cell Carcinoma, anti-angiogenesis
Date(s):	Submission Date: December 19, 2008 PDUFA Date: October 19, 2009 Review Completion Date:
Biometrics Division:	Division of Biometrics V (HFD-711)
Primary Reviewer:	Yu-Ling Chang, Ph.D.
Secondary Reviewer:	Shenghui Tang, Ph.D. Acting Team Leader
Concurring Reviewer:	Rajeshwari Sridhara, Ph.D., Deputy Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Yang-Min Ning, M.D., Ellen Maher, M.D.
Project Manager:	Ms. Kim Robertson
Keywords:	Progression-Free Survival, Overall Survival, Objective Response Rate, Duration of Response, Time to Duration, Subgroup Analysis

The applicant has submitted results from a randomized, double-blind, placebo-controlled, multi-center phase III Study (VEG10592) to evaluate the efficacy and safety of pazopanib (GW786034) compared to placebo in patients with locally advanced and/or metastatic renal cell carcinoma. The primary efficacy endpoint in Study VEG10592 was progression free survival (PFS). The primary PFS efficacy analysis of Study VEG105192 in the ITT population was based on PFS data assessed by the independent review committee (IRC). At the time of data cutoff for the final PFS analysis (23 May 2008), 435 subjects were randomized in a 2:1 ratio: 290 in the pazopanib arm and 145 in the placebo arm. This study was conducted outside of USA. For further details regarding the design, data analyses, and results of this phase 3 study, please refer to the statistical review by Dr. Yu-Ling Chang (September 15, 2009).

The PFS analysis included 148 events (51%) for PFS in the pazopanib arm and 98 events (68%) for PFS in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 9.2 months and 4.2 months respectively. The adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.46 (p-value < 0.0001). The un-adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.44 (p-value < 0.0001).

At the time of PFS analysis, a planed interim analysis for overall survival (OS) included 109 (38%) in pazopanib arm and 67 (46%) deaths in placebo arm. At this time, the estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The adjusted hazard ratio for death in the pazopanib arm, as compared with the placebo arm, was 0.73 (p-value = 0.02), which was not statistically significant at the pre-specified level of 0.004. The final OS survival analysis will be planned when 287 deaths occur. Serious adverse events including hepatotoxicity leading to death were observed in the pazopanib treated arm.

With pazopanib monotherapy, a high incidence of hepatic laboratory abnormalities was associated with four cases that fulfilled Hy's Law (about 0.4%). More importantly, three hepatic deaths related to or associated with pazopanib were also observed in a premarketing setting. These hepatic findings strongly suggest that pazopanib may be associated with a significant risk of severe idiosyncratic hepatic injury if used in a larger patient population after marketing. As such, FDA is concerned about the benefit-to-risk ratio of pazopanib in the intended population of patients. This is particularly true in a setting in which there are other effective products approved for the treatment of advanced renal cell cancer. Please refer to Clinical Review of this application for detailed safety evaluation.

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Yu-Ling Chang) of this application. The inference regarding favorable benefit-risk profile for pazopanib in patients with locally advanced and/or metastatic renal cell carcinoma is deferred to the clinical review team.

This application will be discussed at the Oncology Drugs Advisory Committee meeting on October 5, 2009.

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

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/s/

SHENGHUI TANG
09/16/2009

RAJESHWARI SRIDHARA
09/16/2009

U.S. Department of Health and Human Services
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Table of Contents

1 Executive Summary

1.1 Conclusions and Recommendations

On 19 December 2008, the sponsor submitted an application to evaluate the efficacy and safety of single-agent GW786034 (Pazopanib, Votrient®), a new molecular entity (NME), in patients with locally advanced and/or metastatic renal cell carcinoma. In this application, the sponsor submitted the efficacy and safety data from Study VEG105192, "A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

The primary efficacy endpoint in Study VEG10592 was progression free survival (PFS). The primary PFS efficacy analysis of Study VEG105192 in the ITT population was based on PFS data assessed by the independent review committee (IRC). At the time of data cutoff for the final PFS analysis (23 May 2008), 435 subjects were randomized in a 2:1 ratio: 290 in the pazopanib arm and 145 in the placebo arm. This study was conducted outside of USA. The PFS analysis included 148 events (51%) for PFS in the pazopanib arm and 98 events (68%) for PFS in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 9.2 months and 4.2 months respectively. The adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.46 (p-value < 0.0001). The un-adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.44 (p-value < 0.0001).

At the time of PFS analysis, a planed interim analysis for overall survival (OS) included 109 (38%) in pazopanib arm and 67 (46%) deaths in placebo arm. At this time, the estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The adjusted hazard ratio for death in the pazopanib arm, as compared with the placebo arm, was 0.73 (p-value = 0.02), which was not statistically significant at the pre-specified level of 0.004. The final OS survival analysis will be planned when 287 deaths occur. Serious adverse events including hepatotoxicity leading to death were observed in the pazopanib treated arm.

This application will be discussed at the Oncology Drugs Advisory Committee meeting on October 5, 2009.

1.2 Brief Overview of Clinical Studies

Study VEG105192 was a Phase III, randomized, double-blinded, placebo-controlled multi-center international 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. Patients had to have clear cell or predominantly clear cell RCC histology. 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 established or where systemic cytokine therapy was not recognized as standard care therapy for RCC. Eligible patients were randomized in a 2:1 ratio to receive either blinded continuous treatment with either once daily oral pazopanib tablets at 800 mg, or matching placebo. Treatment continued until patients experienced disease progression, death, or unacceptable toxicity. Efficacy assessment was conducted every 6 weeks up to 24 weeks and then every 8 weeks.

The primary efficacy endpoint in Study VEG 10592 was progression free survival (PFS). The primary PFS efficacy analysis of Study VEG105192 in the ITT population was based on PFS data assessed by the independent review committee (IRC).

1.3 Statistical Issues and Findings

In this application to evaluate the efficacy and safety of pazopanib in patients with locally advanced and/or metastatic renal cell carcinoma, the sponsor submitted efficacy and safety data from Study VEG105192, "A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

Statistical Issues:

1. Study VEG105192 was an international study. None of the subjects in this study was recruited from United States.

2. The planned sample size was to have at least 350 subjects powered for OS with a 2:1 randomization scheme and 287 deaths are required in the final OS analysis with one interim analysis evaluated at 70% of deaths occurred. The actual overall sample size recruited was 435 subjects with 145 subjects in the placebo group and 290 subjects in the pazopanib group. The actual interim analysis of OS was performed with a cut off date of 23 May 2008 when 176 events had occurred (40% of all subjects, or 61% of the events needed for the final analysis). The updated significance level for the interim and final efficacy analyses was 0.004 and 0.0237 determined by using the Lan-DeMets spending function approach with an O'Brien-Fleming boundary.

3. The planned timing of the final PFS analysis was when at least 180 PFS events would occur in the study and at least 90 PFS events would occur

from each of treatment-naïve (1st line) and cytokine-pretreated (2nd line) subgroup as well as at least 160 deaths. Two hundred and forty-six PFS events and 176 deaths occurred in the final PFS analysis. One hundred and thirty PFS events were from the treatment-naïve (1st line) subgroup and 116 PFS events were from the cytokine-pretreated (2nd line) subgroup.

4. Although three stratification factors were planned to use in the stratified log-rank test for the primary analyses, there were only two stratification factors - ECOG performance status and prior systemic therapy for advanced RCC included in the final analyses. The stratification factor, prior nephrectomy, was not incorporated since there were too few subjects who had not had a prior nephrectomy. The sponsor also used the un-stratified log-rank test as a sensitivity analysis to support the primary efficacy analysis.

5. For PFS assessment, the overall agreement between IRC and investigator on PD or censoring was 68.3%.

6. Time from randomization to assessment was calculated. The log-rank test showed that there was no difference between two treatment distributions of time to assessment, except the 2nd assessment. Although the p value in the 2nd assessment was less than 0.05, the median in the 2nd assessment was the same for both arms.

7. At the time of PFS analysis, a planed interim analysis for overall survival (OS) included 109 (38%) in pazopanib arm and 67 (46%) deaths in placebo arm. The estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The hazard ratio for OS was 0.73 (95% CI: 0.53 to 1; p = 0.02), which was not statistically significant (>0.004, the significance level allocated for this interim analysis).

8. The final OS survival analysis will be conducted when 287 deaths occur. However, given the 48% (70 subjects) rate of crossover from placebo to pazopanib in the extension study, longer follow up is unlikely to demonstrate a statistically significant difference in overall survival.

9. Other secondary endpoints were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/ comparisons.

Findings:

The primary efficacy analysis was PFS analysis in the ITT population and the PFS data were assessed by the independent imaging core laboratory. Two hundred forty-six PFS events were independently confirmed. A stratified log-rank test was performed to compare PFS between the pazopanib arm and the placebo arm in the ITT population.

The PFS analysis as of the cut-off date of May 23, 2008 included 148 PFS events in the pazopanib arm and 98 PFS events in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 9.2 months and 4.2 months respectively. The adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.46 (p-value < 0.0001). The un-adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.44 (p-value < 0.0001) (Table 1).

Table 1. Primary Efficacy PFS Analysis in ITT Population

	Pazopanib	**Placebo**
Number of patients (ITT)	290	145
Number of events (%)	148 (51%)	98 (68%)
Median[1] (months), 95% CI	9.2 (7.4, 12.9)	4.2 (2.8, 4.2)
Stratified Log-rank test	P<0.0000001	
Hazard ratio (95% CI)[2]	0.46 (0.34, 0.62)	
Unstratified Log-rank test	P<0.0001	
Unstratified Hazard ratio (95% CI)[2]	0.44 (0.34, 0.58)	

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

At the time of the final PFS analysis, the interim analysis for OS included 109 in the pazopanib arm and 67 deaths in the placebo arm. The estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The adjusted hazard ratio for death in the pazopanib arm, as compared with the placebo arm, was 0.73 (p-value = 0.02), which was not statistically significant (>0.004, the significance level allocated for the OS interim analysis). The final OS survival analysis will be performed when 287 deaths occur.

The difference in overall response rate (CR+PR) between two arms was 26.9% (95% CI: 20.8, 33.0). The median duration of response in pazopanib arm was 58.7 weeks from independent review and 62.4 weeks from investigator review.

Table 2. 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%)
Complete Response (CR) N (%)	0 (0%)	1 (<1%)
Partial Response (PR) N (%)	5 (3%)	87 (30%)
Duration of Response Median (95% CI)	--[1]	58.7 weeks (52.1 - 68.1)
RR in Treatment-Naive Group N (%) (95% CI)	4% (0-8.1%)	32% (24.3%-38.9%)
RR in Cytokine Pretreated Group N (%) (95% CI)	3% (0 -7.1%)	29% (21.2%-36.5%)

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

2 Introduction

2.1 Overview

2.1.1 Background

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 has been developed clinically as an antiangiogenic agent by GlaxoSmithKline (GSK) for the treatment of a variety of malignancies. In this NDA, GSK requested marketing approval of pazopanib for the treatment of advanced renal cell carcinoma (RCC).

The antitumor activity of pazopanib in RCC was observed in the early clinical studies. This prompted the sponsor to conduct a Phase III study, outside the U.S., comparing pazopanib with placebo in patients with advanced RCC. The Phase III study was initiated in April 2006, approximately 4 months after the approvals of sunitinib and sorafenib for the treatment of RCC. The results of this Phase III study constituted the key evidence supporting pazopanib in this NDA.

Since 2005, five targeted products have received FDA approval for the treatment of advanced RCC. Table 3 summarizes these products with their demonstrated efficacy in the key studies supporting their approval.

Table 3. 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 blinded comparison to placebo in patients with advanced RCC after one systemic therapy	PFS	HR: 0.44 (0.35-0.55) Median PFS 167 days with sorafenib vs. 84 days with placebo One interim OS analysis: HR: 0.72 (0.55-0.95) Median OS not available for Sorafenib arm

Sunitinib January, 2006 Accelerated Approval February, 2007 Regular Approval	Two single arm Phase II studies in patients with cytokine-refractory RCC Randomized, double blinded comparison to IFNα in patients with systemic treatment-naive advanced RCC	RR PFS	34.0%, 36.5% HR: 0.42 (0.32-0.54) Median PFS 47 weeks with Sunitinib vs 22 weeks with IFNα OS analysis: HR: 0.65 (0.45-0.94) Median OS not available for Sunitinib arm
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 with Temsirolimus vs 7.3 months with IFNα PFS analysis: HR: 0.66 (0.53-0.81) Median PFS 5.5 months with Temsirolimus vs 3.1 months with IFNα
Everolimus March, 2009 Regular Approval	Randomized, double blinded 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 with Everolimus vs 1.9 months with placebo

			OS analysis: HR: 0.82 (0.58-1.71) Median OS not available for Everolimus arm
Bevacizumab July, 2009 Regular Approval	Randomized, double-blinded 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 with Bevacizumab vs 5.4 months with IFNα alone OS analysis: 0.86 (0.72-01.04) Median OS 23.3 months with Bevacizumab vs 21.3 months with IFNα alone
*All the products received regular approval except for sunitinib, which received accelerated approval in December, 2006 based on RR in a single arm study, followed by the conversion to regular approval in February, 2007 based on a randomized study. PFS: Progression free survival; RR: Response rate; OS: Overall survival			

2.1.2 Statistical Issues

1. Study VEG105192 was an international study. None of the subjects in this study was recruited from United States.

2. The planned sample size was to have at least 350 subjects powered for OS with a 2:1 randomization scheme and 287 deaths are required in the final OS analysis with one interim analysis evaluated at 70% of deaths occurred. The actual overall sample size recruited was 435 subjects with 145 subjects in the placebo group and 290 subjects in the pazopanib group. The actual interim analysis of OS was performed with a cut off date of 23 May 2008 when 176 events had occurred (40% of all subjects, or 61% of the events needed for the final analysis). The updated significance level for the interim and final efficacy analyses was 0.004 and 0.0237 determined by using the Lan-DeMets spending function approach with an O'Brien-Fleming boundary.

3. The planned timing of the final PFS analysis was when at least 180 PFS events would occur in the study and at least 90 PFS events would occur from each of treatment-naïve (1st line) and cytokine-pretreated (2nd line) subgroup as well as at least 160 deaths. Two hundred and forty-six PFS events and 176 deaths occurred in the final PFS analysis. One hundred and thirty PFS events were from the treatment-naïve (1st line) subgroup and 116 PFS events were from the cytokine-pretreated (2nd line) subgroup.

4. Although three stratification factors were planned to use in the stratified log-rank test for the primary analyses, there were only two stratification factors - ECOG performance status and prior systemic therapy for advanced RCC included in the final analyses. The stratification factor, prior nephrectomy, was not incorporated since there were too few subjects who had not had a prior nephrectomy. The sponsor also used the un-stratified log-rank test as a sensitivity analysis to support the primary efficacy analysis.

5. For PFS assessment, the overall agreement between IRC and investigator on PD or censoring was 68.3%.

6. Time from randomization to assessment was calculated. The log-rank test showed that there was no difference between two treatment distributions of time to assessment, except the 2nd assessment. Although the p value in the 2nd assessment was less than 0.05, the median in the 2nd assessment was the same for both arms.

7. At the time of PFS analysis, a planed interim analysis for overall survival (OS) included 109 (38%) in pazopanib arm and 67 (46%) deaths in placebo arm. The estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The hazard ratio for OS was 0.73 (95% CI: 0.53 to 1; p = 0.02), which was not statistically significant (>0.004, the significance level allocated for this interim analysis).

8. The final OS survival analysis will be conducted when 287 deaths occur. However, given the 48% (70 subjects) rate of crossover from placebo to pazopanib in the extension study, longer follow up is unlikely to demonstrate a statistically significant difference in overall survival.

9. Other secondary endpoints were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/ comparisons.

2.2 Data Sources

Data used for review is from the following electronic submissions: the submission No. 0000 received on December 18, 2008 (the network path \\CDSESUB1\EVSPROD\NDA022465\0000).

3 Statistical Evaluation

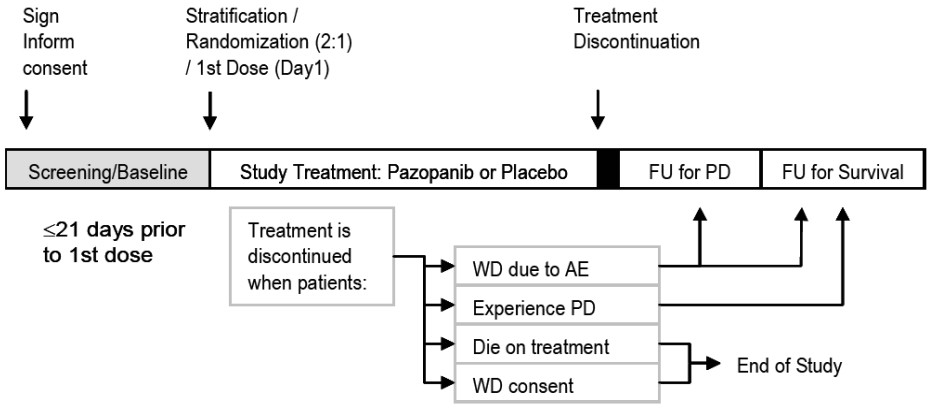
3.1 Evaluation of Efficacy

In this application to evaluate the efficacy and safety of pazopanib in patients with locally advanced and/or metastatic renal cell carcinoma, the sponsor submitted efficacy and safety data from Study VEG105192, "A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

3.1.1 Study Design

Study VEG105192 was a Phase III, randomized, double-blinded, placebo-controlled multi-center international study, conducted at 80 centers in 23 countries/religions. This study was designed to evaluate the efficacy and safety 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. Patients had to have clear cell or predominantly clear cell RCC histology. 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 established or where systemic cytokine therapy was not recognized as standard care therapy for RCC. Eligible Patients were stratified and centrally randomized in a 2:1 ratio to receive blinded continuous treatment with either once daily oral pazopanib tablets at 800 mg, or matching placebo. Treatment continued until patients experienced disease progression, death, or unacceptable toxicity. Efficacy assessment was conducted every 6 weeks up to 24 weeks and then every 8 weeks.

The study consisted of a Screening/Baseline Period, a randomized double-blind Treatment Period and a post-treatment Follow-Up Period. The study design schematic is displayed below:



FU = Follow Up, WD = withdraw, PD = Progressive Disease, AE = Adverse event.
Progression

Figure 1. Study Design
(Source: Figure 1 in sponsor's clinical study report)

The Treatment period began after a patient was randomized and received the first dose of study medication (Day 1). Prior to randomization, eligible patients were stratified with the following stratification factors:
1). ECOG performance status: 0 vs. 1
2). Prior nephrectomy: Yes vs. No
3). Prior systemic therapy for advanced RCC: Treatment naive vs. Cytokine-pretreated

The primary endpoint of this study was PFS, evaluated by the independent review committee (IRC). Overall survival (OS) was the principal secondary endpoint. Other secondary endpoints were to compare ORR, rate of CR + PR + 6-month SD, time to response and response duration between two treatment groups. The differences in PFS between pazopanib- and placebo-treated subjects in the treatment-naïve and cytokine-pretreated subgroups were also evaluated.

Reviewer's Comments:

Study VEG105192 was an international study. None of the subjects in this study was recruited from United States.

3.1.2 Study Objectives

The primary objective of Study VEG105192 was to compare progression free survival (PFS) between the pazopanib and placebo groups in the patients with advanced and/or metastatic RCC.

The principal secondary objective was:

• To compare overall survival (OS) of patients treated with pazopanib to those treated with placebo.

Other secondary objectives were:

• 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 compare the rate of CR + PR + 6-months stable disease (SD) in patients treated with pazopanib to those treated with placebo.

• To compare and estimate time to response and response duration in patients treated with pazopanib to those treated with placebo.

3.1.3 Efficacy Endpoints

Progression free survival (PFS) was defined as the interval between the date of randomization and the earliest date of either disease progression or death due to any cause. In this study, tumor response and progression were evaluated by the independent radiologist using the data from the independent radiological review of imaging scans.

If tumor progression data included more than 1 date, the first date was used. PFS was calculated as (first event date- the date of randomization +1)/7. PFS data was censored on the day following the date of the last on treatment tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment prior to observing objective tumor progression. Patients were also censored if they discontinued for toxicity or had extensive missing visits (12 weeks or more). Patients lacking an evaluation of tumor response after randomization had their event time censored on the date of randomization with a duration of 1 day.

Overall survival (OS) was defined as the time from date of randomization until date of death due to any cause. OS was calculated as (the event date − the date of randomization +1)/7. For patients who were alive, their survival times were

censored at the last date they are known to be alive. Patients lacking data beyond the day of randomization had their survival times censored at the date of randomization with a duration of 1 day. Last date of contact will be defined as the maximum date of any visit date, survival follow-up date, or date of study withdrawal. Patients crossing over to the pazopanib treatment arm were included in the OS analyses.

Overall response rate (ORR) was defined as the percentage of patients, who achieved either a confirmed complete response (CR) or confirmed partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) as their best overall response. The best overall response was defined as the best confirmed response recorded from the start of treatment until disease progression. Subjects who did not demonstrate a confirmed response of CR/PR and progress at or before Week 12 had a best overall response of PD. Subjects who progressed after Week 12 without demonstrating SD of 12 weeks had a best overall response of PD even if there was a disease assessment at or after 12 weeks which was assessed as Unknown (even though the best response could have truly been SD and was not definitively PD).

Rate of CR+PR+6-month SD was defined as the percentage of subjects, who achieved either a confirmed CR or confirmed PR per RECIST criteria as their best overall response or those subjects who have SD after 6 months in the trial. The rate of CR + PR + 6 month SD will be evaluated on the ITT population. Subjects in the ITT population with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage.

Time to response (TTR) was defined as the subset of subjects who achieved a confirmed CR or PR from the date of randomization until the date of first documented evidence of CR or PR (whichever status is recorded first).

Duration of response (DoR) was defined as the subset of subjects who achieved a confirmed CR or PR from the date of first documented evidence of CR or PR until the date of either the first documented sign of PD or death due to any cause. Subjects who have neither died nor progressed will be censored at the date of the last radiologic assessment. If tumor progression data included more than 1 date, the first date was used. Duration of tumor response was calculated as (the end date for DR − first CR or PR that is subsequently confirmed +1)/7. DR data were censored on the day following the date of the last on tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given antitumor treatment other than the study treatment prior to observing objective tumor progression.

3.1.4 Sample Size Considerations

Although the primary endpoint was PFS, the sample size calculation was based on the number of subjects needed for detecting a treatment effect in overall survival. Given one interim analysis planned to occur after approximately 70% of the total deaths, 287 death events were required in the final analysis to detect a 50% improvement in median OS from10 months to 15 months in patients randomized to receive pazopanib with an overall one-sided significance level of 0.025 and the power of 0.90. Applying a 2:1 randomization and an accrual period of over 17.5 months, it was estimated that 350 patients required to be enrolled in order to observe 287 death events by the end of the minimum follow-up period. The nominal significance level for the interim and final efficacy analyses were determined by using the Lan-DeMets spending function approach with an O'Brien-Fleming boundary. The original sample size calculation also allowed at least 90% power to detect an 80% improvement in median PFS (median PFS in placebo group: 3 months) by pazopanib treatment in both the overall study population as well as in each of the treatment-naïve and cytokine-pretreated subgroups. At least 127 PFS events observed from each of the subgroups were required based on the IRC assessment.

However, the clinical cutoff for the final PFS analysis was subsequently modified to require at least 90 PFS events in each of the treatment-naïve and cytokine-pretreated subgroups because of the slow patients recruiting rate and at least 160 deaths from the overall study population for an interim OS analysis at the time of the final PFS analysis. Reducing the number of required PFS events did not substantially affect the overall sample size requirements for the study because the total number of deaths required for the final OS analysis did not change.

Reviewer's Comments:

1. This study was powered for OS with a 2:1 randomization scheme. The planned sample size was to have at least 350 subjects and 287 deaths were required in the final OS analysis with one interim analysis evaluated at 70% of deaths occurred. The actual overall sample size recruited was 435 subjects with 145 subjects in the placebo group and 290 subjects in the pazopanib group. The actual interim analysis of OS was performed with a cut off date of 23 May 2008 when 176 events had occurred (61% of the required number of deaths for the final OS analysis). The updated significance level for the interim and final efficacy analyses were 0.004 and 0.0249 determined by using the Lan-DeMets spending function approach with an O'Brien-Fleming boundary.

2. The planned timing of the final PFS analysis was that at least 180 PFS events would occur in the study and at least 90 PFS events would occur

from each of treatment-naïve (1st line) and cytokine-pretreated (2nd line) subgroup as well as at least 160 deaths. Two hundred and forty-six PFS events and 176 deaths occurred in the final PFS analysis. One hundred and thirty PFS events were from the treatment-naïve (1st line) subgroup and 116 PFS events were from the cytokine-pretreated (2nd line) subgroup. (See the information of Table 4 below).

Table 4. The Number of Events for the Final PFS analysis

	Pazopanib	Placebo	Total	Planned
1st line trt	73	57	130	90
2nd line trt	75	41	116	90
Total	148	98	246	180

3.1.5 Efficacy Analysis Methods

According to the sponsor's statistical analysis plan, the primary efficacy analysis was based on the ITT population which included all randomized subjects and those subjects were analyzed based on the assigned randomized treatment and not based on actual treatment received (or not received). This study would be considered a positive trial if the stratified log-rank test for PFS was significant at a one-sided significance level of 0.025 in favor of pazopanib (Three stratification factors: ECOG performance status: 0 vs. 1; prior nephrectomy: yes vs. no; prior systemic therapy for advanced RCC: treatment naive vs. cytokine-pretreated). Estimates of time-to-event endpoints were obtained using Kaplan-Meier methods and the adjusted hazard ratio was estimated by using a Pike estimator. This reviewer also calculated unadjusted hazard ratio from a Cox proportional hazards model.

Overall Survival (OS) was also analyzed by stratified log-rank test and the estimates of time-to-event endpoints were obtained using Kaplan-Meier methods. All other secondary response endpoints including ORR, the rate of CR + PR + 6 month SD, DR and TTR were calculated from the independent review of best response which records confirmed cases of PR and CR only. The response results evaluated by the investigator's assessment were also calculated and were consistent to the results evaluated by the independent review.

Reviewer's Comments:

1. Although three stratification factors were planned to use in the stratified log-rank test for the primary analyses, there were only two stratification factors - ECOG performance status and prior systemic therapy for advanced RCC included in the final analyses. The stratification factor, prior nephrectomy, was not incorporated since there were too few subjects

who had not had a prior nephrectomy. The sponsor also used the un-stratified log-rank test as a sensitivity analysis to support the primary efficacy analysis.

2. Secondary analyses were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/comparisons in secondary hypothesis tests.

3.1.6 Sponsor's Results and Statistical Reviewer's Findings/ Comments

As of the data cutoff date (23 May 2008) for the final PFS analysis, 435 subjects had been randomized in Study VEG105192; these 435 subjects comprised the ITT population. Among them, 233 of subjects were treatment-naïve and 202 of subjects, who received one prior IL-2 or IFNα-based therapy, were cytokine-pretreated. Two hundred ninety subjects (67%) were randomized to the pazopanib arm, and 145 (33%) were randomized to the placebo arm. The ITT population was the primary population for evaluating all efficacy endpoints as well as subject characteristics.

3.1.6.1 Baseline Characteristics

The baseline Characteristics of the overall population were presented in Table 5.

Table 5. Baseline Characteristics of the Patients in the Study VEG105192

	Placebo (N=145)	Pazopanib (N=290)	Total (N=435)
Age (years)			
Mean (SD)	59.6 (11.04)	59.1 (10.06)	59.3 (10.38)
Median (range)	60.0 (25 to 81)	59.0 (28 to 85)	59.0 (25 to 85)
Age Group n (%)			
<65 years	85 (59)	196 (68)	281 (65)
≥65 years	60 (41)	94 (32)	154 (35)
≥75 years	11 (8)	14 (5)	25 (6)
Sex n (%)			
Female	36 (25)	92 (32)	128 (29)
Male	109 (75)	198 (68)	307 (71)
Race n (%)			
White	122 (84)	252 (87)	374 (86)
Asian	23 (16)	36 (12)	59 (14)
Black	0	1 (<1)	1 (<1)
Other	0	1 (<1)	1 (<1)
Ethnicity n (%)			
Hispanic/Latino	22 (15)	38 (13)	60 (14)
Not Hispanic/Latino	123 (85)	252 (87)	375 (86)

(Source: Table 9 in sponsor's clinical study report)

Reviewer's Comments:

1. In the overall patient population, the baseline characteristics appeared to be balanced between the two treatment arms. Most subjects in the study were white (86%), male (71%). Only one subject was Black and one subject was in Other category.

2. This was an international study. None of the subjects in this study was recruited from United States. The number of subjects for different countries in this study population is shown in Table 4.

Table 6. Subject Number for Different Countries in the Study VEG105192

COUNTRY	treatment group		Total
Frequency	Pazopanib	Placebo	
Argentina	14	11	25
Australia	9	4	13
Austria	9	3	12
Brazil	9	2	11
Chile	13	8	21
China	2	4	6
Czech Republic	11	3	14
Estonia	6	3	9
France	10	12	22
Hong Kong	1	2	3
India	8	5	13
Ireland	1	0	1
Italy	12	4	16
Korea	14	8	22
Latvia	1	1	2
Lithuania	11	8	19
New Zealand	9	3	12
Pakistan	11	4	15
Poland	72	36	108
Russian Federation	22	10	32
Slovakia	14	4	18
UK - CMD	22	6	28
Ukraine	9	4	13
Total	290	145	435

3.1.6.2 Primary Efficacy Analyses

Progression-free Survival Analysis by Independent Review Committee

The primary analysis of PFS was based on blinded imaging assessment by an independent review committee. Two hundred and forty-six PFS events were independently confirmed. A stratified log-rank test was performed to compare PFS between the pazopanib arm and the placebo arm in the ITT population, which included both treatment-naïve and cytokine-pretreated subjects.

The PFS analysis for the data collected until the cut-off date of May 23, 2008 included 148 events (51%) for PFS in the pazopanib arm and 98 events (68%) for PFS in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 9.2 months (95% CI, 7.4-12.9) and 4.2 months (95% CI, 2.8-4.2) respectively. The hazard ratio for progression or death in the pazopanib arm, as compared with the placebo arm, was 0.46 with 95% C.I. from 0.34 to 0.62 (p-value < 0.0000001).

The PFS results were presented in the Table 7. The Kaplan-Meier curves for the ITT population were illustrated in Figure 2.

Table 7. Primary Efficacy PFS Analysis in ITT Population

	Placebo	**Pazopanib**
	(N=145)	**(N=290)**
Subject status, n (%)		
Progressed or Died (event)	98 (68)	148 (51)
Censored	47 (32)	142 (49)
Kaplan-Meier Estimates for PFS (months)		
1st Quartile (95% CI)	1.4 (NC[1], NC[1])	4.2 (2.8, 5.6)
Median (95% CI)	4.2 (2.8, 4.2)	9.2 (7.4, 12.9)
3rd Quartile (95% CI)	7.4 (5.6, 12.9)	18.4 (16.6, NC[1])
Adjusted Hazard Ratio (95% CI)	0.46 (0.34, 0.62)	
Stratified Log-Rank p-value	P<0.0000001	
Unadjusted Hazard Ratio (95% CI)	0.44 (0.34, 0.58)	
Unstratified Log-Rank p-value	P<0.0001	

[1]: NC: not calculable.

(Source: Table 15 in sponsor's clinical study report)

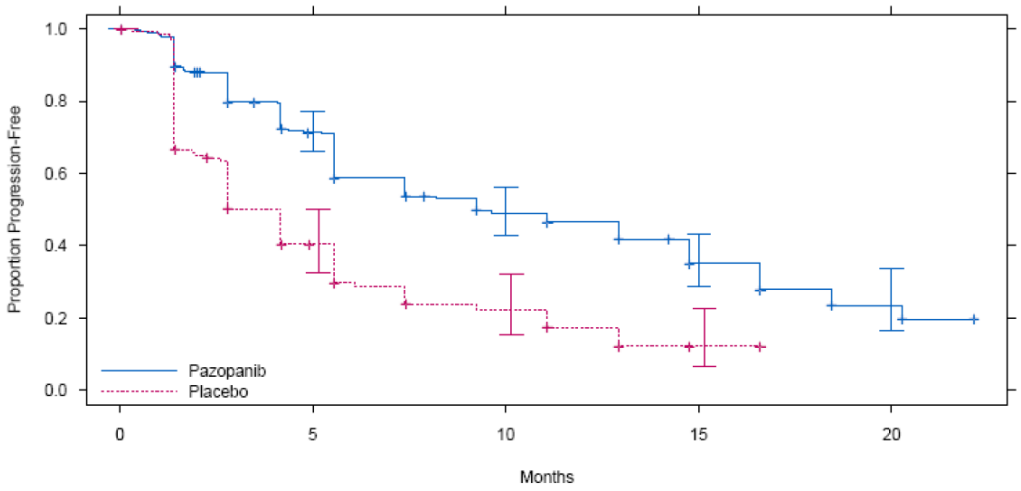


Figure 2: Kaplan-Meier Curves for PFS in the ITT Population
(Source: Figure 2 in sponsor's clinical study report)

Reviewer's Comments:

The estimated hazard ratio for PFS from a unstratified Cox model was 0.44 (95% CI, 0.34 - 0.58), which was consistent with the results based on the stratified primary analysis.

3.1.6.3 Sensitivity Analyses of PFS

Progression-free Survival Analysis by Investigator

A sensitivity analysis of PFS based on investigator assessments of disease status was conducted to confirm the robustness of the primary analysis. Three hundred and four PFS events were observed from the investigator. A stratified log-rank test was also performed to compare PFS between the pazopanib arm and the placebo arm in the ITT population.

This sensitivity PFS analysis included 178 events (61%) for PFS in the pazopanib arm and 126 events (87%) for PFS in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 9 months (95% CI, 7.4-10.9) and 3 months (95% CI, 2.8- 4.2) respectively. The hazard ratio for progression or death in the pazopanib arm, as compared with the placebo arm, was 0.44 with 95% C.I. from 0.34 to 0.57 (p-value < 0.0000001). These results were consistent with those by independent review.

The PFS results based on investigator assessments are presented in the Table 8 and its Kaplan-Meier curves for the ITT population are illustrated in Figure 3.

Table 8. Sensitivity PFS Analysis by Investigator in ITT Population

	Placebo (N=145)	Pazopanib (N=290)
Subject status, n (%)		
Progressed or Died (event)	126 (87)	178 (61)
Censored	19 (13)	112 (39)
Kaplan-Meier Estimates for PFS (months)		
1st Quartile (95% CI)	1.5 (1.4, 1.8)	4.2 (3.9, 5.4)
Median (95% CI)	3.0 (2.8, 4.2)	9.0 (7.4, 10.9)
3rd Quartile (95% CI)	7.4 (5.7, 9.3)	17.8 (16.5, 21.4)
Adjusted Hazard Ratio (95% CI)	0.44 (0.34, 0.57)	
Stratified Log-Rank p-value	P<0.0000001	
Unadjusted Hazard Ratio (95% CI)	0.43 (0.34, 0.54)	
Unstratified Log-Rank p-value	P<0.0001	

(Source: Table 16 in sponsor's clinical study report)

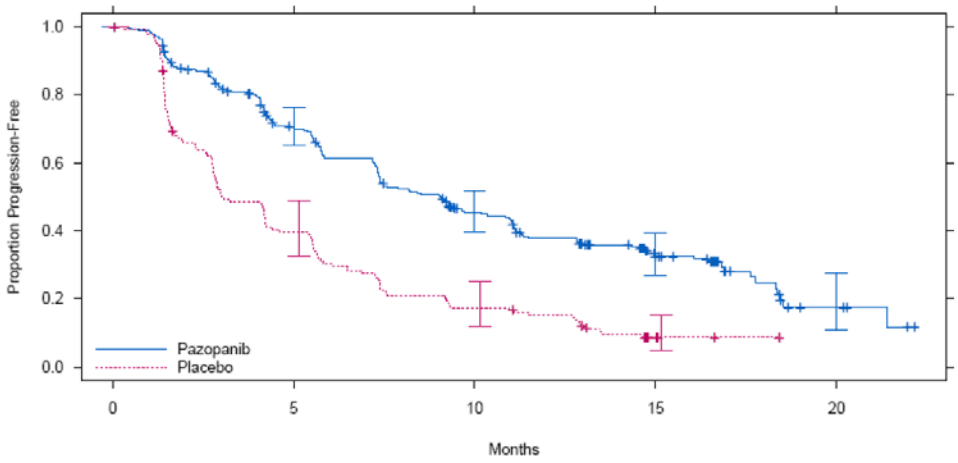


Figure 3: Kaplan-Meier Curves for PFS by Investigator in the ITT Population

(Source: Figure 3 in sponsor's clinical study report)

Reviewer's Comments:

The estimated hazard ratio for PFS from a unstratified Cox model was 0.43 (95% CI, 0.34 - 0.54), which was consistent with the primary results based on the IRC assessments.

In a sensitivity analysis, this reviewer used the first 180 PFS events for the final PFS analysis and censored other PFS events, the estimated hazard ratio for PFS from a unstratified Cox model was 0.41 (p-value<0.0001; 95% CI, 0.31 - 0.55).

This reviewer also used the planned at least 180 events and at least 90 of them would occur from each of treatment-naïve and cytokine-pretreated subgroup for the final PFS analysis, the estimated hazard ratio for PFS from a unstratified Cox model was 0.41 (p-value<0.0001; 95% CI, 0.31 - 0.55).

Comparison of Independent and Investigator Assessment of Progression

The overall PFS results using independent or investigator review assessments were highly consistent: Median PFS by both types of assessment were similar and the Kaplan- Meier curves overlapped.

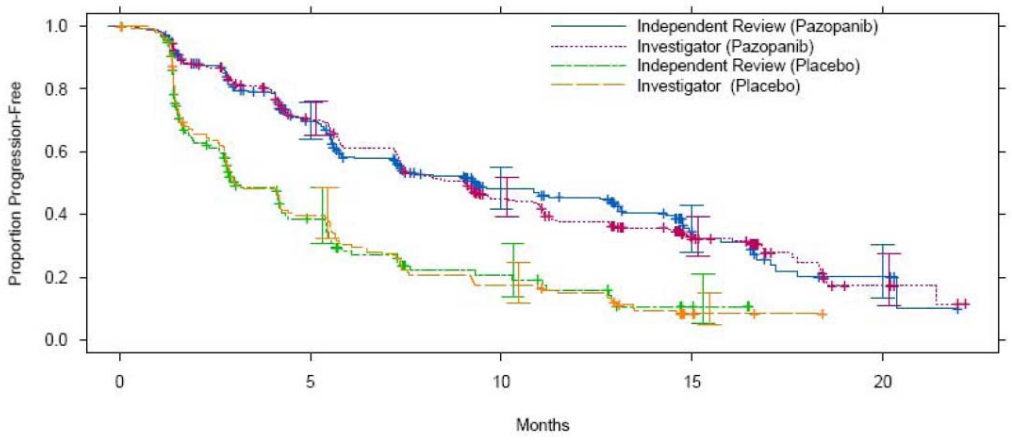


Figure 4: Kaplan Meier Graph of PFS Comparing Independent Radiologist and Investigator Results (ITT Population)

(Source: Figure 4 in sponsor's clinical study report)

The overall agreement between IRC and investigator (categorically) on progression or censoring was 68.3% of subjects in each of the pazopanib and placebo arms. There was more agreement on the assessment of progression in the placebo arm as compared to the pazopanib arm. In contrast, there was more agreement on censoring in the pazopanib arm than the placebo arm (Table 7).

The most common reasons for disagreement in assessment of progression according to the investigator compared with censoring by the IRC were the occurrence of new lesions, and progression on target lesions. There was only one case where the IRC censored the subject and, because of symptomatic progression, the investigator had determined progression. The most common reasons for disagreement in censoring according to the investigator compared with progression by the IRC were also the occurrence of new lesions, and progression on target lesions.

Table 9 Comparison of PFS based on Investigator and IRC-assessments

	Number (%) of subjects	
	Placebo	**Pazopanib**
	(N=145)	**(N=290)**
Overall agreement n (%)	99 (68.3)	198 (68.3)
Progression by IRC		
Progressive disease by investigator	89 (61.4)	117 (40.3)
Censored by investigator	9 (6.2)	31 (10.7)
Censored by IRC		
Censored by investigator	10 (6.9)	81 (27.9)
Progressive disease by investigator	37 (25.5)	61 (21.0)

(Source: Table 17 in sponsor's clinical study report)

Reviewer's Comments:

1. The overall agreement between IRC and investigator on PD or censoring was 68.3% (Table 10).

Table 10 Comparison of PFS based on Investigator and IRC-assessments

		IRC	
		Progression	Censored
Investigator	Progression	206	98
	Censored	40	91

2. In order to evaluate if the time of assessment influenced the PFS outcome, the following exploratory analyses were conducted.

   Time from randomization to assessment was calculated. Log-rank test was used to test if cumulative percentages (survival curves) were equal for IRC assessment. Results from the tests were presented in Table 11.

Table 11. Median (in Months) of Time to Assessment and Log-rank Test

Time from randomization to assessment	Median (in Months)		Log-rank Test
	Pazopanib (N=290)	**Placebo (N=145)**	
1st Assessment	1.4	1.4	0.394
2nd Assessment	2.8	2.8	0.014
3rd Assessment	4.2	4.2	0.148
4th Assessment	5.6	5.6	0.938
5th Assessment	7.4	7.4	0.938
6th Assessment	9.2	9.2	0.643
7th Assessment	11.1	11.0	0.430
8th Assessment	12.9	12.9	0.171
9th Assessment	14.8	14.7	0.461
10th Assessment	16.6	16.4	0.159

The log-rank test showed that there was no difference between two treatment distributions of time to assessment, except the 2nd assessment. Although the p value in the 2nd assessment was less than 0.05, the median in the 2nd assessment was the same for both arms.

3.1.6.4 Secondary Efficacy Analyses

The principal secondary endpoint was Overall Survival (OS), which was analyzed by stratified log-rank test and the estimates of time-to-event endpoints were obtained using Kaplan-Meier methods. Other secondary endpoints were ORR, the rate of CR + PR + 6 month SD, DR and TTR. As per the protocol, all secondary analyses were conducted in the ITT population.

Overall Survival

Overall survival was defined as the duration from randomization to death due to any cause. A planned interim analysis of OS was performed with a cut off date of 23 May 2008 when 176 events had occurred (61% of the total number of deaths required for the final analysis). The significance level for the interim OS analysis is 0.004

One hundred and nine (38%) vs. 67 (46%) subjects on pazopanib vs. placebo, respectively, were known to have died at the time of the final PFS analysis. Data for subjects not known to have died were censored at the time they were last known to be alive. The results from the interim OS analysis is summarized in Table 12 and Kaplan-Meier curves of OS are presented in Figure 5. The hazard ratio was 0.73 (95% CI: 0.53-1; p = 0.02), which was not statistically significant based on the stopping boundaries for this interim analysis.

Table 12 Kaplan-Meier Estimates of Interim Analyses on Overall Survival

	Placebo	**Pazopanib**
	(N=145)	**(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.

(Source: Table 20 in sponsor's clinical study report)

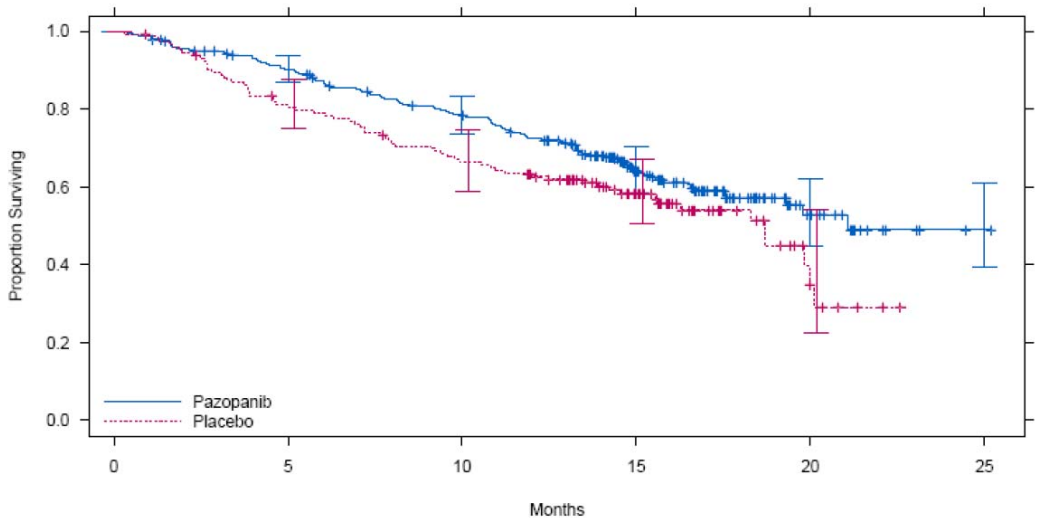


Figure 5 Kaplan Meier Overall Survival Curves: (ITT population)

(Source: Figure 10 in sponsor's clinical study report)

Reviewer's Comments:

The final OS survival analysis will be conducted when 287 deaths occur. However, given the 48% (70 subjects) rate of crossover from placebo to pazopanib in the extension study, longer follow up is unlikely to demonstrate a statistically significant difference in overall survival.

Overall Best Response

Overall response rate was defined as the percentage of subjects who achieved either a confirmed CR or PR according to RECIST criteria was higher in the pazopanib arm compared with placebo arm. By independent review, the difference in RR was 26.9% (95% CI: 20.8-33.0) and by investigator review, it was 29.3% (95% CI: 22.5-36.1). The independent- and investigator-evaluated best confirmed responses by RECIST were similar for both treatment arms.

Table 13 Best Confirmed Response per RECIST using Method A by the IRC and Investigator (ITT Population)

	Independently-Evaluated		**Investigator-Evaluated**	
	Placebo	**Pazopanib**	**Placebo**	**Pazopanib**
	(N=145)	**(N=290)**	**(N=145)**	**(N=290)**
Best Response, n (%)				
Complete Response	0	1 (<1)	0	4 (1)
Partial Response	5 (3)	87 (30)	9 (6)	99 (34)
Stable Disease	59 (41)	110 (38)	62 (43)	118 (41)
Progressive Disease	58 (40)	51 (18)	65 (45)	46 (16)
Unknown	23 (16)	41 (14)	9 (6)	23 (8)
Response Rate (CR+PR), n (%)	**5 (3)**	**88 (30)**	**9 (6)**	**103 (36)**
95% CI	0.5, 6.4	25.1, 35.6	2.3, 10.1	30.0, 41.0
Difference in Response (CR+PR) (%)	26.9		29.3	
95% CI for Difference	20.8, 33.0		22.5, 36.1	
P-value **	P<0.001		P<0.001	

(Source: Table 24 in sponsor's clinical study report)

**without adjustment for multiple comparisons.

Rate of CR, PR or 6-months SD

The rate of CR, PR or 6 month SD was higher in the pazopanib compared with placebo arm. This endpoint is considered as exploratory from a regulatory perspective.

Table 14 Summary of CR+PR+6-months SD Rate per RECIST by the IRC and Investigator (ITT Population)

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

(Source: Table 25 in sponsor's clinical study report)

**without adjustment for multiple comparisons.

Time to Response

The median time to CR or PR with pazopanib treatment was 12 weeks, both by investigator and independent review assessments (Table 15).

Table 15 Summary of Time to Response (RECIST Criteria) by the IRC and Investigator (ITT Population)

	Independently-Evaluated	Investigator-Evaluated
	Pazopanib	**Pazopanib**
	(N=290)	**(N=290)**
Number (%) of Subjects, n	88	103
Time to Response (weeks)		
1st Quartile (95% CI)	6.2 (6.1, 6.7)	6.3 (6.1, 7.0)
Median (95% CI)	11.9 (9.4, 12.3)	12.0 (11.6, 12.3)
3rd Quartile (95% CI)	17.5 (12.9, 18.6)	18.3 (14.7, 23.4)

(Source: Table 26 in sponsor's clinical study report)

Duration of Response

For subjects who had CR or PR, the duration of response was defined as the time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to RCC. For subjects who responded to treatment, the median duration of response was 58.7 weeks for independent review and 62.4 weeks for investigator review (Table 16).

Table 16 Summary of Duration of Response (RECIST Criteria) by the IRC and Investigator (ITT Population)

	Independently-Evaluated	Investigator-Evaluated
	Pazopanib	Pazopanib
	(N=290)	(N=290)
Number (%) of Subjects, n	88	103
Duration of Response (weeks)		
1st Quartile (95% CI)	38.3 (25.7, 52.1)	29.9 (25.1, 36.4)
Median (95% CI)	58.7 (52.1, 68.1)	62.4 (42.0, 68.6)
3rd Quartile (95% CI)	82.1 (64.9, NC[1])	NC[1] (67.7, NC[1])

[1]: NC: not calculable.

(Source: Table 27 in sponsor's clinical study report)

3.2 Evaluation of Safety

With pazopanib monotherapy, a high incidence of hepatic laboratory abnormalities was associated with four cases that fulfilled Hy's Law (about 0.4%). More importantly, three hepatic deaths related to or associated with pazopanib were also observed in a premarketing setting. These hepatic findings strongly suggest that pazopanib may be associated with a significant risk of severe idiosyncratic hepatic injury if used in a larger patient population after marketing. As such, FDA is concerned about the benefit-to-risk ratio of pazopanib in the intended population of patients. This is particularly true in a setting in which there are other effective products approved for the treatment of advanced renal cell cancer. Please refer to Clinical Review of this application for detailed safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

This section focused on PFS analyses by gender (male vs. female, Table 15), age (< 65 years vs. ≥ 65 years, Table 16) and race (white vs. non-white, Table 17). For each subgroup population, a separate unadjusted log-rank test was performed.

Table 17. PFS Analyses by Gender in ITT Population

	Placebo	**Pazopanib**
Male		
Number of Subjects	**(N=109)**	**(N=198)**
Progressed or Died (event)	70	97
Censored	39	101
Estimates for progression free survival (months)		
Median (95% CI)[1]	**4.2 (2.8, 5.6)**	11.1 **(7.4, 14.8)**
Unadjusted Hazard Ratio[2] (95% CI)	0.44 (0.32, 0.61)	
Female		
Number of Subjects	**(N=36)**	**(N=92)**
Progressed or Died (event)	28	51
Censored	8	41
Estimates for progression free survival (months)		
Median (95% CI)[1]	2.8 (1.4, 4.2)	7.4 (5.6, 12.9)
Unadjusted Hazard Ratio[2] (95% CI)	0.41 (0.25, 0.66)	

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

Table 18. PFS Analyses by Age in ITT Population

	Placebo	**Pazopanib**
<65		
Number of Subjects	**(N=85)**	**(N=196)**
Progressed or Died (event)	57	102
Censored	28	94
Estimates for progression free survival (months)		
Median (95% CI)[1]	**2.8 (1.9, 4.2)**	**9.2 (5.6, 14.8)**
Unadjusted Hazard Ratio[2] (95% CI)	0.38 (0.27, 0.53)	
>=65		
Number of Subjects	**(N=60)**	**(N=94)**
Progressed or Died (event)	41	46
Censored	19	48
Estimates for progression free survival (months)		
Median (95% CI)[1]	**4.2 (2.8, 7.4)**	**12.9 (7.4, 16.6)**
Unadjusted Hazard Ratio[2] (95% CI)	0.51 (0.33, 0.79)	

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

Table 19. PFS Analyses by Race in ITT Population

	Placebo	**Pazopanib**
White		
Number of Subjects	**(N=122)**	**(N=250)**
Progressed or Died (event)	84	127
Censored	38	123
Estimates for progression free survival (months)		
Median (95% CI)[1]	**4.2 (2.8, 5.6)**	9.2 **(7.4, 12.9)**
Unadjusted Hazard Ratio[2] Estimate (95% CI)	0.45 (0.34, 0.59)	
Other		
Number (%) of Subjects	**(N=23)**	**(N=40)**
Progressed or Died (event)	15	21
Censored	9	19
Estimates for progression free survival (months)		
Median (95% CI)[1]	2.8 (1.4, 12.9)	12.9 (4.2, 16.6)
Unadjusted Hazard Ratio[2] Estimate (95% CI)	0.43 (0.21, 0.88)	

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

Reviewer's Comments:

The treatment effect appears to be similar across all age, race, and gender subgroups.

4.2 Treatment-naïve and Cytokine-pretreated Groups

In treatment-naïve subgroup, the median PFS in the pazopanib and placebo arms was 11.1 months and 2.8 months, respectively, with an HR of 0.40 (95% CI 0.27-0.60). In the cytokine pre-treated subgroup, the median PFS in the pazopanib and placebo arm was 7.4 months and 4.2 months respectively with a HR of 0.54 (95% CI: 0.35-0.84) (Table 20 and Table 21).

Table 20 Progression-Free Survival in Treatment-naïve Subgroup per Independent Review (ITT Population)

	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)	

(Source: Table 18 in sponsor's clinical study report)

Table 21 Progression-Free Survival in Cytokine-pretreated Subgroup per Independent Review (ITT Population)

	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)	

(Source: Table 19 in sponsor's clinical study report)

Table 22 Summary of Kaplan-Meier Estimates of Overall Survival (Treatment-naïve Subgroup, ITT Population)

	Placebo	**Pazopanib**
	(N=78)	**(N=155)**
Number (%) of Subjects		
Died (event)	35 (45)	65 (42)
Censored	1 (1)	9 (6)
Estimates for overall survival (months) Median (95% CI)	**20.0 (10.5, NC[1])**	**19.8 (15.8, NC[1])**
Adjusted Hazard Ratio		
Estimate (95% CI)	0.74 (0.47, 1.15)	

[1]: NC: not calculable.

(Source: Table 22 in sponsor's clinical study report)

Table 23 Summary of Kaplan-Meier Estimates of Overall Survival (Cytokine-pretreated Subgroup, ITT Population)

	Placebo (N=67)	**Pazopanib (N=135)**
Number (%) of Subjects		
Died (event)	33 (49)	53 (39)
Censored	34(51)	82 (60)
Estimates for overall survival (months) Median (95% CI)	**18.3 (14.2, 20.1)**	**NC[1] (17.6, NC[1])**
Adjusted Hazard Ratiob		
Estimate (95% CI)	0.72 (0.46, 1.14)	

[1]: NC: not calculable.

(Source: Table 23 in sponsor's clinical study report)

Reviewer's Comments:

The treatment effect appears to be similar across subgroups by prior treatment.

4.3 Region

This reviewer looked at the PFS results of subgroup analysis by region. For patients in the Eastern Europe-Russia region, the median PFS for patients treated with pazopanib was 7.39 months as compared to a median PFS of 4.17 months in patients receiving placebo (HR 0.46 with 95% C.I. (0.32, 0.67)). For patients not in the Eastern Europe-Russia region, the median PFS for patients treated with pazopanib was 12.91 months as compared to a median PFS of 2.79 months in patients receiving placebo (HR 0.42 with 95% C.I. (0.29, 0.61)).

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.

Reviewer's Comments:

The treatment effect appears to be similar across subgroups by regions. However the treatment effect in U.S. population can not be extrapolated.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

In this application to evaluate the efficacy and safety of pazopanib in patients with locally advanced and/or metastatic renal cell carcinoma, the sponsor submitted efficacy and safety data from Study VEG105192, "A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

Statistical Issues:

1. Study VEG105192 was an international study. None of the subjects in this study was recruited from United States.

2. The planned sample size was to have at least 350 subjects powered for OS with a 2:1 randomization scheme and 287 deaths are required in the final OS analysis with one interim analysis evaluated at 70% of deaths occurred. The actual overall sample size recruited was 435 subjects with 145 subjects in the placebo group and 290 subjects in the pazopanib group. The actual interim analysis of OS was performed with a cut off date of 23 May 2008 when 176 events had occurred (40% of all subjects, or 61% of the events needed for the final analysis). The updated significance level for the interim and final efficacy analyses was 0.004 and 0.0237 determined by using the Lan-DeMets spending function approach with an O'Brien-Fleming boundary.

3. The planned timing of the final PFS analysis was when at least 180 PFS events would occur in the study and at least 90 PFS events would occur from each of treatment-naïve (1^{st} line) and cytokine-pretreated (2^{nd} line) subgroup as well as at least 160 deaths. Two hundred and forty-six PFS events and 176 deaths occurred in the final PFS analysis. One hundred and thirty PFS events were from the treatment-naïve (1^{st} line) subgroup and 116 PFS events were from the cytokine-pretreated (2^{nd} line) subgroup.

4. Although three stratification factors were planned to use in the stratified log-rank test for the primary analyses, there were only two stratification factors - ECOG performance status and prior systemic therapy for advanced RCC included in the final analyses. The stratification factor, prior nephrectomy, was not incorporated since there were too few subjects who had not had a prior nephrectomy. The sponsor also used the un-stratified log-rank test as a sensitivity analysis to support the primary efficacy analysis.

5. For PFS assessment, the overall agreement between IRC and investigator on PD or censoring was 68.3%.

6. Time from randomization to assessment was calculated. The log-rank test showed that there was no difference between two treatment distributions of time to assessment, except the 2nd assessment. Although the p value in the 2nd assessment was less than 0.05, the median in the 2nd assessment was the same for both arms.

7. At the time of PFS analysis, a planed interim analysis for overall survival (OS) included 109 (38%) in pazopanib arm and 67 (46%) deaths in placebo arm. The estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The hazard ratio for OS was 0.73 (95% CI: 0.53 to 1; p = 0.02), which was not statistically significant (>0.004, the significance level allocated for this interim analysis).

8. The final OS survival analysis will be conducted when 287 deaths occur. However, given the 48% (70 subjects) rate of crossover from placebo to pazopanib in the extension study, longer follow up is unlikely to demonstrate a statistically significant difference in overall survival.

9. Other secondary endpoints were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/ comparisons.

5.2 Conclusions and Recommendations

On 19 December 2008, the sponsor submitted an application to evaluate the efficacy and safety of single-agent GW786034 (Pazopanib, Votrient®), a new molecular entity (NME), in patients with locally advanced and/or metastatic renal cell carcinoma. In this application, the sponsor submitted the efficacy and safety data from Study VEG105192, "A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

The primary efficacy endpoint in Study VEG 10592 was progression free survival (PFS). The primary PFS efficacy analysis of Study VEG105192 in the ITT population was based on PFS data assessed by the independent review committee (IRC). At the time of data cutoff for the final PFS analysis (23 May 2008), 435 subjects were randomized in a 2:1 ratio: 290 in the pazopanib arm and 145 in the placebo arm. The PFS analysis included 148 events (51%) for PFS in the

pazopanib arm and 98 events (68%) for PFS in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 9.2 months and 4.2 months respectively. The adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.46 (p-value < 0.0000001). The un-adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.44 (p-value < 0.0001).

At the time of PFS analysis, a planed interim analysis for overall survival (OS) included 109 (38%) in pazopanib arm and 67 (46%) deaths in placebo arm. The estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The adjusted hazard ratio for death in the pazopanib arm, as compared with the placebo arm, was 0.73 (p-value = 0.02), which was not statistically significant. The final OS survival analysis will be conducted when 287 deaths occur. However, given the 48% (70 subjects) rate of crossover from placebo to pazopanib in the extension study, longer follow up is unlikely to demonstrate a statistically significant difference in overall survival.

This application will be discussed at the Oncology Drugs Advisory Committee meeting on October 5, 2009.

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

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