VOTRIENT® (PAZOPANIB) TABLETS

For Treatment of Patients with Soft Tissue Sarcoma

FDA Oncologic Drugs Advisory Committee

Briefing Document

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EXECUTIVE SUMMARY

Introduction

In June 2011, GlaxoSmithKline (GSK) submitted a supplemental new drug application (sNDA) to support the use of pazopanib in the treatment of metastatic soft tissue sarcoma (STS). Pazopanib, discovered and developed by GSK, is a tyrosine kinase inhibitor targeting the vascular endothelial growth factor receptors (VEGF)-1, 2 and 3, platelet-derived growth factor receptors (PDGFR)-α, and β, fibroblast growth factor receptor (FGFR) -1 and -3, interleukin-2 inducible T-cell kinase (ITK), leukocyte-specific protein tyrosine kinase (LCK), the transmembrane CSF1 receptor tyrosine kinase (c-Fms) and stem cell factor receptor (c-KIT) [Kumar, 2007].

Pazopanib is approved for the treatment of advanced renal cell carcinoma (RCC) in the US and 74 other markets globally. The estimated cumulative worldwide post-marketing exposure of pazopanib since approval is in excess of 2,800 patient years. As of 30 September 2011, a total of 4,115 patients have received pazopanib therapy in clinical trials, including 3,089 patients who received pazopanib as monotherapy and 1,026 who received it in combination with other therapies.

Proposed indication for STS:

Votrient® is indicated for the treatment of patients with advanced STS who have received prior chemotherapy.

Important Limitations of Use:
The Phase III STS trial population excluded patients with adipocytic soft tissue sarcomas or gastrointestinal stromal tumors (GIST).

Dosage:
Pazopanib tablets (oral) at a dose of 800 mg/day.

Evidence to support the STS indication is provided by the pivotal Phase III double-blind, randomized, placebo-controlled study VEG110727 and the supportive open-label Phase II study VEG20002 (Table 1). Both studies were conducted by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG), an academic collaborative group comprised of sarcoma investigators. GSK sponsored both studies.

Table 1 Key STS Studies Supporting the sNDA

Study	Description	N	Study Endpoints
Phase III (Pivotal study) VEG110727	A randomized double-blind Phase III trial of pazopanib versus placebo in patients with STS whose disease has progressed during or following prior therapy	369 2:1 randomization Pazopanib: 246 Placebo: 123	Primary: PFS by independent review Principal secondary: OS Other Secondary: ORR; Duration of response, Time to response Safety
Phase II (Supportive study) VEG20002	A non-randomized proof of concept, open-label, two-stage, Phase II study to evaluate the anti-tumor activity and safety of pazopanib in patients with recurrent, metastatic leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and "other eligible subtypes of STS".	142	Primary: progression-free survival rate at Week 12 Secondary: PFS OS ORR Duration of response, Time to response Safety

PFS=progression-free survival, OS=overall survival, ORR=overall response rate, STS=soft tissue sarcoma

Background

Sarcomas are a rare group of solid tumors originating from mesenchymal cells and their precursors. STS are comprised of over 50 histologic subtypes, the most common among adults in the United States (US) being leiomyosarcoma (20.8%), undifferentiated pleomorphic sarcoma (14.9%) and liposarcoma (12.6%) [Surveillance, Epidemiology, and End Results SEER, 2009; Toro, 2006]. STS accounts for less than 1% of all new malignancies in adults, and approximately 2% of total cancer-related mortality [Fletcher, 2002; Altekruse, 2009]. The incidence of STS reported in the US in 2011 was 10,980 [ACS, 2011].

Metastatic STS are treated with cytotoxic agents and choice of therapy is generally not determined by histologic subtype, although specific combination chemotherapy regimens are used for the treatment of Ewing's family sarcomas and embryonal rhabdomyosarcoma, while specific tyrosine kinase inhibitors are used in the treatment of GIST and dermatofibrosarcoma protuberans. These subtypes with established therapies were excluded from the pazopanib studies. GSK estimates that the incidence of the STS histologic subtypes eligible for the Phase III VEG110727 study with recurrent metastatic disease would be less than 2,500.

The median survival of patients with non-GIST STS is approximately 12 months from the time of diagnosis of metastatic disease [Karavasilis, 2008]. Patients are treated with sequential chemotherapies with the goal of palliation. The most commonly used agent is doxorubicin. Doxorubicin is the only FDA approved agent for treatment of STS and no new agents have been approved in more than 2 decades for STS with the exception of GIST and DFSP. Other agents include ifosfamide, gemcitabine, docetaxel and trabectadine. The evidence for the use of these agents is based largely on Phase II trials. No placebo-controlled trials have been conducted in STS, so the true benefits of current therapies in prolonging progression free (PFS) and overall survival (OS) are unknown. Few high-quality randomized Phase III trials have been reported to date. This is reflected in the recommendations in NCCN guidelines for metastatic STS, which are based on

category 2A or 2B evidence. There is a compelling unmet medical need for effective therapy for patients with recurrent metastatic STS following chemotherapy.

To fulfil this unmet need, pazopanib was investigated in STS. Many receptor tyrosine kinases inhibited by pazopanib regulate angiogenesis. These receptors also directly drive tumorigenesis in some settings (e.g., PDGFR and c-Kit mutations in gastrointestinal stromal tumors). Both the ability to block angiogenesis and inhibit RTKs that may directly promote tumor growth supported testing pazopanib in STS.

Clinical Efficacy of Pazopanib for the Treatment of Patients with Recurrent, Metastatic STS

Pivotal Study: Phase III VEG110727

The primary objective of the Phase III study was to compare PFS in pazopanib-treated patients, versus placebo-treated patients. The principal secondary objective was to compare OS in the two treatment arms. Other secondary objectives were to compare the overall response rate, time to response, duration of response, and safety and tolerability in the two arms. Results from the adequate and well-controlled pivotal study demonstrate that pazopanib provides significant clinical benefit in patients with recurrent, metastatic STS.

Patients enrolled in the study had bulky metastatic disease and all had received extensive prior systemic chemotherapy. The median age of patients was 55 years old, and median sum of target lesions was 16.1cm. Seven percent were eligible based on progression within 12 months of adjuvant therapy, while 93% had progressed within 6 months of therapy for metastatic disease; 54% had received 2 or more lines of systemic therapy, and 21% had received 3 or more lines of systemic therapy for metastatic disease.

- In the primary analysis, pazopanib demonstrated a statistically significant and clinically meaningful increase in PFS compared to placebo (Table 2). The median PFS based on the independent radiologist assessment was 1.6 months (95% CI: 1.0, 1.9) in the placebo arm compared with 4.6 months (95% CI: 4.1, 4.9) in the pazopanib arm, with a corresponding HR of 0.35 (95% CI: 0.26, 0.48, $p<0.001$). PFS results were consistent between independent radiologist and investigator assessments.

Table 2 Key Efficacy Data from Pivotal Phase III Study VEG110727 (ITT population)

Endpoints/ Study population	Placebo	Pazopanib	HR (95% CI)[e]	p-value
PFS	Median (95% CI)[a] in months			
ITT Population[b]	N=123	N=246		
Independent Radiologist	1.6 (1.0, 1.9)	4.6 (4.1, 4.9)	0.35 (0.26, 0.48)[c]	<0.001
Investigator	1.5 (1.0, 1.9)	4.6 (4.4, 5.8)	0.39 (0.30, 0.52)[c]	<0.001
PFS *Histology subgroups (Independent Radiologist)*				
Leiomyosarcoma	n=49	n=109		
	1.9 (1.8, 2.1)	4.6 (3.1, 5.3)	0.37 (0.23, 0.60)[c]	<0.001
Synovial sarcoma	n=13	n=25		
	0.94 (0.9, 2.0)	4.1 (2.0, 6.3)	0.43 (0.19, 0.98)[c]	0.005
"Other" STS	n=61	n=112		
	1.0 (0.9, 1.8)	4.6 (3.0, 6.3)	0.39 (0.25, 0.60)[c]	<0.001
Final OS[d]	Median (95% CI)[a] in months		HR (95% CI) [95.57% CI]	
ITT Population	N=123	N=246	0.87 (0.67, 1.12)	0.256
	10.7 (9.0, 13.1)	12.6 (10.9, 14.9)	[0.67, 1.13][f]	
Response rate, CR+PR	n, (%) [95% CI][g]			
ITT Population[b]	N=123	N=246		
Independent Radiologist	0 [0.0, 3.0]	11 (4) [2.3, 7.9]		0.019
Investigator	0 [0.0, 3.0]	23 (9) [6.0, 13.7]		<0.001

CI: confidence interval, CR: complete response; PR: partial response; ITT: Intent-to-treat; OS: Overall survival; PFS: progression-free survival; STS: soft tissue sarcoma; HR: hazard ratio; WHO: World Health Organization; PS: performance status

a. Confidence intervals for quartiles were estimated using the Brookmeyer-Crowley method.
b. ITT population included 6 patients in the pazopanib arm that did not receive study medication.
c. HR and p-value were adjusted for WHO performance status and number of prior lines of systemic therapy for advanced disease.
d. Final analysis performed after 280 deaths.
e. HRs estimated using the Pike estimator; HR <1 indicates a lower risk with pazopanib compared with placebo
f. Adjusted for interim analysis
g. Exact binomial confidence limit method was used for both treatment arms for response rate.

- The robustness of the PFS benefit is evidenced by consistent results seen across all 10 pre-specified sensitivity analyses and all subgroup analyses. The subgroups consisted of: histology types (leiomyosarcoma, synovial and "other" subgroup STS histologies), baseline WHO PS: 0 vs. 1, number of prior lines of therapy for advanced disease (0, 1 vs. 2+), age, race, gender, region (US, EU/Australia and Japan/Korea), disease status (locally advanced and metastatic disease or metastatic disease only).
- Improvement in PFS with pazopanib was independent of number of prior chemotherapy agents and tumor bulk.
- Overall survival results numerically favored pazopanib; however, the result was not statistically significant. The median OS in the placebo arm was 10.7 months (95%

CI: 9.0, 13.1) and in the pazopanib arm, 12.6 months (95% CI: 10.9, 14.9); HR = 0.87 (95.7% CI: 0.67, 1.13, p=0.256).

- Higher rates of objective responses and stable disease were observed in the pazopanib arm compared with the placebo arm. Some degree of tumor shrinkage from baseline was observed in 50% of patients in the pazopanib arm versus 12% of patients in the placebo arm by independent radiology review across all tumor subgroups.

- Health-related quality of life was assessed using 2 instruments, the EORTC QLQ-C30 and the EQ-5D. The QLQ-C30 is a cancer-specific questionnaire designed to assess quality of life in a wide range of tumors, but is not specifically validated in STS. A modest decline from baseline in the Global Health Status/Quality of Life (QoL) summary scale was observed in each of the treatment arms with no clinically or statistically significant differences between the two treatment arms. The QoL analysis was limited by the restriction of data collection to the first 12 weeks on study and only prior to disease progression, as well as the higher drop-out rate in the placebo arm (due primarily to disease progression).

Supportive Study VEG20002

The efficacy results in the pivotal VEG110727 Phase III study confirmed those initially observed in VEG20002. VEG20002 was a non-randomized proof of concept, two-stage, Phase II study conducted to evaluate the anti-tumor activity and safety of pazopanib in patients with recurrent, metastatic leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and "other eligible subtypes of STS". Enrolled patients had intermediate or high grade, metastatic STS with documented evidence of disease progression within 6 months of chemotherapy for advanced disease. Progression-free survival rate at Week 12 was the primary endpoint.

- In VEG20002, antitumor activity with pazopanib (>40% progression-free rate at Week 12) was demonstrated in leiomyosarcoma, synovial sarcoma, and "other STS" strata. These were the subgroups that were evaluated in the VEG110727 Phase III study. Activity in the adipocytic sarcoma stratum did not meet the pre-specified threshold in VEG20002 and was therefore not investigated in the Phase III study.

Table 3 Key Efficacy Data from Supportive Phase II Study VEG20002 (ITT population)

	Leiomyo-sarcoma N=41	Adipocytic sarcoma N=19[a]	Synovial sarcoma N=37	Other STS N=41	Total N=138
Progression-free Survival Rate at Week 12[b] - Peer + Investigator Assessment[c]					
CR+PR+SD, n (%) 90% CI p-value[d]	18 (44) (30.6, 57.9) <0.001	5 (26) (11.0, 47.6) 0.653	18 (49) (34.3, 63.2) <0.001	17 (41) (28.4, 55.5) 0.003	58 (42) (34.9, 49.4) <0.001
Progression-free Survival (months) – Investigator Assessment					
Median (90% CI)	4.0 (2.8, 5.6)	2.6 (1.6, 2.7)	5.4 (2.7, 6.8)	3.2 (2.8, 8.4)	2.8 (2.8, 5.2)

a. The adipocytic stratum had 17 patients enrolled at the end of Stage 1. Progression-free rate at Week 12 was noted in 2 of the 17 patients. This result did not meet the prerequisite progression-free rate at Week 12 to progress to Stage 2. One additional patient was enrolled into this stratum around the time this decision was made bringing the total patients to 18. This patient was also reported to have stable disease (SD) at Week 12. Subsequently, a Central Pathology Review was conducted after enrolment was completed in the study. A total of 19 patients were assigned to the adipocytic stratum by the end of the study due to additional interchanging of patients amongst the strata after central pathology review. By the end of the study 5 of 19 patients were progression-free at Week 12.

b. The CRF does not explicitly state which assessment is Week 12 for the investigator data. The analysis used the first post-baseline assessment.

c. Scans assessed by investigator as CR, PR and SD were peer reviewed, but scans assessed by investigator as PD were not.

d. p-value=the strength of evidence to reject the null hypothesis of the response rate being equal to 20% with an alpha level of 0.10.

Clinical Safety of Pazopanib

The safety data presented in this document are primarily derived from the pivotal Phase III VEG110727 study, however, integrated data of pazopanib-treated patients from the Phase III study and the supporting Phase II study VEG20002 are used to better characterize liver chemistry abnormalities and AEs of special interest (severe drug-induced liver injury, cardiac and vascular events, hemorrhagic events, and pneumothorax).

- The median duration of treatment exposure in VEG110727 was approximately 1.9 months (8.14 weeks) in the placebo arm and approximately 4.5 months (19.36 weeks) in the pazopanib arm. Patients had a mean daily exposure of 87.5% (700mg) of the targeted daily dose of 800 mg.
- The overall safety profile of pazopanib-treated patients in VEG20002 and VEG110727 is generally consistent with the Votrient® Prescribing Information for RCC with a few exceptions. Three new safety signals are myocardial dysfunction, venous thromboembolic events, and pneumothorax.
- New AEs identified in the STS population were myocardial dysfunction, venous thromboembolic events (VTE) and pneumothorax .
    - Myocardial dysfunction as an AE was seen in 9% of patients in the pazopanib arm and 5% of patients in the placebo arm. Majority of these patients had asymptomatic LVEF decline. Improvement in LVEF was observed in patients

with adequate follow up assessments. The majority of patients with cardiac dysfunction had documented hypertension; control of hypertension by pazopanib dose modification (dose interruption/reduction) and/or antihypertensive medications was generally effective in managing the cardiac dysfunction.

  - Venous thromboembolic events were reported in 5% of patients in the pazopanib arm and in 2% in the placebo arm. Exposure adjusted rates for VTE were not significantly different between the two arms. Rare but fatal events of pulmonary embolism were observed in the pazopanib arm.

  - Pneumothorax, is a known complication in patients with STS, particularly those who have received active therapy. Pneumothorax was reported in 3% on pazopanib and none on placebo. No fatalities were associated with pneumothorax and these events were reversible in the majority of patients.

- The most common AEs reported in the pazopanib arm were fatigue, diarrhea, nausea, weight decrease, hypertension, decreased appetite, hair color change and vomiting. The most frequent AEs which occurred at a higher rate in the pazopanib arm compared to placebo (based on relative risk) were hair color change, alopecia, skin disorder, dysguesia, hypertension, diarrhea, stomatitis, weight decrease. Most events were Grade 1 or Grade 2 and few led to permanent discontinuation.

- The most common SAEs associated with pazopanib were dyspnea, transaminase increase, hemoglobin decrease, pneumothorax and embolism (VTE). Fatal SAEs were reported at a similar rate in both arms; the majority of fatal events in the pazopanib arm were attributed to complications from disease progression. One patient in the pazopanib arm died of multi-organ failure/possible drug-induced liver injury.

- Hepatoxicity is of concern for VEGF-TKI including pazopanib. Transaminase elevations were common but reversible in the majority of patients. The frequency, severity and time course were consistent with that reported in the Votrient® Prescribing Information. As over 90% of all transaminase elevations occur in the first 18 weeks of treatment, frequent monitoring during this period allows for early identification and intervention. Of all patients treated with pazopanib on GSK-sponsored clinical trials, fatal cases of possible drug-induced liver failure was reported in 3 out of 4,115 patients (0.07%).

EFFICACY AND SAFETY OF PAZOPANIB IN THE CONTEXT OF COMMONLY USED CHEMOTHERAPIES FOR STS

The median PFS of pazopanib compares favorably to the PFS or TTP reported with chemotherapy agents including doxorubicin, ifosfamide, gemcitabine, docetaxel and trabectedin. In study VEG110727, the first Phase III study to be conducted in heavily pre-treated patients with recurrent metastatic STS, and the only placebo controlled study in non-GIST STS, PFS benefit was observed in a patient population that has already received many of the commonly prescribed chemotherapy agents.

Common to most cytotoxic agents used in STS are myelosuppression and associated complications, gastrointestinal toxicities (nausea, vomiting, diarrhea, and mucositis),

fatigue, and alopecia. Toxicities such as cardiotoxicity, neurotoxicity, nephrotoxicity, and urotoxicity are unique to individual chemotherapies. Pazopanib has a different and relatively favorable toxicity profile compared to the commonly prescribed chemotherapy agents. Myelosuppression is common with chemotherapy agents but extremely rare with pazopanib. The myocardial dysfunction observed with pazopanib is largely asymptomatic and generally reversible. Toxicities such as neurotoxicity and urotoxicity have not been associated with pazopanib. In addition, all of the commonly prescribed chemotherapies are administered intravenously, and carry the added safety risks of thrombophlebitis, extravasation, and infection.

Conclusion

Patients with recurrent, metastatic STS constitute a population with a significant unmet medical need. The efficacy and safety of pazopanib was confirmed in a well conducted, randomized double-blind placebo controlled Phase III trial in patients with bulky disease who had progressed on, or following, chemotherapy. This trial demonstrated a clinically compelling and statistically significant improvement in PFS with pazopanib. The PFS benefit was observed irrespective of the extent of prior chemotherapy treatment. The OS result favored pazopanib, although it was not statistically significant. The observed hazard ratio for OS however, is within the expected range if the 3 month median benefit in PFS that was observed with pazopanib translated into OS.

The risks associated with pazopanib have been well characterized through a large clinical development program and post-marketing experience. The safety profile of pazopanib in the STS patient population is generally consistent with the Votrient® Prescribing Information for RCC with few exceptions (myocardial dysfunction, venous thromboembolic events and pneumothorax). GSK is proposing updated labelling in the USPI for patients and prescribers with respect to managing these new events. Rare toxicities such as liver failure and cardiac failure were observed; however, close surveillance and prompt intervention could mitigate these toxicities. The majority of toxicities are mild to moderate in severity and can be managed with prompt dose modification of this oral agent and other interventions as indicated. Oral administration of pazopanib is convenient for patients and permits rapid dose adjustments for toxicity.

The safety profile and activity of pazopanib in heavily pre-treated patients appears favorable when compared with published studies of chemotherapies in either treatment naïve or less heavily pre-treated patients with STS. The benefit in disease control with pazopanib is retained irrespective of the number of prior chemotherapies, indicating a lack of cross-resistance with cytotoxic chemotherapy.

Pazopanib is a viable and important treatment option with a favorable benefit to risk profile for patients with recurrent, metastatic STS.

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ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence Interval
c-KIT	Stem cell factor receptor
CR	Complete response
CRF	Case report form
CT	Computerized tomography
DFSP	Dermatofibrosarcoma protuberans
DVT	Deep vein thrombosis
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GIST	Gastrointestinal stromal tumor
GSK	GlaxoSmithKline
HR	Hazard ratio
IP	Investigational product
ITT	Intent-to-treat
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MID	Minimally important difference
MFH	Malignant fibrohistiocytic
MUGA	multigated acquisition scan
NOS	Not otherwise specified
OS	Overall Survival
PD	Progressive disease
PDGF	Platelet derived growth factor
PDGFR	Platelet derived growth factor receptor
PE	Pulmonary embolism
PFS	Progression-Free survival
PNET	Primitive neuroectodermal tumor
PR	Partial response
PS	Performance status
QOL	Quality of life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SEER	Surveillance, Epidemiology and End Results
sNDA	Supplemental New Drug Application
STBSG	Soft tissue and bone sarcoma group
STS	Soft tissue sarcoma
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal

UPC	Urine protein creatinine
US	United States
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VTE	Venous thromboembolic event
WHO	World Health Organization

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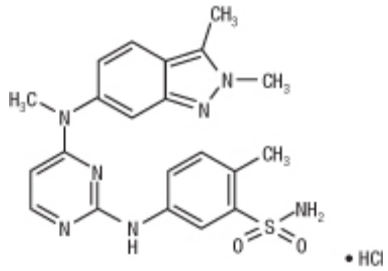
1. INTRODUCTION AND BACKGROUND

Pazopanib, discovered and developed by GlaxoSmithKline (GSK), is an angiogenesis inhibitor targeting the tyrosine kinase activity of vascular endothelial growth factor receptor (VEGFR)-1, 2 and 3, platelet-derived growth factor receptor (PDGFR)-α, and β, stem cell factor receptor (c-KIT), interleukin-2 inducible kinase (ITK), leukocyte specific tyrosine kinase (Lck) and transmembrane glycoprotein receptor tyrosine kinase (c-Fms) [Kumar, 2007; Figure 1]. Pazopanib affinity for selected receptors is shown in Table 4.

Figure 1 Structure of Pazopanib



Molecular formula: C21H23N7O2S•HCl

Chemical name: 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride

Mol. Wt: 473.99

Table 4 Kinase Affinity Profile

	$K_{i\ app}$	IC50 (nm)
VEGFR-1	15	10
VEGFR-2	8	30
VEGFR-3	10	47
PDGFR-α	30	71
PDGFR-β	14	84
c-KIT	2.4	74
FGFR1	-	140
FGFR3	-	130

$K_{i\ app}$ = apparent inhibition constant
IC50= concentration of compound producing half-maximal inhibition

Tumors require new vasculature for growth and produce signals to promote angiogenesis. Many angiogenic factors transmit their signals via receptor tyrosine kinases that are targeted by pazopanib, including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and fibroblast growth factor (FGF). These receptors are often expressed on tumor cells and VEGFR and PDGFR are also expressed on vasculature (endothelial cells express VEGFR and pericytes express PDGFR). A number

of anti-angiogenic strategies to treat cancer have been tested, including inhibitors of angiogenic factor signalling (e.g., VEGFR inhibitors), disruption of existing tumor vasculature, and inhibition of angiogenic factor release. Several anti-angiogenic agents have received regulatory approval for treating specific cancers.

GlaxoSmithKline (GSK) initiated a comprehensive clinical development program in 2002 to investigate pazopanib either as monotherapy or in combination with other therapies for the treatment of various cancers. Pazopanib has since been evaluated in multiple Phase I, II, and III cancer studies, and shown anti-tumor activity in patients with renal cell carcinoma (RCC) and soft tissue sarcoma (STS), as well as ovarian cancer, non-small cell lung cancer, thyroid cancer, and cervical cancer. Pazopanib was approved in 2009 by the Food and Drug Administration (FDA) as a monotherapy treatment for patients with advanced RCC.

Currently, pazopanib is approved for use in 74 markets globally, for the treatment of RCC. The estimated cumulative worldwide post-marketing exposure of pazopanib since approval is in excess of 2,800 patient years. As of 30 September 2011, a total of 4,115 patients have received pazopanib therapy in clinical trials, including 3089 patients who received pazopanib as monotherapy and 1,026 who received it in combination with other therapies.

In June 2011, GSK submitted a supplemental new drug application (sNDA) to support the use of pazopanib in the treatment of metastatic STS. Evidence to support the STS indication is provided by the pivotal Phase III double-blind, randomized, placebo-controlled study VEG110727 and the supportive open-label Phase II study VEG20002.

1.1. Soft Tissue Sarcoma

Sarcomas are a group of solid tumors originating from mesenchymal cells and their precursors. Soft tissue sarcomas arise from fat, nerves, muscles, joints, blood vessels and other connective tissues and osteosarcomas and chondrosarcomas arise from bone and cartilage, respectively. STS are comprised of over 50 histologic subtypes, the most common among adults in the United States (US) being leiomyosarcoma (20.8%), undifferentiated pleomorphic sarcoma (14.9%) and liposarcoma (12.6%) [Surveillance, Epidemiology, and End Results SEER, 2009; Toro, 2006]. STS accounts for less than 1% of all new malignancies in adults, and approximately 2% of total cancer-related mortality [Fletcher, 2002; Altekruse, 2009]. The incidence of STS reported in the US in 2011 was 10,980 [ACS, 2011].

1.2. Therapies for Metastatic STS

Surgery, often combined with radiation therapy, offers the only potential cure for localized STS. Adjuvant chemotherapy has not been shown to increase overall survival. Over half of patients with STS develop metastatic disease. With the exception of Ewing's family sarcomas and embryonal rhabdomyosarcoma, metastatic STS are incurable. The median OS from the time metastases are found is 12-18 months.

Metastatic STS are treated with cytotoxic agents and choice of therapy is generally not determined by histologic subtype, although specific therapies are used for Ewing's family

sarcomas, embryonal rhabdomyosarcoma, gastrointestinal stroma tumor (GIST) and dermatofibrosarcoma protuberans (DFSP). Doxorubicin is the only FDA approved agent for treatment of STS and no new agents have been approved in more than 2 decades for STS with the exception of GIST and DFSP.

In the first line metastatic setting single agent doxorubicin or combination therapy with either doxorubicin and ifosfamide or gemcitabine and docetaxel are generally used. No single agent has been shown to be superior to doxorubicin [Lorigan, 2007] and although response rates are higher with combination therapy, there is no increase in overall survival when ifosfamide is added to doxorubicin [Le Cesne, 2000]. One study showed that the combination of gemcitabine plus docetaxel led to longer OS compared with gemcitabine alone, in patients with performance status 0 who had received 0-3 prior regimens [Maki, 2007]. A second study comparing the same regimens found no benefit of the combination [Duffaud, 2008].

Sequential single agents are generally used in second and later lines of therapy for metastatic disease, including ifosfamide, trabectedin, gemcitabine, taxanes and decarbazine. The use of these therapies is based largely on data from Phase II clinical trials. The efficacy and safety of these agents in representative Phase II STS studies is summarized in Table 29.

No placebo-controlled trials have been conducted in STS, so the true benefits of current therapies in prolonging progression-free and overall survival are unknown. This is reflected in the recommendations in National Comprehensive Cancer Network (NCCN) guidelines for metastatic STS, which are based on category 2A or 2B evidence [NCCN, 2011]. There is a compelling unmet medical need for new therapies for metastatic STS whose benefits are demonstrated by randomized Phase III trials.

1.3. Rationale for Pazopanib in STS

Angiogenesis is a hallmark of cancer progression [Hanahan, 2011]. VEGF is a critical driver of angiogenesis and several agents targeting either the ligand or its receptors have shown clinical benefit in patients with diverse tumor types. VEGF expression has been observed in many STS, including leiomyosarcoma, angiosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma and carcinosarcoma [Potti, 2004] and is associated with a higher tumor grade [Pakos, 2005] and shorter metastasis-free and OS [Yudoh, 2001]. Further, circulating VEGF levels are higher in patients with STS and are associated with histological grade of the tumor [Graeven, 1999; Hayes, 2004; Yoon, 2004; Yoon, 2006]. More recently, mutation in VEGFR-2 gene has been observed in 10% of angiosarcomas [Antonescu, 2009].

Platelet-derived growth factor (PDGF) is expressed by the majority of STS and basic fibroblast growth factor (bFGF) is expressed by many. High PDGFR expression is correlated with higher tumor grade and increased cell proliferation [Graeven, 1999; Wang, 1994; Yoon, 2004; Yoon, 2006]. Taken together, these findings provide a strong rationale for the commonality of angiogenesis as a target across STS subtypes and for evaluating pazopanib in STS as an angiogenesis inhibitor targeting VEGFR, PDGFR and FGFR kinases.

1.4. Regulatory History

In December 2007, GSK held an End of Phase II meeting with FDA to discuss the proposed development program of pazopanib for treatment of STS. Preliminary agreement was reached on the proposed patient population and comparator for the proposed Phase III study VEG110727. With regard to PFS as the primary endpoint to support approval, FDA recommended that the study be powered for OS, and that the study should incorporate an independent blinded radiologic review. FDA also stated that for PFS to support potential approval, the magnitude of effect should be robust and there should be an appropriate risk benefit ratio.

In June 2008, Protocol VEG110727 was initiated; it was subsequently amended twice as follows:

- Amendment 1 (June 2009): The first protocol amendment affected all sites and included modifications/clarifications to the eligibility criteria, additional dose and safety guidance, and modifications of visits schedule and follow up. While the original protocol included a pre-specified allowance for an increase in sample size (i.e. if supported by feasibility), this amendment specifically included an increase in sample size from 255 to 360 patients which allowed for a better estimate of the overall survival and safety in this study.
- Amendment 2 (June 2010): The second protocol amendment also affected all sites and clarified use of other agents post last dose; added additional safety guidelines and monitoring, and clarified unblinding.

In October 2009 pazopanib was granted an orphan-drug designation for the “treatment of soft tissue sarcoma” by the FDA Office of Orphan Products Development.

In May 2011, GSK held a pre-sNDA meeting with FDA where agreement was reached on the overall format and content of the proposed sNDA.

In June 2011, GSK submitted to FDA the initial sNDA.

In October 2011, GSK submitted to FDA the 120-day Safety Update to the pending supplemental application.

In January 2012, GSK submitted to FDA the final OS data for study VEG110727.

2. CLINICAL PHARMACOLOGY OF PAZOPANIB

A dose of 800 mg once daily was studied in STS based on the recommended Phase II dose in study VEG10003(first time in human Phase I dose finding study) and the effectiveness of this dose in treating advanced RCC and other tumor types. Pharmacodynamic effects were observed at a dose of 800 mg once daily, indicating inhibition of VEGFR-2. There was a concentration-effect relationship between trough plasma pazopanib concentrations and a clinically significant increase in blood pressure in Study VEG10003 and with the percent change from baseline in sVEGFR-2 nadir in study VEG102616 (Phase II trial in RCC).

3. CLINICAL STUDIES SUPPORTING EFFICACY IN METASTATIC SOFT TISSUE SARCOMA

The clinical development plan to support efficacy in metastatic STS is provided by the pivotal Phase III double-blind, randomized, placebo-controlled study VEG110727 and the supportive open-label Phase II study VEG20002. Both studies were conducted by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG), an academic collaborative group comprised of sarcoma investigators. GSK sponsored both studies.

Details of the study designs and outcomes are presented following Table 5.

Table 5 Overview of Studies Supporting the Registration Application for Pazopanib in STS

Study	VEG110727	VEG20002
	Pivotal	Supportive
Critical Design Features	Phase III Randomized (2:1, pazopanib: placebo) Double-blind Placebo-controlled 800 mg once daily dose	Phase II, Simon 2-stage Non-randomized Open-label Single-arm 800 mg once daily dose
Study Population	Metastatic STS with confirmed disease progression during or following therapy (up to 4 prior lines of systemic treatment for advanced disease). Progression within 6 months of prior therapy for advanced disease or within 12 months of neoadjuvant/adjuvant therapy Disease progression on or after anthracycline-based regimen WHO PS 0 or 1 -Leiomyosarcoma -Synovial sarcoma -Other types of STS (excluding GIST and adipocytic sarcoma)	Advanced and/or metastatic STS that was refractory or relapsed (no more than 1 combination or two single agents of chemotherapy regimen for advanced disease); Objective progression within the last 6 months WHO PS 0 or 1 -Leiomyosarcoma -Synovial sarcoma -Adipocytic tumors -Other types of STS (excluding GIST)
Number of patients	369 patients Pazopanib: 246 Placebo: 123	142 patients
Efficacy endpoints		
Primary	PFS (by independent review)	Progression-free rate at Week 12
Secondary	OS (principal); ORR; Duration of response, Time to response	PFS OS ORR Duration of response, Time to response
Assessment Measure and Timing of Assessments for PFS	RECIST v1.0 of scans (CT/MRI) Blinded independent radiologist for primary efficacy Assessed at baseline, Week 4, Week 8, Week 12, and every 8 weeks thereafter.	RECIST v1.0 of scans (CT/MRI) Investigator plus peer reviewer[a] for primary efficacy; investigator for PFS and other secondary efficacy Assessed at baseline and every 12 weeks.

CT: computerized tomography; GIST: gastrointestinal stromal tumor; MRI: magnetic resonance imaging; OS: overall survival; ORR: overall response rate; PFS: progression-free survival; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumors; STS: soft tissue sarcoma; WHO: World Health Organization

a. Peer Review: Patients who were alive and assessed by the investigator as complete response, partial response or stable disease at Week 12 also had their scans reviewed by peers at Erasmus University Medical Center in Rotterdam.

3.1. VEG20002

3.1.1. VEG20002 Study Design

VEG20002 was a non-randomized proof of concept, two-stage, Phase II study conducted by EORTC in collaboration with GSK to evaluate the anti-tumor activity and safety of pazopanib in patients with recurrent, metastatic leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and “other eligible subtypes of STS”.

3.1.1.1. Study Population

The study population consisted of patients with intermediate or high grade, metastatic STS with documented evidence of disease progression within 6 months of chemotherapy for advanced disease.

Patients with GIST and DFSP, embryonal rhabdomyosarcoma and Ewing tumors were ineligible since accepted standard of care therapies are available for these subtypes. Other tumors that do not generally metastasize or that are not classified as sarcomas were also excluded.

3.1.1.2. Choice of Endpoint

The progression-free survival rate at Week 12 was the primary endpoint. This was selected based on data from the EORTC-STBSG historical data for differentiation of active and inactive agents in patients with STS treated with second-line therapy, in which active therapies had a progression-free survival rate at 12 weeks of >40% and inactive therapies of <20% [Van Glabbeke, 2002]. Only doxorubicin and ifosfamide were considered to have demonstrated significant antitumor activity among the 11 different agents studied by the EORTC-STBSG.

Secondary endpoints were overall progression-free survival, OS, objective response rate, time to response, duration of response, and safety.

3.1.1.3. Study Design and Statistical Assumptions

Prior to randomization, patients were stratified into one of 4 histological subgroups:

- Leiomyosarcoma (uterine, skin or non organ origin)
- Adipocytic tumors (liposarcoma dedifferentiated, myxoid/round cell, pleomorphic, mixed type, not otherwise specified [NOS])
- Synovial sarcoma
- Other eligible types of high or intermediate grade malignant STS (Fibroblastic, so-called malignant fibrohistiocytic (MFH) [pleomorphic “MFH”, giant cell “MFH”, inflammatory “MFH”], malignant glomus tumors, skeletal muscles [rhabdomyosarcoma, alveolar or pleomorphic, excluding embryonal rhabdomyosarcoma], vascular [epithelioid haemangioendothelioma, angiosarcoma], uncertain differentiation [epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma], malignant peripheral nerve sheath tumors, malignant solitary fibrous tumors, undifferentiated soft tissue sarcomas NOS, other types of sarcoma (not listed as ineligible).

The Simon optimal one sample two stages testing procedure (optimal design) was used [Simon, 1988], with the following hypotheses:

- 12 week progression-free rate of less than or equal to 20% in one of the strata is consistent with the null hypothesis, and would not warrant further investigation.

- 12 week progression-free rate greater than or equal to 40% in one of the strata will support the alternate hypothesis warranting further investigation of the drug in this stratum.

Up to 37 patients were to be recruited into each stratum in two stages, contingent upon a prerequisite progression-free rate following Stage 1 to continue enrolment into Stage 2. Patients received oral pazopanib 800 mg once daily. Treatment was continued until PD, death, unacceptable drug related AEs, intercurrent illnesses preventing further drug administration, or patient refusal. Patients were followed for survival.

3.1.2. VEG20002 Study Processes

3.1.2.1. Pathology Review

Allocation of a patient to a stratum at study entry was based on the diagnosis by the local pathologist. After enrolment, a tissue sample was sent to an independent expert sarcoma pathology panel for STS classification.

Final allocation for analysis purposes was based upon determination by a single central pathologist. Where a tissue sample was not reviewed or diagnosis was unavailable, the local pathologist classification was used.

3.1.2.2. Radiology Review

The progression-free survival rate at Week 12 was based on peer radiology review of the investigator-assessed complete response (CR), partial response (PR) and stable disease (SD) responses at Week 12. Patients who were assessed by the investigator as CR, PR or SD at Week 12 had their scans “peer reviewed” by the Protocol Chair, Dr. Stefan Sleijfer and Professor Jaap Verweij in conjunction with radiologists at Erasmus Medical Center. The primary analysis used the response assigned by the peer reviewer; if the response by the peer review was missing the investigator response was used.

The primary analysis was also repeated using the investigator response to remove any bias which may have been introduced by not all patients having their scans peer reviewed.

3.1.3. VEG20002 Study Population Results

The study was conducted at 15 centers in 5 European countries. A total of 142 patients were enrolled. Four patients were considered not evaluable for efficacy because of absence of target lesions or lack of evidence of documented disease progression at trial entry; these patients were therefore excluded from the Intent-to-Treat (ITT) Population.

A total of 140 (99%) patients received one or two prior cytotoxic chemotherapies either in the neo-adjuvant/adjuvant and/or advanced disease settings. Two patients were considered unsuitable for chemotherapy. The median age was 51 years. There was an equal proportion of male and female patients (50% each), and similar proportions of patients who were World Health Organization (WHO) performance status (PS) 0 vs. 1 at baseline (48% vs. 51%, respectively).

3.1.4. VEG20002 Efficacy Results

Efficacy data are presented in Table 6. Progression-free survival at Week 12 greater than 40% was demonstrated in the leiomyosarcoma, synovial sarcoma, and "other STS" strata following Stage 2.

The adipocytic stratum had 17 patients enrolled at the end of Stage 1 based on local pathology. Two of these patients were progression-free at Week 12. This result did not meet the prerequisite progression-free rate at Week 12 to progress to Stage 2, so enrolment was closed at the end of Stage 1. However, one additional patient who had SD at Week 12 was enrolled into this stratum around the time of this decision who was progression-free at Week 12. Following central pathology review, a total of 19 patients were assigned to the adipocytic stratum. Five of these 19 patients were progression-free at Week 12. Therefore, the activity of pazopanib in patients with adipocytic STS was indeterminant.

Table 6 Key Efficacy Data from Supportive Study VEG20002 (ITT population)

	Leiomyo-sarcoma N=41	Adipocytic sarcoma N=19[a]	Synovial sarcoma N=37	Other STS N=41	Total N=138
Progression-free Survival Rate at Week 12[b] - Peer + Investigator Assessment[c]					
CR+PR+SD, n (%) 90% CI p-value[d]	18 (44) (30.6, 57.9) <0.001	5 (26) (11.0, 47.6) 0.653	18 (49) (34.3, 63.2) <0.001	17 (41) (28.4, 55.5) 0.003	58 (42) (34.9, 49.4) <0.001
Progression-free Survival (months)– Investigator Assessment					
Median (90% CI)[e]	4.0 (2.8, 5.6)	2.6 (1.6, 2.7)	5.4 (2.7, 6.8)	3.2 (2.8, 8.4)	2.8 (2.8, 5.2)
Overall Survival (months)					
Median (90% CI)[e]	11.7 (10.6, 17.6)	6.5 (4.2, 19.3)	10.3 (7.6, 13.2)	9.8 (7.6, 11.3)	10.6 (9.5, 11.7)
Best Overall Response Rate – Investigator Assessment					
CR+PR, n (%) 90% CI[c]	1 (2) (0.1, 11.1)	0 (0.0, 11.4)	4 (11) (3.8, 23.1)	3 (7) (2.0, 17.8)	8 (6) (2.9, 10.2)

CI: confidence interval, CR: complete response; ITT: Intent-to-treat; PR: partial response; SD: stable disease; STS: soft tissue sarcoma

a. The adipocytic stratum had 17 patients enrolled at the end of Stage 1. Progression-free survival rate at Week 12 was noted in 2 of the 17 patients. This result did not meet the prerequisite progression-free survival rate at Week 12 to progress to Stage 2. One additional patient was enrolled into this stratum around the time this decision was made bringing the total patients to 18. This patient was also reported to have SD at Week 12. Subsequently, a Central Pathology Review was conducted after enrolment was completed in the study. A total of 19 patients were assigned to the adipocytic stratum by the end of the study due to additional interchanging of patients amongst the strata after central pathology review. By the end of the study 5 of 19 patients were progression-free at Week 12.

b. The case report form does not explicitly state which assessment is Week 12 for the investigator data. The analysis used the first post-baseline assessment.

c. Scans assessed by investigator as CR, PR and SD were peer reviewed, but scans assessed by investigator as PD were not.

d. p-value=the strength of evidence to reject the null hypothesis of the response rate being equal to 20% with an alpha level of 0.10.

3.2. VEG110727

3.2.1. VEG110727 Study Design

VEG110727 was a pivotal Phase III, randomized, double-blind, placebo-controlled, multicenter international study. It was conducted by EORTC in collaboration with GSK.

3.2.1.1. Patient Population

The study population consisted of patients who had metastatic high or intermediate grade malignant STS and confirmed disease progression within the past 6 months (or 12 months for those who had only received prior systemic [neo]-adjuvant therapy). Low grade tumors that were metastatic and had progressed on therapy were also included. Patients were required to have received no more than 4 prior lines of systemic therapies for advanced disease and no more than 2 combination regimens. In addition, all patients were required to meet the following criteria:

- Disease progression on or after an anthracycline-based regimen (except if medically contraindicated or refused by patient)
- Disease progression on or after available standard chemotherapies (except if anthracyclines were medically contraindicated or refused by patient)
- No previous treatment with angiogenesis inhibitors or VEGF- or VEGFR-targeting agents; mammalian target of rapamycin (mTor) inhibitors were not considered as inhibitors of angiogenesis

The following tumor types were eligible (grouped according to WHO classification):

- Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumors)
- So-called fibrohistiocytic (pleomorphic malignant fibrous histiocytoma [“MFH”], giant cell “MFH”, inflammatory “MFH”)
- Leiomyosarcoma
- Malignant glomus tumors
- Skeletal muscles (pleomorphic and alveolar rhabdomyosarcoma)
- Vascular (epithelioid hemangioendothelioma, angiosarcoma)
- Uncertain differentiation (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma) excluding chondrosarcoma, Ewing tumors / primitive neuroectodermal tumor (PNET)
- Malignant peripheral nerve sheath tumors
- Undifferentiated soft tissue sarcomas NOS
- Other types of sarcoma (not listed as ineligible), if approved by the medical monitors prior to registration

Tumor types listed below were ineligible for the study. Patients with adipocytic sarcoma were excluded based on indeterminate anti-tumor activity in VEG20002. Patients with gastrointestinal stromal cell tumors (GIST) and dermatofibrosarcoma protuberans (DFSP), embryonal rhabdomyosarcoma and Ewing tumors were ineligible since accepted standard of care therapies are available for these subtypes. Other tumors that do not generally metastasize or that are not classified as sarcomas were also excluded.

- Adipocytic sarcoma (all subtypes)
- All rhabdomyosarcoma that are NOT alveolar or pleomorphic
- Chondrosarcoma
- Osteosarcoma
- Ewing tumors / PNET
- GIST
- Dermofibromatosis sarcoma protuberans
- Inflammatory myofibroblastic sarcoma
- Malignant mesothelioma
- Mixed mesodermal tumors of the uterus

3.2.1.2. Choice of Primary Endpoint

Recurrent, metastatic STS is associated with substantial morbidity as a result of the tumor bulk, locations within the body, and aggressiveness of the disease. The endpoint of PFS is considered by experts in the field of STS, who designed the study, a direct measure of anti-tumor activity, and if of sufficient magnitude, clinical benefit.

3.2.1.3. Selection of Control Arm

As this was be an international multicenter study, a single comparator arm other than placebo was not considered feasible by investigators (EORTC-SBSTG and sarcoma experts) given the extensive and varied prior therapies received by patients, and the lack of proven active treatments after progression following doxorubicin.

A “physician’s choice” (allowing for more than one treatment option) for the comparator arm was considered inappropriate because patients had already received available standard chemotherapies at the treating institution. Such a control would not allow the study to be designed as a blinded study or permit a robust assessment of the safety profile of pazopanib in STS, given the diversity of salvage chemotherapy in STS with different inherent toxicities.

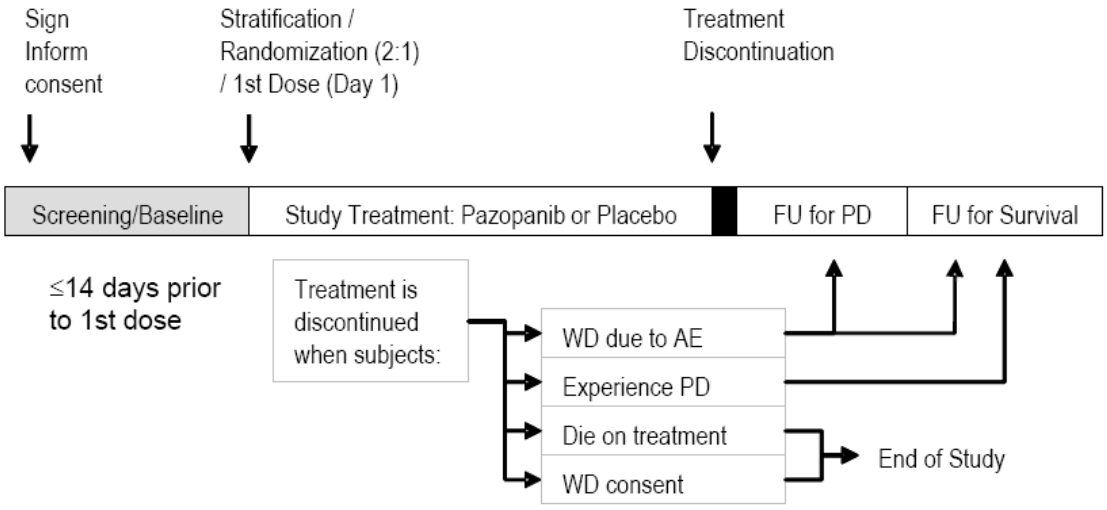
A placebo-controlled study was chosen to allow for the determination of efficacy and the clear delineation of the safety profile of pazopanib from symptomatology of disease in an objective and blinded fashion. The acceptance of this study design by investigators, Ethics Committees, and patients is testament to the paucity of therapies with proven efficacy and regulatory approval available for patients with recurrent, advanced STS.

3.2.1.4. Study Design and Statistical Assumptions

The primary objective of the study was to evaluate and compare PFS in pazopanib- vs. placebo-treated patients. The principal secondary objective was to evaluate and compare OS in the two treatment arms. Other secondary objectives were to evaluate PFS in the 3 histology subtypes (leiomyosarcoma, synovial sarcoma and "other" STS eligible histologies) recruited into the study, to compare the two treatment arms for overall response rate, to compare the two treatment arms for time to response and duration of response, and to assess safety and tolerability.

Eligible patients were stratified according to the following factors: WHO PS: 0 vs. 1 and the number of prior lines of systemic treatment for advanced disease: 0, 1 vs. 2+. Patients were then centrally randomized in a 2:1 ratio of pazopanib: placebo to receive 800 mg pazopanib daily dosing or matching placebo. Patients continued on study drug (pazopanib or placebo) until disease progression, death, unacceptable toxicity or withdrawal of consent (Figure 2).

Figure 2 Study Design



Note – subjects who withdrew from IP but did not withdraw consent for the study continued to be followed for PD and survival. Abbreviations: FU = Follow Up; WD = withdrew; PD = Progressive Disease; AE = Adverse Event, IP=investigational product.

Visits occurred every 4 weeks for the first 12 weeks of treatment, followed by visits every 8 weeks. Radiological assessments were performed for all patients at baseline (within 4 weeks prior to start of treatment), every 4 weeks until Week 12 and every 8 weeks thereafter until progression or starting a new anti-cancer treatment. Clinical assessments for safety occurred at baseline, every 4 weeks until Week 12 and every 8 weeks after Week 12. Adverse events were assessed throughout the study and were graded according to National Cancer Institute- Common Toxicity Criteria (NCI-CTC) for AEs, Version 3.0.

There was no cross-over to pazopanib at the time of progression for those patients randomised to placebo.

Patients who discontinued study drug prior to disease progression were to continue disease assessments according to the pre-defined protocol schedule until progression was documented or another anti-cancer treatment was initiated. All patients were followed for survival until death due to any cause or withdrawal of consent, whichever came first.

3.2.1.4.1. Statistical Assumptions, Sample Size and Analysis Methods

The trial was initially powered to detect a 37% decrease of the hazard rate for PFS (hazard ratio less than or equal to 0.63), corresponding to a 15% treatment difference (from 15% to 30%) in 6 months progression free survival. The 15% 6 months PFS estimate in the control group was based on STBSG experience [Van Glabbeke, 2002] and the 30% 6 months PFS estimate in the pazopanib treated group was based on the VEG20002 Phase II trial [Sleijfer, 2010]. A total of 224 PFS events were required to detect the targeted difference with 90% power and a 5% two-sided alpha level.

Overall survival was an important secondary end-point. The survival analysis was powered at 80% to detect a 33% decrease in the death hazard rate (hazard ratio less than or equal to 0.67), corresponding to an increase from 8 to 12 months in median OS.

Since STS is a rare disease, a high recruitment rate in this refractory setting was not expected; however the original protocol design allowed sample size to be increased based on a feasibility assessment during conduct of the study. After observing a recruitment rate greater than expected during the first six months of the study, GSK increased the sample size to 360 patients allowing for a better estimate of overall survival and safety in this study. At this time, approximately 130 patients had been recruited and there was no unblinding of any data.

When increasing the sample size, assumptions regarding PFS were not changed. However, the number of PFS events was increased from 224 events to 274 PFS events which provided at least 95% power on the primary endpoint at the time of the final analysis. The increase in sample size was not sufficient to allow detection of a small or moderate survival effect. The number of death events required for the final analysis of survival was increased from 206 to 279 which provided 90% power to detect a 4 month improvement in OS. An interim analysis of OS was to be performed at the time of analysis of the primary endpoint. This was to occur when the following criteria were met: at least 274 PFS events were documented, at least 195 deaths were documented (70% maturity for survival) and all patients had been followed for at least 3 months after registration.

A Lan & DeMets alpha-spending function, with O'Brien & Fleming like 2-sided boundaries (for efficacy and harm) was introduced to control the type I error rate (for OS), with a global alpha level of 5% (two-sided), and a global power of 90% (based on the 4 month treatment difference) due to the interim and final analysis for OS [Lan, 1983; O'Brien, 1979].

PFS and OS were to be summarized using Kaplan-Meier survival curves, and compared between treatment arms using a stratified log-rank test. The Pike estimator [Berry, 1991] of the treatment hazard ratio (HR) based on the corresponding stratified log-rank test statistic was provided together with a 95% CI and p-value.

For each treatment group, the Kaplan-Meier estimates for the median PFS time, and the first and third quartiles were to be calculated, along with approximate naïve 95% CI if there were a sufficient number of progressions or deaths (values could be undefined if there were not a sufficient number of deaths). Greenwood's formula [Collett, 2003] was used to calculate the standard error of the estimates from the Kaplan-Meier curve.

Sensitivity analyses for PFS were planned to assess the robustness of the data and are summarized in Table 7. These sensitivity analyses varied the assumptions for defining progression and censoring dates, the source of the assessment (investigator or independent radiologist), the population, the type of analysis and the statistical model.

The following subgroups were explored in the analysis of PFS and/or data by Kaplan-Meier analysis:

- Histology types: leiomyosarcoma, synovial and "other" STS histologies
- Baseline WHO PS: 0 vs. 1
- Number of prior lines of therapy for advanced disease (0, 1 vs. 2+)
- Age: Patients aged 65 or above at the time of screening; Patients aged 64 or below at the time of screening
- Race (White vs. Asian/Other)
- Gender
- Recruitment region: US, Europe/Australia and Japan/Korea
- Disease status: locally advanced and metastatic disease or metastatic disease only
- Number of prior agents (post-hoc analysis)
- Tumor grade at initial diagnosis (post-hoc analysis)

Table 7 Summary of Independent Reviewer Analyses of PFS – Primary and Sensitivity Analyses (ITT Population, VEG110727)

Analysis[a]	Description	Assessed by:	Statistical Analysis	Adjusted for:	Additional Unique Features of Analysis
Primary		Independent reviewer	Stratified log rank test; Pike estimator	Randomization strata	
Sensitivity Analyses					
1	Per protocol population	Independent reviewer	Stratified log rank test; Pike estimator	Randomization strata	
2	Unadjusted for stratification factors	Independent reviewer	Log rank test; Pike estimator	Unadjusted	
3	Investigator assessment	Investigator	Stratified log rank test; Pike estimator	Randomization strata	
4	Investigator assessment unadjusted for stratification factors	Investigator	Log rank test; Pike estimator	Unadjusted	
5	Investigator assessment including clinical progressions	Investigator	Stratified log rank test; Pike estimator	Randomization strata	Includes symptomatic progressions as an event for patients who have symptomatic progression without later having radiologic documented progression
6	Without censoring for PD/death after extended period of inadequate assessment	Independent reviewer	Stratified log rank test; Pike estimator	Randomization strata	No censoring for extended loss to follow-up
7	With adjustment for earlier investigator assessments of progression	Independent reviewer	Stratified log rank test; Pike estimator	Randomization strata	Patients treated as progression at the next scheduled visit if investigator calls progression and the independent review would lead to censoring
9	Censoring patients who permanently stopped investigational product prior to radiological progression	Independent reviewer	Stratified log rank test; Pike estimator	Randomization strata	Patients censored if study medication stopped without radiologically documented progression
10	Cox regression adjusted for stratification factors	Independent reviewer	Cox proportional hazards model	Randomization strata	
11	Cox regression stepwise selection of covariates	Independent reviewer	Cox proportional hazards model with stepwise variable selection	Selected covariates	Covariates selected from baseline WHO PS, number of prior lines of systemic treatment for advanced disease, age, gender, race, metastatic disease and histology types

ITT: Intent-to-Treat population; WHO PS: World Health Organization Performance Status

a. Sensitivity analysis 8 (which adjusted for the impact of surgery) was not conducted because less than 5% patients in either treatment group received surgery due to a reduction in their tumors.

3.2.2. VEG110727 Study Processes

3.2.2.1. Pathology Review

Eligibility was based on the diagnosis by the local pathologist. Once the patient was randomized, a tissue sample was sent to one of two independent expert pathologists to assess the STS histology subtype.

Classification for analysis purposes was based upon determination by the expert. Where a tissue sample was not reviewed or diagnosis was unavailable, the local pathologist classification was used.

3.2.2.2. Disease Assessment (Radiology Review)

The primary method for assessing disease progression was based on radiological assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.0.

A blinded central radiologic review of all patients was implemented. Each scan was reviewed by one of two expert sarcoma radiologists. There was no adjudication. This review was the basis of the primary efficacy analysis, whereas the investigator assessment of progression was used as a sensitivity analysis for the PFS endpoint. Every effort was to be made to document objective disease progression using the appropriate imaging modality. For patients that required discontinuation of treatment without objective evidence of progression, investigators were instructed to follow them for objective progression by continued RECIST evaluations.

3.2.3. VEG110727 Study Population Results

3.2.3.1. Patient Disposition

A total of 369 patients with STS as specified in the protocol were centrally enrolled between October 2008 and February 2010 at 72 centers in 13 countries. Two hundred forty-six patients were randomized to pazopanib and 123 patients to placebo. The clinical cut-off for the PFS analysis was 22 November 2010 and 24 October 2011 for the final OS analysis.

As of the final OS analysis, 6 patients remained on pazopanib treatment (Table 8). All patients in the placebo group had discontinued study treatment. A total of 70 patients were off study treatment and continuing follow up in the study.

Table 8 Summary of Final Treatment Status and Reason for Discontinuation (VEG110727, ITT Population)

	Placebo (n=123)	Pazopanib (n=246)
Patient Status, n (%)		
Died	95 (77)	185 (75)
Ongoing	24 (20)	52 (21)
On study treatment	0	6 (2)
In follow up	24 (20)	46 (19)
Withdrawn from study	4 (3)	9 (4)
Primary reason for discontinuation of study treatment		
Reasons not associated with AEs or toxicities, n (%)		
Progression of disease/relapse/clinical progression/death due to PD	119 (97)	178 (72)
Patient refusal/patient decision	1 (<1)	14 (6)
Protocol violation	0	3 (1)
Lost to follow up	0	0
Study closed/terminated	0	0
Missing	0	0
Discontinuations due to toxicities/AEs/or death (not due to PD), n (%)		
Toxicity related to the study drug (or toxic death)	1 (<1)	34 (14)
Adverse event not related to the study drug	2 (2)	7 (3)[a]
Intercurrent death (not due to malignant disease or toxicity)	0	3 (1)[b]
Other	0	1 (<1)[c]

Abbreviations: AE=adverse event, PD=progressive disease

a. Includes Patients 38 (acute renal failure), 47 (abdominal pain due to tumor invasion that caused perforation, peritonitis, and bleeding of the sigmoid), 86 (acute abdominal pain due to PD), 147 (recurrent infection [septicaemia]), 165 (pulmonary embolism occurred), 290 (not recovered from pericardial effusion), and 300 (congestive heart failure). Patients 47, 86 and 165 did not receive study drug.

b. Patients 310, 246, 366

c. Patient 353 (surgery unrelated to disease under study)

3.2.3.2. Demographic and disease characteristics

Demographic characteristics were well balanced between the treatment arms (Table 9). The median age of all patients was 55 years, 59% were female, 72% white and 23% Asian. Prior to randomization, patients were stratified by WHO performance status (0 vs. 1) and the number of prior lines of systemic treatment for advanced disease (0, 1 vs. 2+) (Table 9).

Table 9 Summary of Demographic Characteristics (VEG110727, ITT Population)

	Placebo (N=123)	Pazopanib (N=246)	Total (N=369)
Age (yrs)			
Median (min.-max.)	51.0 (18-78)	56.0 (20-83)	55.0 (18-83)
Sex, n (%)			
Female	69 (56)	147 (60)	216 (59)
Male	54 (44)	99 (40)	153 (41)
Race, n (%)			
African American/African Heritage	2 (2)	4 (2)	6 (2)
Asian	27 (22)	57 (23)	84 (23)
White	91 (74)	175 (71)	266 (72)
Mixed Race	1 (<1)	0	1 (<1)
Unknown	2 (2)	9 (4)	11 (3)
Region, n (%)			
Europe & Australia	82 (67)	163 (66)	245 (66)
Japan & Korea	24 (19)	57 (23)	81 (22)
US	17 (14)	26 (11)	43 (12)
Performance Status (WHO), n (%)			
0	60 (49)	118 (48)	178 (48)
1	63 (51)	128 (52)	191 (52)
Prior lines of systemic treatment for advanced disease, n (%)			
0 or 1 prior lines if therapy	52 (42)	110 (45)	162 (44)
2+ prior lines of therapy	71 (58)	136 (55)	207 (56)

The leiomyosarcoma subgroup was 43% of the population, synovial sarcoma 10%, and the "other STS histologies" 47% (Table 10). Forty-three percent of patients had 3 or more sites of disease and the median sum of the longest diameter of target lesions was 13.11 cm.

As shown in Table 10, slightly more patients on the placebo arm had high grade tumors (73%) than patients on the pazopanib arm (65%). Nearly all of the histologic grades reported were from biopsies at the time of the patients' initial diagnosis at a median of 26.7 months prior to enrolment. Tumor grade is known to change or "migrate" over time and therefore, tumor grade from original pathology tissue in patients may not reflect the patients' diagnosis at the time of enrolment [Ferguson, 2004; Tsujimoto, 1988].

Table 10 Baseline Disease Characteristics (VEG110727, ITT Population)

	Placebo (N=123)	Pazopanib (N=246)	Total (N=369)
Histology subgroups, n (%)			
Leiomyosarcoma	49 (40)	109 (44)	158 (43)
Synovial	13 (11)	25 (10)	38 (10)
"Other"	61 (50)	112 (46)	173 (47)
Grade at initial diagnosis (local pathology assessment), n (%)			
Low grade	3 (2)	24 (10)	27 (7)
Intermediate grade	30 (24)	63 (26)	93 (25)
High grade	90 (73)	159 (65)	249 (67)
Number of sites of disease[a], n (%)			
1	31 (25)	60 (24)	91 (25)
2	35 (28)	87 (35)	122 (33)
3-4	48 (39)	83 (34)	131 (36)
>4	9 (7)	16 (7)	25 (7)
Time since initial diagnosis (months)	n=123	n=240	n=363
Median	27.0	26.6	26.7
Time since last progression (months)[b]			
Median	0.6	0.7	0.6
Patients with at least one target lesion, n (%)	118 (96)	234 (95)	352 (95)
Sum of the longest diameters (cm)			
Min.	1.3	1.0	1.0
1st quartile	6.83	7.03	7.02
Median	12.55	13.53	13.11
Mean	15.11	16.60	16.10
3rd quartile	20.70	21.82	21.66
Max.	50.2	66.9	66.9

a. As indicated by the investigator using the eligibility form.
b. Time since last progression was defined as the time from last progression prior to study entry until randomization. The protocol allowed for patients to have radiological progression within the past 6 months or 12 months for those patients who had only received prior systemic (neo)-adjuvant therapy.

3.2.3.3. Histology

As per protocol, tissue was submitted for central pathology review. Ninety three percent (N=344) of all patients enrolled in the study had a centrally-reviewed pathology diagnosis (Table 11). In instances where the central pathologists were unable to assign definitively a histologic diagnosis due to inadequate tissue or other reasons (7% of patients; N=25), the diagnostic determination of the local pathologist was used in accordance with the Statistical Analysis Plan.

In contrast to central radiology review where the exact images can be viewed by the local and a central reviewer, expert sarcoma pathologists sometimes have significant limitations, including the amount of tissue available for review and clinical information, as compared to the local pathologist. Even when examining the same histologic

specimens, inter-observer discordances can exceed 25-35% between experts [Arbiser, 2001; Lehnhardt, 2008; Lurkin, 2010; Thway, 2009].

Of the 344 patients with both central and local pathology diagnosis, the overall agreement on histology was 71%. In the 29% of specimens where disagreement was noted between central pathology and local pathology diagnosis, all but 4 patients had a protocol eligible soft tissue sarcoma subtype based on the central review.

Table 11 Summary of Tumor Description (VEG110727, ITT Population)

Tumor type[a]	Tumor subtype[a]	Number (%) of Patients	
		Placebo (N=123)	Pazopanib (N=246)
Smooth muscle tumours	Leiomyosarcoma (excluding skin)	49 (40)	109 (44)
Tumours of uncertain differentiation	Synovial sarcoma	13 (11)	25 (10)
	Epithelioid sarcoma	5 (4)	7 (3)
	Alveolar soft part sarcoma	4 (3)	6 (2)
	Desmoplastic small round cell tumour	1 (<1)	3 (1)
	Clear cell sarcoma	2 (2)	1 (<1)
	Extra-renal rhabdoid tumour	0	1 (<1)
	Neoplasms with perivascular epithelioid cell differentiation (PEComa)	0	1 (<1)
	PNET/Extraskeletal Ewing tumour	2 (2)	0
Fibroblastic	Myxofibrosarcoma	6 (5)	8 (3)
	Solitary fibrous tumour	4 (3)	8 (3)
	Sclerosing epithelioid fibrosarcoma	0	3 (1)
	Adult fibrosarcoma	0	2 (<1)
	Low grade fibro myxoid sarcoma/hyalinizing spindle cell tumour	0	1 (<1)
So-called fibrohistiocytic tumours	Undifferentiated pleomorphic sarcoma (pleomorphic MFH)	11 (9)	20 (8)
	Undifferentiated pleomorphic sarcoma with giant cells (giant cell "MFH")	0	1 (<1)
Undifferentiated sarcoma NOS	N/A	5 (4)	15 (6)
MPNST	N/A	4 (3)	8 (3)
Vascular tumours	Angiosarcoma	3 (2)	3 (1)
	Epithelioid haemangioendothelioma	0	1 (<1)
Skeletal muscle tumours (rhabdomyo-sarcoma)	Embryonal (incl spindle cell, botryoid, anaplastic)	1 (<1)	0
	Alveolar rhabdomyosarcoma (incl solid anaplastic)	1 (<1)	0
Adipocytic (liposarcoma)	Dedifferentiated	0	1 (<1)
Pericytic	Malignant glomus tumour	1 (<1)	0
Chondro-osseous tumours	Extraskeletal osteosarcoma	1 (<1)	0
Other	N/A	10 (8)	22 (9)

Abbreviations: MFH=Malignant fibrous histiocytoma; MPNST=Malignant Peripheral Nerve Stromal Tumors; N/A=Not applicable; NOS=Not otherwise specified; PNET=Primitive neuroectodermal tumor

a. Tumor type and tumor subtype are from the WHO classification of soft tissue sarcoma 2002 (modified June 2008)

b. Note: Tumor type and tumor subtype are reported from the central review data unless the review was not conducted. If the review was not conducted, the investigator assessment has been used. Patients without the tumor type of Leiomyosarcoma or Synovial sarcoma are included in the Other histologies ITT population

3.2.3.4. Prior Anti-cancer Therapy

All patients received prior anti-cancer chemotherapy either in the neo-adjuvant, adjuvant, and/or advanced disease settings for the treatment of STS and most were heavily pre-

treated. Prior anti-cancer therapy was generally well balanced between the treatment arms. The majority of patients (93%) had received therapy for metastatic (advanced) disease. Twenty seven patients (7%) received neoadjuvant/adjuvant therapy only, and all of them received an anthracycline containing regimen; 22 patients (6%) had progressed within 6 months and 5 patients (1%) had progressed within 6-12 months of such therapy. Fifty-four percent of patients had received 2 or more lines of prior therapy for advanced disease while 21% received 3 or more lines. The most common prior systemic therapy was doxorubicin, which was given to 98% of patients in both treatment arms. The frequencies of prior surgery and prior radiotherapy were similar between treatment arms (93% vs. 91% with prior surgery and 61% vs. 52% with prior radiotherapy for the placebo and pazopanib groups, respectively).

Table 12 Summary of Prior Systemic Therapy for Neo-adjuvant, Adjuvant, Maintenance and Advanced Disease (ITT Population)

	Number (%) of Patients		
	Placebo (N=123)	Pazopanib (N=246)	Total (N=369)
Systemic therapy			
Neo-adjuvant	19 (15)	31 (13)	50 (14)
Adjuvant	26 (21)	43 (17)	69 (19)
Maintenance	4 (3)	10 (4)	14 (4)
Advanced, 1st line	110 (89)	232 (94)	342 (93)
Advanced, 2nd line	67 (54)	132 (54)	199 (54)
Advanced, 3rd line	28 (23)	51 (21)	79 (21)
Advanced, 4th line	9 (7)	16 (7)	25 (7)
Surgery	114 (93)	224 (91)	338 (92)
Radiotherapy	75 (61)	128 (52)	203 (55)
Other therapy[a]	15 (12)	11 (4)	26 (7)
Systemic therapy received by ≥2% of patients in both treatment group			
Any systemic therapy	123 (100)	246 (100)	369 (100)
Anthracycline[b]	121 (98)	243 (99)	364 (99)
Ifosfamide	97 (79)	167 (68)	264 (71)
Gemcitabine	42 (34)	85 (35)	127 (34)
Taxane	37 (30)	74 (30)	111 (30)
Dacarbazine	20 (16)	41 (17)	61 (16)
Trabectedin	22 (18)	38 (15)	60 (16)
Cisplatin/Carboplatin	16 (13)	38 (15)	54 (15)
Etoposide	8 (7)	29 (12)	37 (10)
mTOR inhibitor	5 (4)	12 (5)	17 (5)
Navelbine	5 (4)	11 (4)	16 (4)

Abbreviations: mTOR=Mammalian target of rapamycin

a. Other therapy includes major hormonal therapy, immunotherapy or other Investigational agent.

b. Doxorubicin was received by 98% of patients in each treatment group

3.2.3.5. Follow up Anti-cancer Therapy

Anti-cancer therapy received after discontinuation of study drug (follow up anti-cancer therapy) is shown in Table 13. The majority of patients in both treatment arms received follow up anti-cancer therapy. Seventy-five percent of patients in the placebo arm and 61% of patients in the pazopanib arm received follow up anticancer therapy. Patients randomized to the placebo arm were not allowed to cross over and receive pazopanib after discontinuation of study treatment. One (<1%) patient randomized to placebo and 11 (4%) patients randomized to the pazopanib arm are alive and remain eligible to receive new anti-cancer treatment; an additional 1 (<1%) patient on placebo and 6 (2%) patients on pazopanib were lost to follow up as of the 24 Oct 2011 data cut-off for the final OS analysis. Excluding patients who were still eligible to receive follow up anti-cancer therapy and those who were lost to follow up, 11% more patients on the placebo arm received follow up anti-cancer therapy than on the pazopanib arm.

Table 13 Summary of Final Follow up Anti-cancer Therapy (VEG110727, ITT Population)

	Placebo (N=123)	Pazopanib (N=246)
Any anti-cancer therapy, n (%)		
Yes	92 (75)	149 (61)
No	31 (25)	97 (39)
Type of anti-cancer therapy[a], n (%)		
Chemotherapy	78 (63)	118 (48)
Targeted therapy	24 (20)	26 (11)
Radiotherapy	33 (27)	49 (20)
Surgery	9 (7)	20 (8)
Other	6 (5)	12 (5)

a. Patients may have received more than one anti-cancer therapy

Fifty-three percent of patients in the pazopanib arm compared with 69% of patients in the placebo arm received follow up systemic anti-cancer therapy (chemotherapy and/or targeted therapy) excluding surgery and radiotherapy, as shown in Table 14.

Table 14 Follow up Systemic Anti-cancer Therapy (VEG110727, ITT Population)

Type of Therapy excluding surgery and radiotherapy	Placebo (N=123)	Pazopanib (N=246)
Any therapy, n (%)	85 (69)	130 (53)
Trabectedin	39 (32)	62 (25)
Gemcitabine	28 (23)	42 (17)
Taxane	22 (18)	25 (10)
Ifosfamide	21 (17)	25 (10)
Dacarbazine	17 (14)	23 (9)
Angiogenesis inhibitor	16 (13)	20 (8)
Etoposide	10 (8)	17 (7)
Other	15 (12)	11 (4)
Anthracyclines	9 (7)	15 (6)
Cyclophosphamide	8 (7)	14 (6)
Carboplatin/Cisplatin	8 (7)	10 (4)
Not categorized	2 (2)	6 (2)
Vinorelbine	4 (3)	4 (2)
mTor	6 (5)	1 (<1)
Paclitaxel	1 (<1)	2 (<1)
Mitomycin C	1 (<1)	1 (<1)
Premetrexed	1 (<1)	1 (<1)
Temozolomide	0	2 (<1)
Eribulin	0	1 (<1)
Irinotecan	1 (<1)	0
Topotecan	0	1 (<1)
Vincristine	0	1 (<1)

3.2.4. VEG110727 Efficacy Results

Efficacy analyses were conducted on the ITT population, defined as all randomized patients.

3.2.4.1. Progression-Free Survival (Primary Endpoint)

In the ITT population, a clinically meaningful and statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm (Table 15, Figure 3). Median PFS based on the independent radiologist assessment was 1.6 months (95% CI: 1.0, 1.9) in the placebo arm compared with 4.6 months (95% CI: 4.1, 4.9) in the pazopanib arm, with a corresponding HR of 0.35 (95% CI: 0.26, 0.48, p<0.001). PFS results were consistent between independent radiologist and investigator assessments.

The improvement in median PFS and HR with pazopanib compared with placebo in each of the histology subgroups (leiomyosarcoma, synovial sarcoma and “other” STS) was consistent with the overall population as assessed by the independent radiologist.

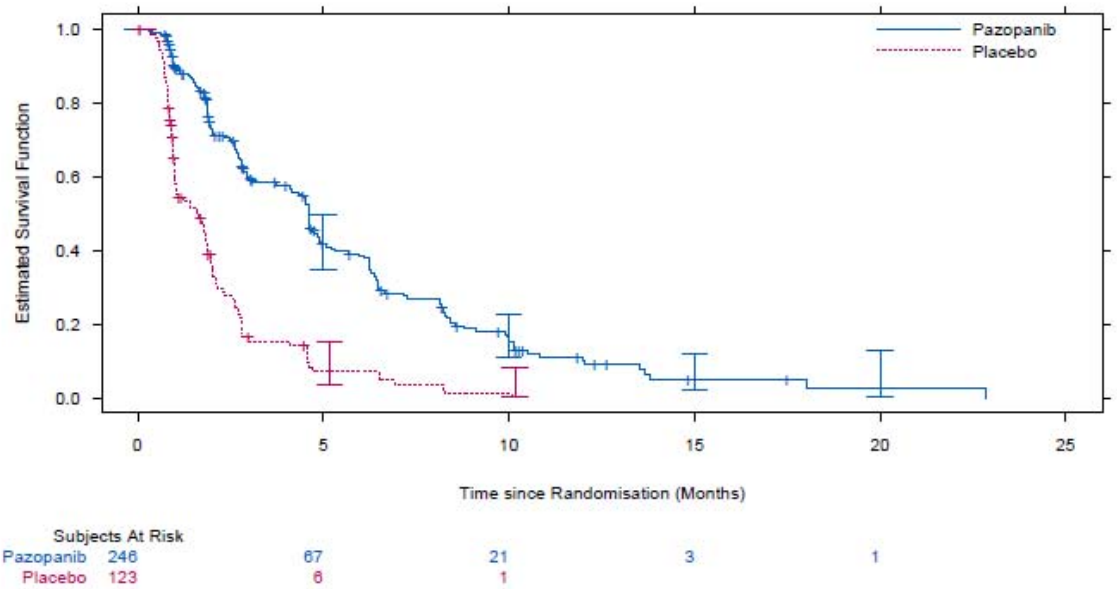
Table 15 Progression-Free Survival (VEG110727, ITT Population)

Endpoints/ Study population	Placebo	Pazopanib	HR (95% CI)	p-value
PFS	Median (95% CI)[a] in months			
ITT Population[b]	N=123	N=246		
Independent Radiologist	1.6 (1.0, 1.9)	4.6 (4.1, 4.9)	0.35 (0.26, 0.48)[c]	<0.001
Investigator	1.5 (1.0, 1.9)	4.6 (4.3, 5.7)	0.39 (0.30, 0.52)[c]	<0.001
PFS *Histology subgroups (Independent Radiologist)*				
Leiomyosarcoma	n=49	n=109		
	1.9 (1.7, 2.1)	4.6 (3.0, 5.3)	0.37 (0.23, 0.60)[c]	<0.001
Synovial sarcoma	n=13	n=25		
	0.94 (0.8, 2.0)	4.1 (2.0, 6.2)	0.43 (0.19, 0.98)[c]	0.005
"Other" STS	n=61	n=112		
	1.0 (0.9, 1.8)	4.6 (3.0, 6.2)	0.39 (0.25, 0.60)[c]	<0.001

Abbreviations: CI: confidence interval, CR: complete response; PR: partial response; HR: hazard ratio; ITT: Intent-to-treat; OS: Overall survival; PFS: progression-free survival.; STS: soft tissue sarcoma

a. Confidence intervals for quartiles are estimated using the Brookmeyer-Crowley method.
b. ITT population includes 6 patients in the pazopanib arm that did not receive study medication.
c. HR and p-value are adjusted for WHO performance status and number of prior lines of systemic therapy for advanced disease.

Figure 3 Independent Radiologist Assessed Kaplan-Meier Graph of Progression-Free Survival (VEG110727, ITT Population)

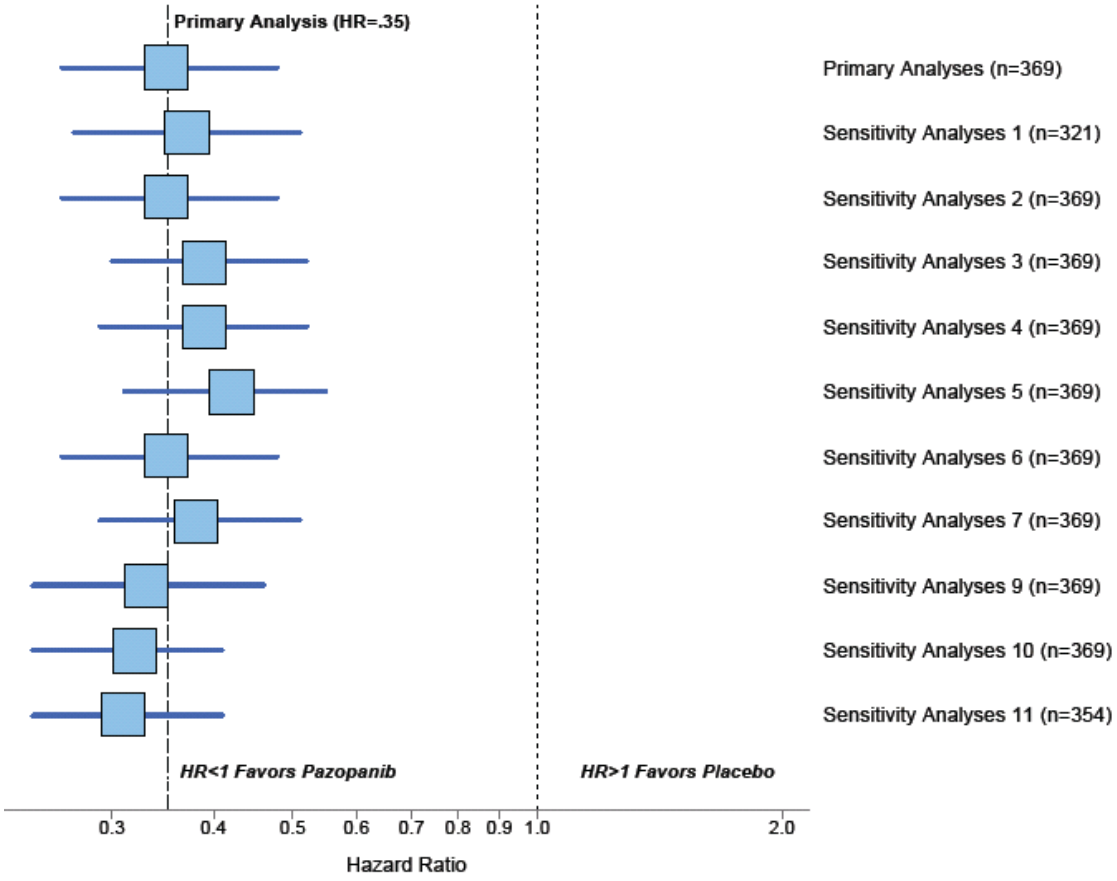


3.2.4.1.1. Sensitivity Analyses

The robustness of the PFS benefit in the primary analysis is evidenced by the consistency of results seen across all 10 pre-specified sensitivity analyses shown in the accompanying forest plot (Figure 4). The analyses used varying assumptions on defining progression and censoring dates based upon information from investigator and independent assessments. The data was analyzed using log-rank tests and Cox models incorporating stratification factors and other covariates.

In an adhoc analysis, stepwise selection was employed to evaluate a number of covariates which were potentially prognostic for PFS: baseline WHO PS, number of prior lines of systemic treatment for advanced disease, age, gender, race, metastatic disease, histology type and tumor grade at screening. WHO PS 0 (vs. PS 1) and low and intermediate (vs. high) tumor grade were the only variables selected as prognostic for longer PFS. These prognostic factors and other variables were further explored in subgroup analyses.

Figure 4 Forest Plot of Primary and Sensitivity Analyses of PFS (VEG110727, ITT Population)



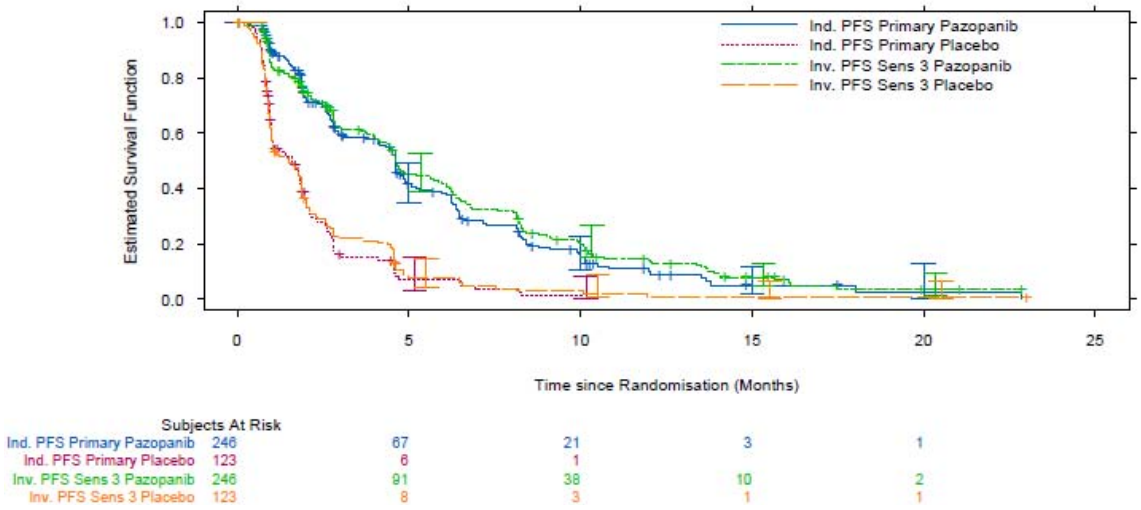
Abbreviations: n = number of patients in the analysis; HR = hazard ratio; PD = progressive disease; PFS=progression-free survival.
Sensitivity analysis 1: Per Protocol population
Sensitivity analysis 2: unadjusted for stratification factors
Sensitivity analysis 3: investigator assessment
Sensitivity analysis 4: investigator assessment unadjusted for stratification factors
Sensitivity analysis 5: investigator assessment including clinical progressions
Sensitivity analysis 6: without censoring for PD/death after extended period of inadequate assessment
Sensitivity analysis 7: with adjustment for earlier investigator assessments of progression
Sensitivity analysis 9: censoring patients who permanently stopped investigational product prior to radiological progression
Sensitivity analysis 10: Cox regression adjusted for stratification factors
Sensitivity analysis 11: Cox regression stepwise selection of covariates
Note: Sensitivity analysis 8 was not conducted because there were not enough patients with surgery due to reduction of their tumors to warrant this analysis.

3.2.4.1.2. Comparison between PFS based on independent or investigator assessment

The comparison of independent and investigator assessments in the pivotal study provides strong evidence against systematic bias in the investigator assessment of PFS (Figure 5). The PFS Kaplan-Meier curves are virtually superimposable, suggesting not

only a lack of bias in estimating treatment effect (via the hazard ratio), but also a lack of bias in estimating the overall PFS (via the Kaplan-Meier curve).

Figure 5 Kaplan-Meier Graph of PFS per Independent Radiologist and Investigator Assessments (VEG110727, ITT population)



Subjects At Risk

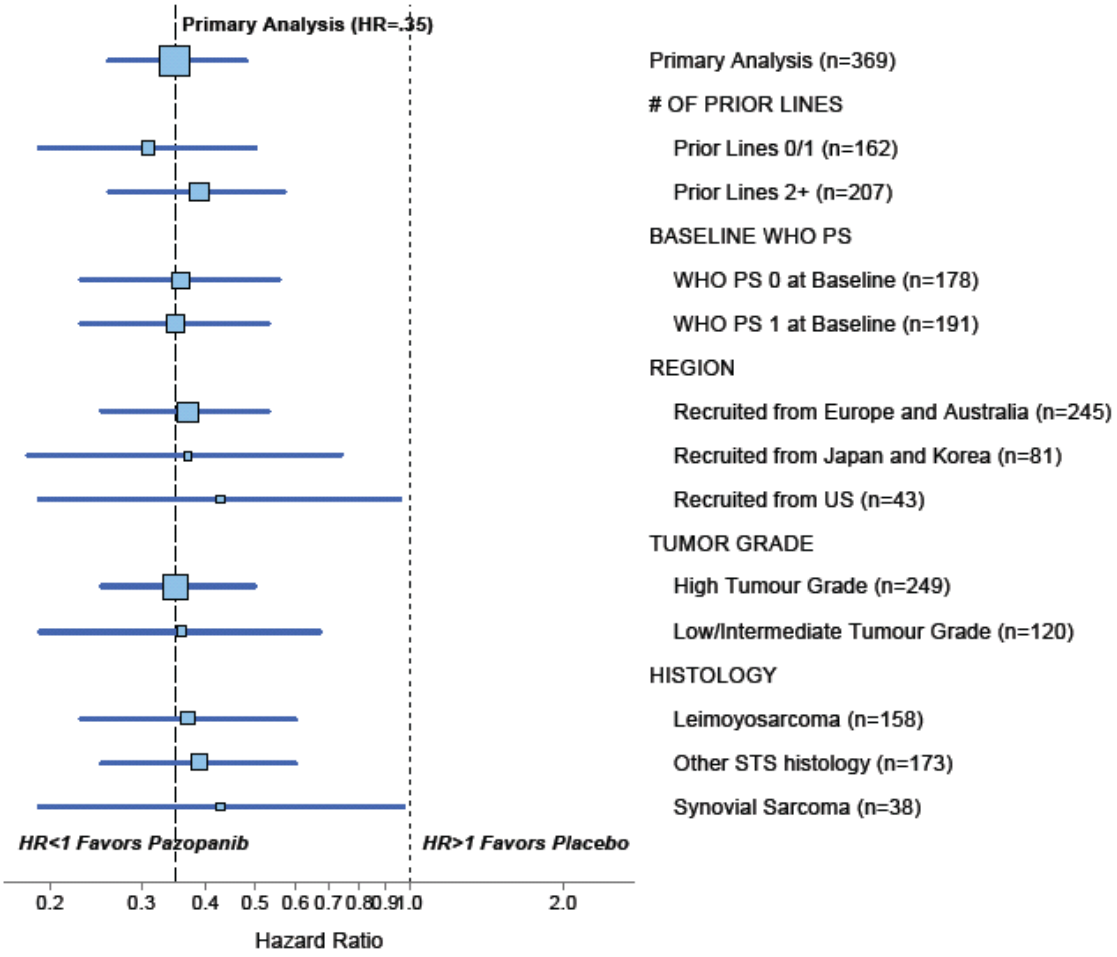
Ind. PFS Primary Pazopanib	246	67	21	3	1
Ind. PFS Primary Placebo	123	6	1		
Inv. PFS Sens 3 Pazopanib	246	91	38	10	2
Inv. PFS Sens 3 Placebo	123	8	3	1	1

Abbreviations: PFS: progression-free survival, Ind PFS Primary Pazopanib: Independent radiologist-assessed PFS for primary analysis, Inv PFS Sens 3: Investigator assessed PFS for sensitivity analysis 3
Note: 95% confidence interval bands are shown for each treatment.

3.2.4.1.3. Subgroup Analyses

Subgroup analyses for prior lines of treatment, WHO performance status, geographical region (US, Europe and Australia, Japan and South Korea), histology type and tumor grade (at initial diagnosis), are shown in Figure 6. In addition, subgroups analyzed for PFS included age of <65 years and ≥65 years, gender, and race of White and Asian/Other. In all cases, the subgroup analyses results were consistent with the primary analysis of PFS; PFS was longer in the pazopanib arm compared with the placebo arm in each of the subgroups with statistically significant treatment differences (upper bound of CI excluded 1) even in the subgroups with small sample size.

Figure 6 Forest Plot of Subgroup Analyses of PFS per Independent Radiologist (VEG110727, ITT Population)



Abbreviations: HR = hazard ratio; n = number of patients in the analysis; PFS=progression-free survival; PS = performance status; STS = soft tissue sarcoma; WHO = World Health Organization

3.2.4.1.4. PFS according to number of prior systemic chemotherapies

A post-hoc analysis was conducted to determine whether the treatment benefit was observed irrespective of the number of prior chemotherapies patients received. The analysis demonstrated that the PFS benefit compared with placebo is independent of the number of prior systemic chemotherapies (Table 16). See Table 12 for specific prior chemotherapies received by at least 2% of patients in either treatment arm.

Table 16 Independent Radiologist-Assessed PFS According to the Number of Prior Chemotherapies Received (VEG110727, ITT Population)

Number of prior chemotherapies	Placebo Median PFS, Months (95% CI)	Pazopanib Median PFS Months (95% CI)	HR (95% CI)[a]	p-value
1	n=11 2.6 (1.0, 4.6)	n=43 6.1 (4.5, 8.2)	0.27 (0.08, 0.88)	<0.001
2	n=40 1.1 (0.9, 2.0)	n=58 4.6 (2.8, 6.4)	0.37 (0.22, 0.63)	<0.001
3	n=24 1.8 (0.9, 2.0)	n=46 3.1 (2.0, 4.6)	0.33 (0.16, 0.67)	<0.001
4	n=25 1.7 (1.0, 2.1)	n=45 4.5 (2.9, 5.1)	0.49 (0.26, 0.90)	0.006
5+	n=23 1.4 (0.9, 2.0)	n=54 4.6 (2.0, 6.5)	0.34 (0.17, 0.70)	<0.001

a. HRs estimated using the Pike estimator; HR <1 indicates a lower risk with pazopanib compared with placebo

3.2.4.2. Overall Survival

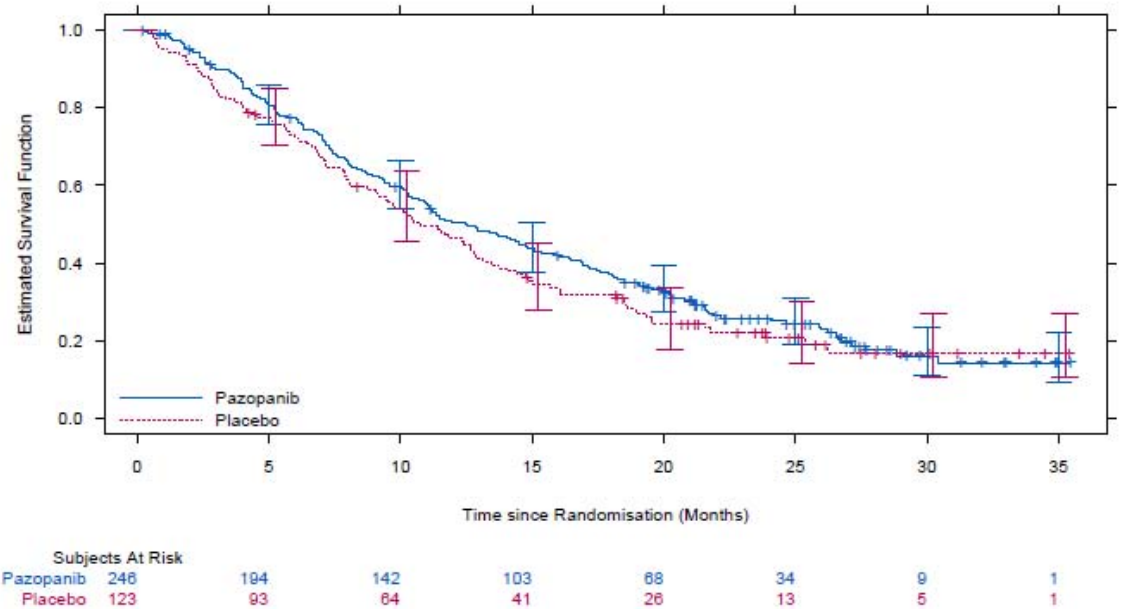
Overall survival, defined as the time from randomization until death due to any cause, was the principal secondary efficacy endpoint for VEG110727. The final OS analysis was conducted 11 months after the primary analysis when 280 death events had occurred in the study equating to 76% of all patients (required number of death events for the final analysis was 279). In the final analysis, the median OS in the placebo arm was 10.7 months (95% CI: 9.0, 13.1) and in the pazopanib arm, 12.6 months (95% CI: 10.9, 14.9); HR = 0.87 (95.7% CI: 0.67, 1.13, p=0.256) (Table 17). The Kaplan-Meier curves for OS are shown in Figure 7.

Table 17 Summary of Final Analysis of Overall Survival (VEG110727, ITT Population)

	Placebo (n=123)	Pazopanib (n=246)
Patient classification, n (%)		
Died (event)	95 (77)	185 (75)
Censored, follow up ended[a]	4 (3)	9 (4)
Censored, follow up ongoing[b]	24 (20)	52 (21)
Estimate of overall survival (months)[c]		
1st quartile (95% CI)	5.6 (3.7,7.1)	6.3 (5.2,7.3)
Median (95% CI)	10.7 (9.0,13.1)	12.6 (10.9,14.9)
3rd quartile (95% CI)	19.5 (16.1,26.3)	24.6 (20.3,27.1)
Adjusted hazard ratio[d]		
Estimate (95% CI) [95.57% CI]	0.87 (0.67,1.12) [0.67,1.13]	
Stratified log-rank p-value[d]	0.256	

a. Lost to follow up or withdrew consent
b. Alive and continuing in follow up
c. CIs for quartiles were estimated using the Brookmeyer-Crowley method.
d. Hazard ratios were estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk compared with placebo. The hazard ratio and p-value from the stratified log-rank test are adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease. P-value < 0.04434 was statistically significant after adjusting for previously conducted interim analysis.

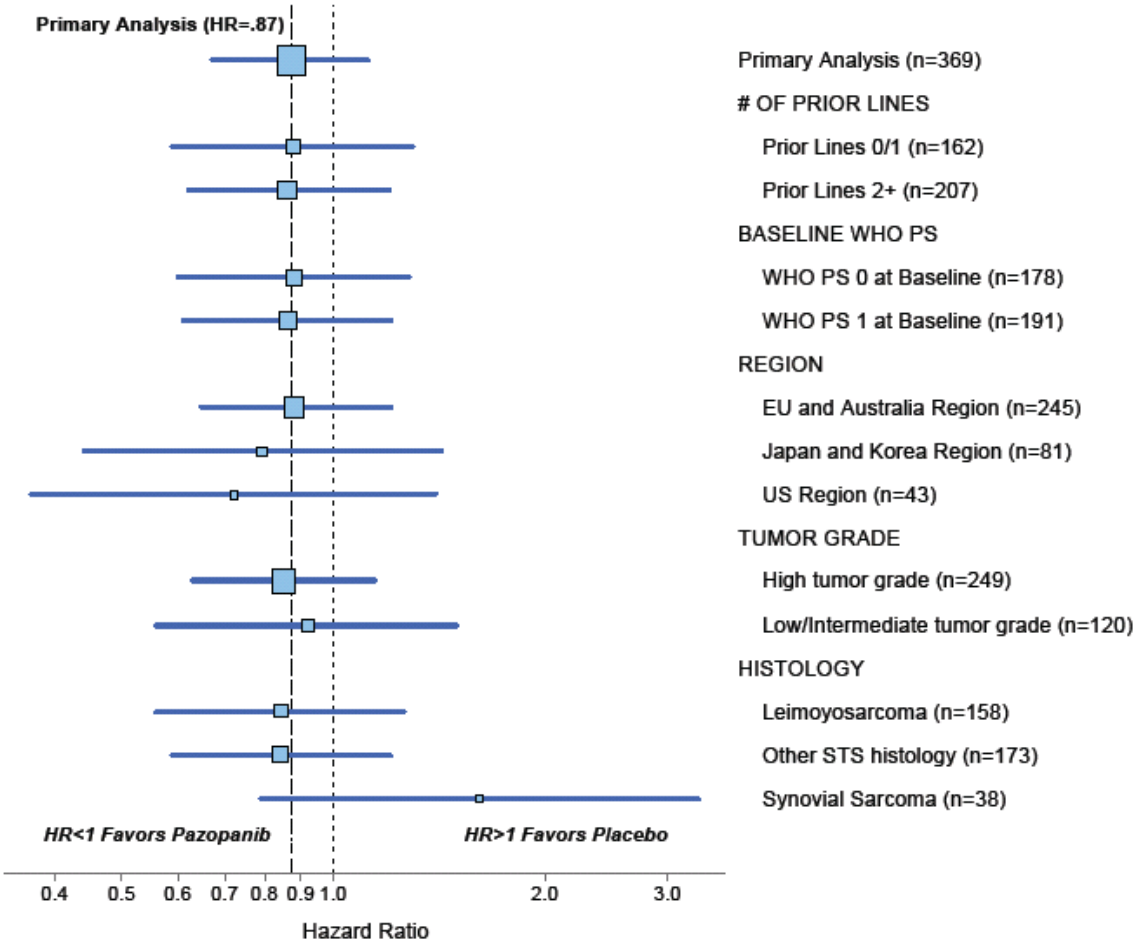
Figure 7 Kaplan Meier Final Overall Survival Curves (VEG110727, ITT Population)



3.2.4.3. Overall Survival by Subgroups

Results of the pre-specified subgroup analyses, as shown in Figure 8, are generally consistent with each other and with the overall result. Variations in estimates as shown in Figure 8 are typical when partitioning patient populations, especially in view of the small sample sizes. Only the synovial subgroup (point estimate of HR=1.62), which had the smallest sample size among the subgroups, had a HR point estimate >1. Also, when treatment by covariate interaction terms were considered, no interaction terms (in the presence of the associated lower order terms), were statistically significant (all p>0.19), indicating no statistical difference in the treatment effect depending on each covariate and consistent with random variation.

Figure 8 Pre-specified Overall Survival Subgroup Analyses (VEG110727, ITT Population)



Area of the squares marking the point estimates of HR are proportional to the inverse of the variance of the HR estimate on the log scale, and thus indicate the relative precision with which each HR is estimated.

3.2.4.4. Overall Response Rate, Duration of Response, Time to Response

At the time of the primary analysis, 11 (4%) patients and 23 (9%) patients in the pazopanib arm experienced a confirmed PR as their best objective response by independent radiology and investigator assessment, respectively (Table 18). No confirmed PRs occurred in the placebo arm. No CRs were observed in either treatment arm. A greater percentage of patients in the pazopanib arm experienced a best response of SD (at a minimum of 8 weeks) as compared with patients in the placebo arm (54% vs. 27% by independent radiologist, 56% vs. 29% by investigator).

Among the patients in the pazopanib arm who experienced a partial response, the median duration of response was 38.9 (95% CI, 16.7, 40.0) weeks by independent radiologist review and 32.1 (95% CI, 22.6, 44.0) weeks by investigator assessment. The median time to response was 8.4 (95% CI, 4.7, 19.1) weeks by independent radiologist review and 8.1 (95% CI, 4.6, 11.7) weeks by investigator assessment.

Table 18 Best Confirmed Response per RECIST by Independent Radiologist and Investigator (ITT Population)

	Independent		Investigator	
	Placebo (N=123)	Pazopanib (N=246)	Placebo (N=123)	Pazopanib (N=246)
Best Response, n (%)				
Complete Response	0	0	0	0
Partial Response	0	11 (4)	0	23 (9)
Stable Disease[a]	33 (27)	134 (54)	36 (29)	138 (56)
Progressive Disease	76 (62)	66 (27)	83 (67)	70 (28)
Not evaluable[b]	14 (11)	35 (14)	4 (3)	15 (6)
Response Rate (CR+PR), n (%)	0	11 (4)	0	23 (9)
95% CI[c]	0.0, 3.0	2.3, 7.9	0.0, 3.0	6.0, 13.7
Difference in Response (CR+PR) (%)	4		9	
95% CI for Difference	1.9, 7.1		5.7, 13.0	
P-value	0.019		<0.001	

Abbreviations: CR=complete response; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

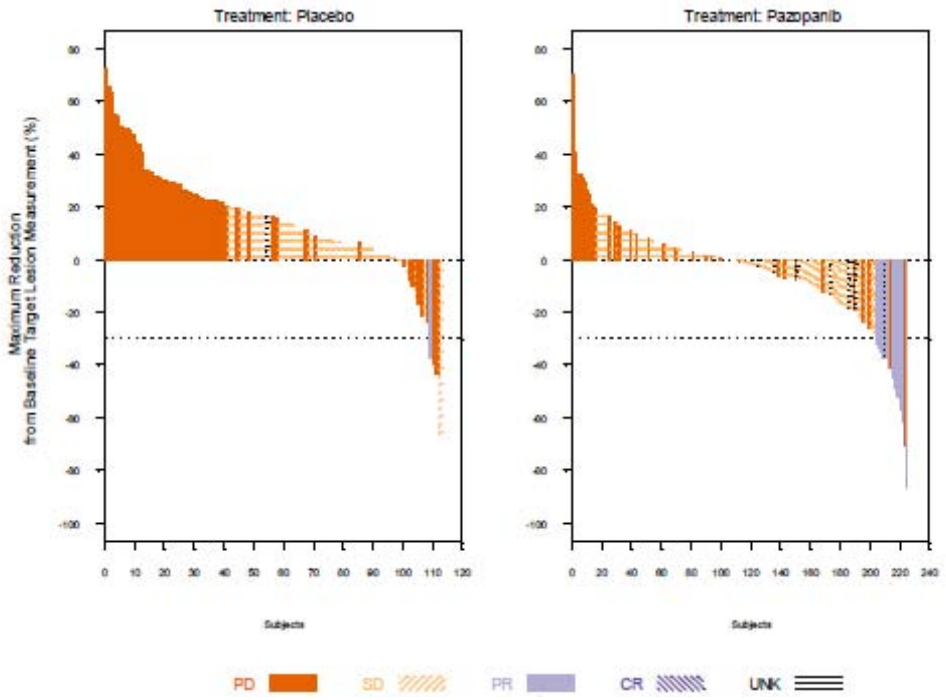
a. In order to qualify as a best response of SD, a response of SD has to be observed at a minimum of 8 weeks.

b. A patient was classified as not evaluable if they never had at least one follow up radiological disease assessment.

c. Exact binomial confidence limit method has been used for both treatment arms for response rate.

Some degree of tumor shrinkage from baseline was observed in 50% of patients in the pazopanib arm by independent radiology review and in 54% of such patients by investigator assessment. By comparison, in the placebo arm, tumor shrinkage was seen in 12% of patients by independent radiology review, and 11% by investigator assessment.

Figure 9 Reduction from Baseline in Tumor Measurement: Percent Change at Maximum (VEG110727, ITT Population)



Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; UNK=unknown

Note: X-axis for pazopanib treatment contains twice as many subjects as X-axis for placebo treatment.

3.2.5. VEG110727 Health-Related Quality of Life Outcomes

Health-related quality of life was assessed using 2 instruments, the EORTC QLQ-C30 and the EQ-5D. The QLQ-C30 is a cancer-specific questionnaire designed to assess quality of life in a wide range of tumors, but is not specifically validated in STS.

The QLQ-C30 incorporates nine multi-item scales: five functional scales (Physical, Role, Cognitive, Emotional and Social Functioning); three symptom scales (Fatigue, Pain and Nausea/Vomiting); and a Global Health Status/QOL scale. Six single item scales are also included (Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea and Financial Difficulties).

The EQ-5D is a generic instrument used across a wide range of diseases. It is comprised of 5 single-item domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) which are used to calculate a utility value and a visual analogue scale (VAS, or thermometer) to rate overall health as a summary score.

The QLQ-C30 was administered at screening and weeks 4, 8 and 12 in order to capture the impact of pazopanib on patients' quality of life during drug administration. Importantly, data were not collected after disease progression, so the impact that pazopanib might have on disease course following progression could not be assessed. Also, by limiting trial inclusion criteria to performance status 0 or 1, it was unlikely that

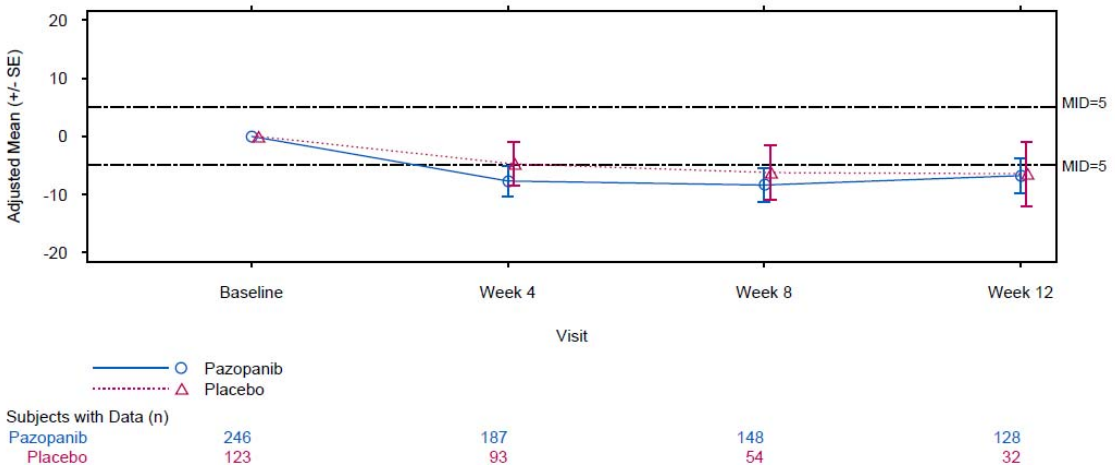
an improvement in quality of life during the evaluated period could be expected compared to baseline, as patients with a good baseline performance status would be expected to have a corresponding high quality of life. The EQ-5D was administered at screening and week 4 to confirm the impact pazopanib had on global quality of life.

3.2.5.1. EORTC QLQ-C30

Completion rates for the QLQ-C30 were acceptable at 78% or greater for patients remaining in the study at each timepoint. However, there was a significant dropout rate in both arms (Figure 10). The dropout rate was particularly high in the placebo arm mostly due to a higher rate of progressive disease. The pazopanib and placebo groups appeared to be well-balanced at baseline for QLQ-C30 Global Health Status/QOL summary score and domain scores.

The Mixed-Model Repeated Measures (MMRM) analyses of change from baseline in Global Health Status/QOL were used to test whether there was a difference between the two arms across the different timepoints. No statistically significant differences were observed between pazopanib and placebo across each of the 3 assessment timepoints (Figure 10). The point estimates showed a slightly greater decline for pazopanib than placebo (note: higher QOL scores are better, the scale ranges from 0-100), but the differences were not considered clinically significant because they did not differ by more than the established minimally important difference (MID) of 5-10 [Osoba, 1998].

Figure 10 Mixed-Model Repeated Measures Analysis of Change from Baseline for EORTC QLQ-C30 Global Health Status/QOL Score (ITT Population)



Abbreviations: MID=minimally important difference; 5 to10; QLQ=quality of life questionnaire; QOL=quality of life
Note: The analysis method was analysis of covariance adjusted for baseline score using mixed-model repeated with intercept, time, treatment, baseline score by time of interaction and treatment by time of interaction as fixed effects and time was treated as the repeated variable within patient. Unstructured covariance matrix was used.

There were differences between the treatment groups in mean change from baseline of ≥10 at one or more timepoints for several symptom scales. Differences of ≥10 may be

clinically significant, but have not been validated in STS. Fatigue, nausea and vomiting, appetite loss, and diarrhea were worse in the pazopanib arm. These findings are consistent with the AE profile for pazopanib and did not appear to impact global quality of life.

3.2.5.2. EQ-5D

Completion rates for the EQ-5D for each treatment group across the assessment timepoints were acceptable at greater than 82% at both screening and Week 4.

The pazopanib and placebo groups were balanced at baseline for EQ-5D domain scores, Utility (Index) and VAS (Thermometer). Change from baseline showed a decline at 4 weeks in both the pazopanib and placebo groups for the EQ-5D Index and VAS, but there were no statistically significant differences between treatment groups. Neither the decline in the Index nor the VAS was clinically significant, based on the published minimally important differences [Pickard, 2007].

3.2.6. Efficacy Discussion

The Phase III study, VEG110727, met its primary endpoint of PFS as assessed by independent review.

The magnitude of the PFS improvement observed with pazopanib as compared to placebo in this heavily pre-treated study population with bulky disease is both statistically significant and regarded as clinically meaningful by experts in STS. The 3 month median advantage of pazopanib in PFS time is noteworthy given the very short median PFS time in the placebo arm (pazopanib 4.6 months vs. placebo 1.6 months).

PFS results were consistent between blinded independent radiologist and investigator assessments. The robustness of the PFS benefit with pazopanib was observed across all 10 pre-specified sensitivity analyses. Consistency of treatment effect was furthermore seen in all subgroups examined (tumor grade , WHO PS, number of lines of prior systemic therapy for advanced disease, age, gender, race, and in each of the geographical regions). The improvement in median PFS with pazopanib in the leiomyosarcoma, synovial sarcoma and “other” STS subgroups was consistent with the overall population.

Sensitivity analysis indicated that WHO PS and tumor grade were prognostic for PFS. The WHO PS was controlled for by stratification and was thus balanced across treatment groups. With respect to tumor grade, a slightly greater percentage of patients on the placebo arm had high grade disease than patients on the pazopanib arm by central pathology review (7% greater in placebo arm). However, regardless of tumor grade, a consistent treatment effect was observed with pazopanib.

Overall response

Overall partial responses in the pazopanib arm according to RECIST were modest (<10%) as assessed by either independent radiology or investigator assessment. In contrast to the utility of RECIST to assess disease progression, RECIST may significantly underestimate the activity of targeted agents such as imatinib in patients with gastrointestinal stroma tumors, a subset of STS [Choi, 2008]. Some degree of tumor

shrinkage from baseline was observed in 50% of pazopanib patients by independent radiology review compared with 12% of placebo patients. These latter observations suggest that the endpoint of response rate by RECIST underestimates the activity of pazopanib in STS.

Overall Survival

Final OS analysis of VEG110727, conducted when 76% of all 369 enrolled patients died, numerically favored pazopanib (median OS 12.6 months) versus placebo (median OS 10.7 months) with a hazard ratio of 0.87 (95% CI: 0.67, 1.12). The treatment comparison was not statistically significant by the log rank test (p=0.256).

Pazopanib provided a 3-month improvement in median PFS, the primary endpoint for this study, as compared to placebo (pazopanib median PFS 4.6 months vs. placebo median 1.6 months). If this 3-month benefit observed in PFS directly translated into OS, based upon the 10.7 month median OS time in the placebo arm of this study, the expected hazard ratio for OS would be 0.78 (0.78 = 10.7 months (placebo OS) / 13.7 months (placebo OS + 3 months), assuming an exponential distribution of event times. The expected hazard ratio of 0.78 for OS is within the observed confidence interval (95% CI: 0.67, 1. 12). Additionally, given that the median OS in the placebo arm was 10.7 months, the actual power of this study to detect a 3-month benefit in OS with pazopanib was less than 50%. A trial adequately powered (80% power) to detect a 3 month OS benefit, would require a sample size in excess of 750 patients which would be impractical for the specific subtypes of STS included in VEG110727.

Subgroup analysis results for PFS and OS were generally consistent with the overall analysis. Only in the synovial sarcoma subgroup did the HR point estimate exceed 1; the sample size was small and this is reflected in the wide confidence interval. Furthermore, the interactions of treatment by subgroup were not statistically significant for any subgroups (all p>0.19).

A modest decline in QOL was observed in each of the treatment arms with no clinically or statistically significant differences between the two treatment arms.

Efficacy Conclusion

In summary, the robust treatment effect for PFS, the primary endpoint of this study, and the directional difference observed for OS support the benefit of pazopanib over placebo in this patient population.

4. SAFETY SUMMARY

4.1. Overview of Safety

More than 4,115 patients with cancer have been exposed to pazopanib in clinical trials. The estimated cumulative worldwide post-marketing exposure of pazopanib as of 30 September 2011 was 2,800 patient years.

The safety data presented in this document are primarily derived from the randomized, double-blind, placebo controlled Phase III study VEG110727 (N=123 in the placebo arm

and N=240 in the pazopanib arm) which allows for a robust characterization of the safety profile of pazopanib in the context of the underlying disease. The toxicities observed in Phase II study, VEG20002 were consistent with the pazopanib arm of the Phase III study. The integrated database of 382 pazopanib-treated patients from the Phase III study (N=240) and the Phase II study VEG20002 (N=142) was used to better characterize liver chemistry abnormalities and AEs of special interest (severe drug-induced liver injury, cardiac and vascular events, hemorrhagic events, and pneumothorax).

The overall safety profile of pazopanib in STS is similar to the established profile in the Votrient® Prescribing Information for RCC. The previously identified safety signals in the RCC study populations including hepatotoxicity, hypertension, diarrhea, arterial thromboembolic events, hemorrhagic events, thyroid function abnormalities, bowel perforations and fistulae were observed in the STS population. Three new safety signals: myocardial dysfunction, venous thromboembolic events (VTE) and pneumothorax were identified in STS patients who may have been predisposed to these toxicities. These toxicities could generally be managed with appropriate monitoring and prompt intervention. The current prescribing information addresses many of the toxicities reported in the STS studies, while the proposed updates to the Votrient®Prescribing Information for this indication will expand on these toxicities and provide guidance on new toxicities observed in the STS population.

4.2. Exposure

The median duration of treatment exposure in the Phase III study was approximately 1.9 months (8.14 weeks) in the placebo arm and approximately 4.5 months (19.36 weeks) in the pazopanib arm. Of note, AEs other than venous thromboembolism are not adjusted for the difference in exposure between the treatment arms. In the pazopanib arm, 14% of patients remained on study treatment over 12 months compared with 1% of patients in the placebo arm. The mean daily dose was 792 mg in the placebo arm and 700 mg in the pazopanib arm. The targeted dose was 800 mg daily for both treatment arms (Table 19).

Table 19 Summary of Exposure to Study Treatment (VEG110727, Safety Population)

	Placebo (N=123)	Pazopanib (N=240)
Time on study treatment (weeks)		
Min.	1.1	0.3
1st quartile	4.00	7.14
Median	8.14	19.36
3rd quartile	16.29	36.00
Max.	131.9	146.3
Daily dose (mg)		
Mean	791.61	700.19
SD	40.10	138.30
Median	800.00	793.08
Min.	432.1	249.4
Max.	800.0	800.0

4.3. Common Adverse Events Regardless of Relationship to Investigational Product

In the pivotal Phase III study, 89% of patients in the placebo arm and 99% in the pazopanib arm reported AEs (Table 20). The most commonly reported AEs in ≥ 40% of patients in the pazopanib arm included fatigue, diarrhea, nausea, weight decrease, hypertension and decreased appetite. Each of these events was reported in a greater proportion of patients in the pazopanib arm than the placebo arm. Of note, fatigue also occurred at a high rate in the placebo arm, and AEs such as tumor pain, musculoskeletal pain, dyspnea, fever and constipation occurred at similar rates in the two arms, indicating common constitutional symptoms of patients with STS. Because of the high frequency of some AEs in the placebo arm, the relative risk of AEs provides a better description of toxicities caused by pazopanib (Table 21).

For any individual AE, most patients experienced Grade 1/2 toxicity. More Grade 3 AEs (50%) were reported in the pazopanib arm compared with placebo (19%). The most frequent AEs of maximum Grade 3 severity in the pazopanib arm include fatigue, tumor pain, hypertension, decreased appetite, dyspnea, and diarrhea. The rates of dyspnea were consistent across the 2 arms, while the other AEs noted occurred at a higher rate in the pazopanib arm compared to placebo. Grade 4 AEs were reported in 10% of patients in the pazopanib arm and in 6% of patients in the placebo arm. The incidence of Grade 4 AE in the pazopanib arm was <1% for any specific event reported. Grade 5 events are discussed in Section 4.3.1.1.

Table 20 Summary of On-therapy AEs in at Least 10% of Patients in the Pazopanib Arm by Maximum Grade (VEG110727, Safety Population)

Preferred Term	Number (%) of Patients					
	Placebo (N=123)			Pazopanib (N=240)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Patients with any event	110 (89)	23 (19)	7 (6)	237 (99)	119 (50)	24 (10)
Fatigue	59 (48)	5 (4)	1 (<1)	157 (65)	31 (13)	2 (<1)
Diarrhoea	19 (15)	1 (<1)	0	141 (59)	11 (5)	0
Nausea	27 (22)	2 (2)	0	135 (56)	8 (3)	0
Weight decreased	19 (15)	0	0	122 (51)	13 (5)	0
Hypertension	7 (6)	0	0	101 (42)	16 (7)	0
Decreased appetite	23 (19)	0	0	97 (40)	14 (6)	0
Hair colour changes	3 (2)	0	0	93 (39)	0	0
Vomiting	14 (11)	1 (<1)	0	80 (33)	8 (3)	0
Tumour pain	26 (21)	8 (7)	2 (2)	71 (30)	20 (8)	0
Dysgeusia	4 (3)	0	0	66 (28)	0	0
Headache	10 (8)	0	0	56 (23)	2 (<1)	0
Gastrointestinal pain	11 (9)	5 (4)	0	56 (23)	6 (3)	0
Musculoskeletal pain	24 (20)	2 (2)	0	56 (23)	5 (2)	0
Myalgia	11 (9)	0	0	56 (23)	5 (2)	0
Dyspnoea	21 (17)	6 (5)	1 (<1)	49 (20)	13 (5)	2 (<1)
Exfoliative rash	11 (9)	0	0	45 (19)	1 (<1)	0
Cough	15 (12)	1 (<1)	0	42 (18)	1 (<1)	0
Constipation	21 (17)	3 (2)	0	39 (16)	1 (<1)	0
Oedema peripheral	11 (9)	2 (2)	0	33 (14)	5 (2)	0
Ear, nose and throat examination abnormal	3 (2)	0	0	29 (12)	4 (2)	0
Alopecia	1 (<1)	0	0	29 (12)	0	0
Skin disorder[a]	1 (<1)	0	0	28 (12)	4 (2)	0
Skin hypopigmentation	0	0	0	28 (12)	0	0
Dizziness	5 (4)	0	0	26 (11)	2 (<1)	0
Stomatitis	4 (3)	0	0	27 (11)	1 (<1)	0
Chest pain	7 (6)	0	0	25 (10)	4 (2)	0
Pyrexia	12 (10)	1 (<1)	0	25 (10)	0	0

a. Skin disorder includes 27 patients (26 in the pazopanib arm and 1 in the placebo arm) who experienced hand-foot syndrome

b. Note: AEs are sorted from highest to lowest incidence in the pazopanib treatment arm.

Table 21 AE Rates and Relative Risk for Common AEs in the Pazopanib vs. Placebo Treatment Group (VEG110727, Safety Population)

Adverse Event	Placebo AE rate	Pazopanib AE rate	Relative Risk	95% Confidence Interval
Hair colour changes	2	39	15.89	(5.14, 49.13)
Alopecia	<1	12	14.35	(1.98, 104.23)
Skin disorder	<1	11	13.84	(1.90, 100.63)
Dysgeusia	3	28	8.46	(3.16, 22.66)
Hypertension	6	42	7.40	(3.55, 15.41)
Ear, nose and throat examination abnormal	2	12	4.95	(1.54, 15.94)
Diarrhoea	15	59	3.80	(2.48, 5.83)
Stomatitis	3	11	3.46	(1.24, 9.66)
Weight decreased	15	48	3.30	(2.11, 5.16)
Vomiting	11	33	2.93	(1.73, 4.95)
Headache	8	23	2.87	(1.52, 5.43)
Dizziness	4	11	2.77	(1.09, 7.01)
Myalgia	9	23	2.61	(1.42, 4.80)
Nausea	22	56	2.56	(1.80, 3.64)
Gastrointestinal pain	9	23	2.56	(1.39, 4.72)
Decreased appetite	19	40	2.16	(1.45, 3.22)
Exfoliative rash	9	18	2.05	(1.10, 3.83)
Chest pain	6	10	1.54	(0.81, 2.94)
Edema peripheral	9	14	1.40	(0.81, 2.43)
Cough	12	17	1.38	(0.93, 2.05)
Tumour pain	21	29	1.36	(1.11, 1.68)
Fatigue	48	65	1.20	(0.78, 1.83)
Musculosketal pain	20	23	1.17	(0.74, 1.86)
Dyspnoea	17	20	1.07	(0.56, 2.05)
Pyrexia	10	10	0.93	(0.57, 1.51)
Constipation	17	16	1.54	(0.81, 2.94)

4.3.1. Serious Adverse Events

4.3.1.1. Fatal SAEs

Seven fatal serious adverse events were reported for 6 (5%) patients in the placebo arm. Nine fatal SAEs were reported for 8 (3%) patients in the pazopanib arm (Table 22).

Of the 8 patients in the pazopanib arm who experienced fatal SAEs, one patient experienced multi-organ failure, a serious adverse event (SAE) the investigators noted as being possibly related to pazopanib treatment. None of the other SAEs reported were considered by the investigator to be related to pazopanib treatment. The primary cause of death for 5 of the remaining 7 patients in the pazopanib arm was noted as disease progression. One patient died of inhalation pneumonitis, another patient died at home and an autopsy was not performed therefore, the cause of death was listed as “unknown”.

Table 22 Summary of Fatal Serious Adverse Events (VEG110727, Safety Population)

Preferred term	Number (%) of Patients	
	Placebo (N=123)	Pazopanib (N=240)
Patients with any event	6 (5)	8 (3)
Embolism[a]	0	2 (<1)
Disease progression[b]	1 (<1)	1 (<1)
Cardio-respiratory arrest[c]	0	1 (<1)
Death[d]	0	1 (<1)
Lung disorder[e]	0	1 (<1)
Multi-organ failure	0	1 (<1)
Pericardial effusion[f]	0	1 (<1)
Pneumonia[g]	0	1 (<1)
Dyspnoea	1 (<1)	0
Ileus	1 (<1)	0
Localised oedema	1 (<1)	0
Respiratory failure	2 (2)	0
Sepsis	1 (<1)	0

Note – Fatal SAEs are sorted from highest to lowest incidence in the pazopanib treatment arm.
Footnotes for pazopanib treated subjects only

a. Embolism was reported as "Embolism arterial", but both cases were queried and reclassified as pulmonary embolisms.
b. Disease progression: investigator thought the progression was greater than expected.
c. Cardio-respiratory arrest: pulmonary embolus in the setting of disease progression.
d. Death – "unexplained death".
e. Lung disorder - inhalation pneumonitis.
f. Pericardial effusion - malignant pericardial effusion with cardiac tamponade.
g. Pneumonia – pneumonia secondary to ambulant chest drain.

4.3.1.2. All SAEs

Patients in the pazopanib arm experienced greater proportions of SAEs (41%) compared with patients in the placebo arm (24%) (Table 23). The most frequent SAEs in the pazopanib arm included dyspnea, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased, hemoglobin decreased, pneumothorax and venous thromboembolism (preferred term "embolism"; see Section 4.4.2 for definition). Six patients in the pazopanib arm had the 3 events of ALT increased, AST increased and gamma-glutamyltransferase (GGT) increased all were reported as SAEs.

Table 23 Summary of Serious Adverse Events in at Least 2 Patients in Either Treatment Group (VEG110727, Safety Population)

Preferred term	Number (%) of Patients	
	Placebo (N=123)	Pazopanib (N=240)
	All Events	All Events
Patients with any event	29 (24)	99 (41)
Dyspnoea	3 (2)	10 (4)
Alanine aminotransferase increased	1 (<1)	9 (4)
Haemoglobin decreased	2 (2)	8 (3)
Aspartate aminotransferase increased	0	6 (3)
Gamma-glutamyltransferase increased	0	6 (3)
Pneumothorax	0	6 (3)
Embolism[b]	2 (2)	6 (3)
Fatigue	1 (<1)	5 (2)
Left ventricular dysfunction	0	5 (2)
Pleural effusion	1 (<1)	4 (2)
Gastrointestinal pain	2 (2)	4 (2)
Vomiting	1 (<1)	4 (2)
Chest pain	0	4 (2)
Tumour pain	3 (2)	4 (2)
Platelet count decreased	1 (<1)	3 (1)
Pneumonia	0	3 (1)
Performance status decreased	0	3 (1)
Blood bilirubin increased	1 (<1)	2 (<1)
Neutrophil percentage	1 (<1)	2 (<1)
Aspartate aminotransferase	0	2 (<1)
Neutrophil count decreased	0	2 (<1)
Weight decreased	0	2 (<1)
Lung disorder	0	2 (<1)
Small intestinal obstruction	0	2 (<1)
Malignant pleural effusion	1 (<1)	2 (<1)
Decreased appetite	0	2 (<1)
Dehydration	0	2 (<1)
Myalgia	1 (<1)	2 (<1)
Renal failure	0	2 (<1)
Febrile neutropenia	0	2 (<1)
Pyrexia	3 (2)	1 (<1)
Lymphocyte percentage	2 (2)	0
Respiratory failure	2 (2)	0

a. Related SAE are also included in the All Events columns
b. Embolism was reported as “Embolism arterial”, but all cases were queried and reclassified as pulmonary embolisms and thrombosis (see AEs of special interest Section 4.4).

Note – SAEs are sorted from highest to lowest incidence in the pazopanib treatment arm.

4.3.2. Summary of All Deaths

The majority of patients in each treatment arm died as the result of progression of disease. The duration of time to death from the first dose and from the last dose of investigational product (IP) was >28 days for the majority of patients in each treatment arm. Eleven percent of patients in each arm died within 28 days of the last dose of IP.

A summary of deaths occurring at any time from informed consent to study conclusion is provided in Table 24.

Table 24 Summary of Deaths (VEG110727, Safety Population)

	Number (%) of Patients	
	Placebo (N=123)	Pazopanib (N=240)
Patient status		
Death	95 (77)	181 (75)
Death not reported	28 (23)	59 (25)
Primary cause of death[a]		
Progression of disease	86 (70)	165 (69)
Hematologic toxicity	0	0
Non-hematologic toxicity[b]	1 (<1)	2 (<1)
Cardiovascular disease (not due to toxicity or PD)	0	1 (<1)
Pulmonary embolism (not due to toxicity or PD)	0	0
New primary cancer	1 (<1)	0
Other chronic disease (not due to toxicity or PD)	0	0
Other unrelated adverse events	2 (2)	3 (1)
Other (not due to any of the above)	1 (<1)	3 (1)
Unknown	4 (3)	7 (3)
Time to death from first dose		
≤28 days	6 (5)	3 (1)
>28 days	89 (72)	178 (74)
Time to death from last dose		
≤28 days	13 (11)	26 (11)
>28 days	82 (67)	155 (65)

Abbreviations: PD=progressive disease

a. As assessed by the investigator

b. Placebo: Patient 20-cardiac-related AEs; Pazopanib: Patient 140-renal failure due to new anti-cancer treatment started 140 days after stopping study drug, Patient 260-liver event.

4.3.3. Common Laboratory Abnormalities

4.3.3.1. Hematological Assessments

Hematology shifts from baseline were mostly Grade 1 or Grade 2 for both arms (Table 25).

Any grade shifts in neutrophils, platelets, and white blood cells (WBC) occurred at greater frequency in the pazopanib arm compared with placebo. Increases to Grade 4

thrombocytopenia occurred in 2 patients on pazopanib. In both cases, the investigators deemed the events related to disease progression, and the patient died shortly thereafter.

Table 25 Summary of Worst-case Hematology Grade Shifts from Baseline Grade (VEG110727, Safety Population)

Test	Placebo, n(%) (N=123)				Pazopanib, n(%) (N=240)			
	n[a]	Any increase In Grade	Increase to Grade 3	Increase to Grade 4	n[a]	Any increase In Grade	Increase to Grade 3	Increase to Grade 4
Hemoglobin (G/L)	123	28 (23)	1 (<1)	1 (<1)	239	65 (27)	11 (5)	4 (2)
Lymphocytes (GI/L)	123	44 (36)	11 (9)	2 (2)	238	102 (43)	23 (10)	0
Neutrophils (GI/L)	123	8 (7)	0	0	239	79 (33)	10 (4)	0
Platelets (GI/L)	123	7 (6)	0	0	239	86 (36)	7 (3)	2 (<1)
WBC (GI/L)	123	18 (15)	0	0	239	106 (44)	3 (1)	0

n = number of patients with lab values.
Note: Patients with missing baseline grade are assumed to have baseline grade of 0. Increase means an increase in grade from baseline. Day 1 of the first treatment period is considered as baseline.

4.3.3.2. Clinical Chemistry

Worst-case chemistry shifts from baseline are presented in Table 26. Most shifts were mild in grade, with few Grade 3 or 4 shifts reported for any parameter.

Table 26 Summary of Worst-case Chemistry Grade Shifts from Baseline Grade (VEG110727, Safety Population)

Test	Placebo, n(%) (N=123)				Pazopanib, n(%) (N=240)			
	n[a]	Any increase In Grade	Increase to Grade 3	Increase to Grade 4	n[a]	Any increase In Grade	Increase to Grade 3	Increase to Grade 4
Creatinine (UMOL/L)	123	9 (7)	0	0	238	28 (12)	1 (<1)	0
Hyperglycemia (MMOL/L)	122	43 (35)	2 (2)	0	238	106 (45)	1 (<1)	0
Hyperkalemia (MMOL/L)	123	13 (11)	0	0	238	37 (16)	3 (1)	0
Hypernatremia (MMOL/L)	123	3 (2)	0	0	238	10 (4)	0	0
Hypoglycemia (MMOL/L)	122	4 (3)	0	0	238	21 (9)	1 (<1)	0
Hypokalemia (MMOL/L)	123	11 (9)	1 (<1)	0	238	32 (13)	6 (3)	1 (<1)
Hyponatremia (MMOL/L)	123	25 (20)	4 (3)	0	238	74 (31)	9 (4)	0

n = number of patients with lab values.
Note: Patients with missing baseline grade are assumed to have baseline grade of 0. Increase means an increase in grade from baseline. Day 1 of the first treatment period is considered as baseline.

4.3.3.3. Thyroid Function Abnormalities

Thyroid function abnormalities have been reported with VEGF tyrokinase inhibitors (TKI) including pazopanib [Torino, 2009; Votrient® Prescribing Information]. Thyroid function abnormalities were more common in the pazopanib arm than in the placebo arm. Ten (4%) patients in the pazopanib arm experienced concomitant elevations in thyroid stimulating hormone (TSH) and decreases in T4 ($5 < TSH \leq 10$ MU/L or > 10 MU/L and T4 < lower limit of normal [LLN]) that were consistent with hypothyroidism. Of these 10 patients, 3 patients had a reported clinical history of hypothyroidism or thyroid disease prior to study entry. Laboratory evidence of hyperthyroidism (TSH < 0.3 MU/L and T4 > upper limit of normal [ULN]) was confirmed in 5 (2%) patients in the pazopanib arm. An AE of hypothyroidism was reported for 19 (8%) patients in the pazopanib treatment arm. One patient on pazopanib reported an AE of hyperthyroidism.

4.3.3.4. Proteinuria

Proteinuria is a recognized AE with VEGFR tyrosine kinase inhibitors including pazopanib [Izzedine, 2010; Votrient® Prescribing Information]. Three (1%) patients in the pazopanib arm and 3 (3%) patients in the placebo arm experienced a urine protein creatinine (UPC) ratio ≥3. An SAE of nephritic syndrome was reported in one of these patients. One additional patient treated with pazopanib experienced an SAE of increased UPC ratio but did not have a 24-hour urine protein ≥3 g. All 4 patients had resolution or evidence of improvement of proteinuria with discontinuation of IP.

4.3.4. Discontinuation or Dose Changes Due to Adverse Events

4.3.4.1. Adverse Events Leading to Permanent Discontinuation of Investigational Product

The rate of patients discontinuing pazopanib due to treatment emergent toxicities was (17%) 41/240 patients in the safety population compared to 2% in the placebo arm.

The most common AEs leading to discontinuation of pazopanib in VEG110727 included ALT increased (2%), dyspnea (2%), left ventricular dysfunction (2%), fatigue (1%), hypertension (1%) and vomiting (1%).

4.3.4.2. Dose Reductions and Dose Interruption of Investigational Product Due to AEs

AEs leading to dose reductions occurred in 32% of patients on the pazopanib arm and <1% of patients on the placebo arm. The most frequent of these events in patients receiving pazopanib included fatigue (9%), hypertension (7%), diarrhea (6%) and nausea (5%).

Dose interruptions were also more common in the pazopanib arm (50%) than the placebo arm (10%). The most frequent of these events in patients receiving pazopanib paralleled those for dose reductions and included fatigue (10%), hypertension (10%), nausea (8%) and diarrhea (7%).

4.4. Adverse Events of Special Interest

The following toxicities have been selected for elaboration in this section as they are important to the evaluation of the risk-benefit profile of pazopanib in patients with metastatic STS: liver chemistry abnormalities and AEs, cardiac and vascular events, hemorrhagic events and pneumothorax. All but pneumothorax were previously included in the Votrient® prescribing information. Patients with STS responding to anti-cancer therapy may be at higher risk of pneumothorax [Hoag, 2010]. Since pneumothorax is a potential complication from sarcoma, the incidence of this AE was evaluated in the STS studies.

Due to the low frequency of some of the AEs of interest, the Phase II and Phase III safety populations were integrated to create a larger database. The integrated population, referred to as the 'STS population', is comprised of 382 patients.

4.4.1. Liver Chemistry Abnormalities and Adverse Events

Hepatotoxicity is a recognized class toxicity of TKIs including pazopanib. Liver chemistry monitoring and dose modification guidelines are implemented in all pazopanib studies. The analysis of liver chemistry abnormalities in the STS population was performed according to the criteria described in the FDA Draft Guidance for drug-induced liver injury [FDA Guidance on Drug-Induced Liver Injury, 2009]. The frequency, severity, and time course of liver chemistry abnormalities in the sarcoma studies are consistent with the current RCC prescribing information [Votrient® Prescribing Information].

Alanine aminotransferase (ALT) elevations to ≥3x ULN were seen in 14% to 18% of pazopanib-treated patients. Of these patients, ALT elevations >8x ULN occurred in 4% to 5% of patients and ALT elevations >20x ULN occurred in 1% to 2% of patients (Table 27). Bilirubin >2x ULN was observed in 5% to 7% of patients. Elevation of bilirubin due to an impairment in conjugation as is seen with Gilbert's syndrome or an inhibition of UGT1A1 transporter by pazopanib has been described [Votrient® Prescribing Information]. The concurrent elevation of ALT and bilirubin as a marker for potential severe liver injury is discussed in Section 4.4.1.1.

Table 27 Summary of Liver Chemistry Abnormalities (VEG110727 and across All STS Studies Safety Population)

Laboratory Criteria[a]	Number (%) of Patients		
	VEG110727		STS Studies
	Placebo (N=123)	Pazopanib (N=240)	Pazopanib (N=382)
	n=122	n=237	n=375
Possible Hy's Law:> 3x ULN ALT & >2x ULN BIL[b] & (<3x ULN ALP or ALP missing)	1 (<1)	4 (2)	5 (1)
>3x ULN ALT & >2x ULN BIL[b]	1 (<1)	5 (2)	7 (2)
ALT or AST elevations	n=123	n=237	n=375
>3x ULN ALT or AST	6 (5)	48 (20)	63 (17)
>5x ULN ALT or AST	5 (4)	27 (11)	33 (9)
>8x ULN ALT or AST	2 (2)	17 (7)	21 (6)
>20x ULN ALT or AST	1 (<1)	6 (3)	6 (2)
ALT elevations	n=123	n=237	n=375
>3x ULN ALT	6 (5)	42 (18)	54 (14)
>5x ULN ALT	4 (3)	23 (10)	29 (8)
>8x ULN ALT	2 (2)	13 (5)	16 (4)
>20x ULN ALT	1 (<1)	5 (2)	5 (1)
>3x ULN ALT and <3x ULN ALT baseline (or baseline ALT missing)	6 (5)	42 (18)	54 (14)
Total bilirubin elevations	n=122	n=237	n=375
>2x ULN BIL[b]	3 (2)	12 (5)	28 (7)
>2x ULN BIL and <2x ULN BIL baseline (or baseline BIL missing)	3 (2)	12 (5)	27 (7)
Alkaline phosphatase elevations	n=123	n=237	n=375
>3x ULN ALP	5 (4)	13 (5)	33 (9)
>3x ULN ALP and <3x ULN ALP baseline (or baseline ALP missing)	2 (2)	10 (4)	24 (6)

a. Patients may be counted in more than one category of 'Laboratory Criteria'.
b. Bilirubin value can occur up to 28 days on or after ALT value.
ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase; BIL= total bilirubin; INR=international normalized ratio; ULN=Upper Limit of Normal.

4.4.1.1. Hy's Law Cases and Fatal Liver Events

The concurrent elevation of ALT and bilirubin is often referred to as "Hy's Law". Hy's Law is essentially a translation of an observation that pure hepatocellular injury (i.e., aminotransferase elevation) sufficient to cause hyperbilirubinemia is an indicator of the potential for a drug to cause serious liver injury. In patients who meet these criteria, it is critical to rule out the following: other causes of liver injury (e.g., other drugs or viral hepatitis); an obstructive basis for the elevated bilirubin (e.g., gall bladder or bile duct disease, or malignancy); impaired glucuronidation capacity (e.g., Gilbert's syndrome or drugs that impair glucuronidation) as a basis for the elevated bilirubin. Severe drug-induced liver injury (irreversible liver failure that is fatal or requires liver transplantation)

is expected to occur at a rate of roughly 1/10 the rate of Hy's Law cases [FDA Guidance on Drug-Induced Liver Injury, 2009].

An analysis of patients with ALT >3x ULN, bilirubin >2x ULN, and ALP < 3x ULN was performed across the STS population (Table 27). ALT is the more liver-specific transaminase and therefore, ALT rather than AST was utilized in the analysis as agreed with the FDA in 2009 [Pazopanib ODAC Briefing Document, 2009].

This analysis identified 5 patients who met the laboratory criteria for Hy's Law; 2 of these patients had fatal liver events. An additional 2 patients (Patient 130 and Patient 97) had fatal liver events but did not meet the criteria for drug induced liver injury because their bilirubin was not sufficiently elevated.

- Patients 22, 167, 210, 260, 130 and 97 were from study VEG110727
- Patient 25 was from study VEG20002.

A brief description of each patient is provided below:

- Patient 22 experienced elevations in ALT, AST and bilirubin. The bilirubin was primarily unconjugated. Pazopanib was continued without interruption. The patient experienced normalization of transaminases but had continued elevation of bilirubin which was predominantly unconjugated. The patient was later discontinued for unrelated toxicity.
- Patient 167 experienced ALT, AST and bilirubin elevations. The bilirubin was primarily unconjugated, (the patient was heterozygous for the Gilbert's uridine-diphosphoglucuronate glucuronosyltransferase 1A1 [UGT1A1] TA6TA7 [*1*28] genotype). The patient was re-challenged with pazopanib at a reduced dose after an interruption for transaminase elevation, and at that point developed laboratory values compatible with possible Hy's law criteria. After a second interruption and further dose reduction, pazopanib was successfully reintroduced with no further transaminase elevation.
- Patient 210 experienced elevation in ALT, AST and bilirubin which was primarily unconjugated. The patient was found to have Gilbert's syndrome (UGT1A1 TA7TA7 (*28*28) genotype) which explained the bilirubin elevation. Pazopanib was interrupted for elevated transaminases. The patient was re-challenged after recovery and had recurrent ALT and bilirubin elevation. Pazopanib was discontinued and the patient's transaminases and bilirubin recovered.
- Patient 260 had pre-existing drug-related (trabectedin) liver injury. Bilirubin was elevated at screening and study day one. On study day 55, and 3 days after starting moxifloxacin for a pulmonary infection, the patient developed markedly elevated ALT, AST, and bilirubin (primarily conjugated), thrombocytopenia and coagulopathy. The patient died of multi-organ failure including liver failure (see paragraph below for assessment by Prof. Paul Watkins, an independent consultant hepatologist).
- Patient 25 with known metastatic disease to the liver experienced ALT, AST, bilirubin, and alkaline phosphatase elevation. Pazopanib was discontinued due to

transaminase elevation. At follow up, 2 months after IP discontinuation, the patient had a cholestatic process with markedly elevated bilirubin and alkaline phosphatase and lesser elevation of ALT and AST. These findings were attributed to progression of disease in the liver.

- Patient 130 had right heart failure as a consequence of massive pulmonary embolus in the setting of progressive metastatic disease.
- Patient 97 had cardiac tamponade (malignant pericardial effusion) and extensive thrombosis in the setting of progressive disease.

All 7 patients described above were independently adjudicated by a consultant hepatologist (Prof. Paul Watkins, University of North Carolina). The consultant concluded that four of the five patients who met the definition of Hy's Law based on laboratory criteria, did not qualify as Hy's Law cases based on clinical evaluation. In 3 patients the bilirubin was primarily unconjugated. All 3 patients experienced recovery of liver chemistry abnormalities. The fourth patient had a cholestatic process due to progressive disease in the liver. The consultant concluded that there was a possible contribution of pazopanib and/or moxifloxacin to drug-induced liver injury in the fifth patient (Patient 260). Flouroquinolone hepatotoxicity characteristically occurs early after starting treatment as was the case in this patient. The two additional patients with fatal liver events were assessed as having ischemic hepatitis due to massive pulmonary embolus in one patient and cardiac tamponade in the other patient, both events occurring in the setting of progressive metastatic disease.

4.4.1.2. Outcomes of Patients with Transaminase Elevations

4.4.1.2.1. Recovery of Transaminase Elevations

Recovery of transaminase level after Grade 3 elevation was assessed for the STS population (N=382). Recovery was defined as any ALT <2.5x ULN for 2 consecutive visits or ALT <2.5x ULN for one visit if no additional data were available. A total of 54 (14%) patients had an elevation in ALT >3x ULN. Liver enzyme elevations were reversible upon cessation of the drug in many cases, and in other cases while continuing on pazopanib (see 'adaptation" below). Outcomes for these 54 patients were:

- Recovery documented in 46/54 (85%) patients.
- Recovery not documented in 8/54 (15%) patients. Of these:
    - Three patients had no follow up data; their liver events occurred 4 weeks or more after discontinuing investigational drug. All three patients had a cholestatic process due to progressive metastatic disease involving the liver.
    - Five patients did not recover, based on clinical evaluation, 4 had ongoing liver dysfunction at the time of death confounded by medical conditions and were described in Section 4.4.1.1.
    - One patient was still on treatment at data cut-off.

The median time to recovery following interruption of study treatment was 22 days (range 5-39 days).

Adaptation and Re-challenge:

It was noted early in pazopanib clinical development that some of the patients with transaminase elevations remained on study treatment despite the elevations and had recovery of their transaminases ("adaptation"). Others had improvement of transaminses following dose interruptions and subsequent resumption of study drug at the same or reduced doses ('re-challenge"). The following definitions were used in these analyses:

- Adaptation was defined as return to Grade 0 or baseline levels of ALT from >3x ULN without any interruption of study drug.
- Successful rechallenge was defined as returned to Grade 1 or below (ALT <2.5x ULN) following interruption of study drug for Patients with ALT ≥3x ULN while receiving study drug, with subsequent resumption of study drug at either the same or reduced dose. These patients were evaluated for recurrence of ALT abnormalities following the re-challenge.

Adaptation: Ten patients remained on study drug despite elevations of ALT >3x ULN (and ≤8x ULN) and experienced adaptation while remaining on the same dose of pazopanib. The majority of these patients had a peak ALT ≤5x ULN (8 of 10 patients). The median time to adaptation was 46 days (range of 8 to 168 days).

Rechallenge: Sixteen patients who had a dose interruption following an ALT elevation to >3x ULN were re-challenged. Peak ALT before re-challenge was >8x ULN for 6 of the 16 (38%) patients. Three (19%) patients were re-challenged at the same dose and 13 (81%) at a lower dose. The dose was reduced from 800 mg to 600 mg in 7 patients, 800 mg to 400 mg in 5 patients, and 600 mg to 400 mg in one patient.

Of the 16 patients, 10 patients (63%) tolerated a re-challenge without recurrent ALT elevation, whereas 6 patients (38%) had recurrent ALT elevations. None of the patients with a positive rechallenge had an adverse clinical outcome. All 6 patients had recovery of the ALT elevations following discontinuation of study drug. One patient was re-challenged a second time and recovered without further transaminase elevations (Patient 167).

The median time to recurrent ALT elevation following re-challenge for these 6 patients was 12 days (range 7 to 45 days). The median duration of re-treatment among all re-challenge patients was 60 days (range 4 to 545 days).

4.4.1.3. Time Course of ALT abnormalities

Most (92.9%) post-baseline ALT elevations >3x ULN are detected in the first 18 weeks of treatment with pazopanib. This is consistent with previous data in RCC where 92.5% of all transaminase elevations occurred in the first 18 weeks of treatment. Therefore, the current monitoring guidelines in the Votrient® Prescribing Information which requires close monitoring in the first 4 months will detect the vast majority of transaminase elevations.

4.4.2. Cardiac and Vascular Adverse Events

Cardiac and vascular events were categorized as follows:

1. Non-vascular cardiac events which included myocardial dysfunction and arrhythmia.
2. Venous embolic and thrombotic events, which included pulmonary embolism (PE), DVT and other venous thromboembolic events (see note below).
3. Arterial embolic and thrombotic events, which included myocardial infarction/ ischemia, cerebral vascular event, peripheral vascular disease and transient ischemic attack (TIA), and other arterial thromboembolic events.

Both venous and arterial thromboembolic AEs were captured on the CRFs using the terminology from the CTCAE v3.0 ('embolism'). For regulatory reporting, GSK coded these AEs to the preferred term level using the MedDRA dictionary. Subsequently, the sites were asked to provide clarification regarding the actual medical conditions which comprised arterial and/or venous thromboembolic events for some patients.

4.4.2.1. Myocardial dysfunction and LVEF

The AE term "myocardial dysfunction" includes a comprehensive list of MedDRA terms. No reports of myocardial dysfunction were identified in the Phase II study VEG20002 when the same MedDRA terms for the Phase III study, VEG110727 were applied (Table 28). It should be noted that LVEF monitoring was conducted only at baseline in the Phase II study, and at baseline and Week 12 in the Phase III study (with later amendment for monitoring beyond Week 12 as described below). Baseline and on-therapy LVEF measurements were implemented in the Phase III study because patients were expected to have received prior anthracycline therapy (clinical and subclinical cardiotoxicity associated with anthracyclines is well documented). The differences in LVEF monitoring in the two studies may explain in part the disparity in myocardial dysfunction in the two studies.

In the Phase III study, AEs of myocardial dysfunction were reported in 21 (9%) of patients in the pazopanib arm as compared to placebo 6 (5%) of patients in the placebo arm (Table 28). All subjects had prior exposure to anthracycline therapy. The majority of events were of lower grade toxicity and were reported as 'left ventricular dysfunction' based on LVEF assessments. It should be noted that data on LVEF Week 12 change from baseline was available for 58% of patients on pazopanib and 32% of patients on placebo; the difference reflects in part the withdrawal of patients from respective treatment prior to the Week 12 scheduled LVEF assessment. Four patients in the pazopanib arm (2%) had Grade 3 (n=3) or 4 (n=1) toxicity, all reported as 'left ventricular dysfunction'. Symptomatic left ventricular decline was reported in 3 of the patients (Patients 103, 223 and 300) while asymptomatic decline was reported in one patient. No fatal events were reported.

An independent review of the LVEF data, including prior medical history (with particular attention to prior or current hypertension, heart disease and prior exposure to potentially

cardiotoxic therapy) was performed by a cardiologist (Dr. Michael Ewer, MD Anderson Cancer Center, Houston, Texas, US) and is summarized below.

Given the intra-patient variability of LVEF measurements, particularly with echocardiography and to a lesser extent MUGA, myocardial dysfunction was assessed in Study VEG110727 by criteria which account for variability of LVEF measurements:

- symptoms of myocardial dysfunction or,
- ≥15% absolute decline compared to baseline or,
- ≥10% compared to baseline that is also below the lower limit of normal (LLN)

As assessed by the same method (echocardiogram or MUGA) performed at baseline.

Among patients with on-therapy LVEF assessments, using independent review criteria described above, myocardial dysfunction manifested as decreased LVEF was seen in (16/142, 11%) patients treated with pazopanib and 2 (2/40, 5%) patient treated with placebo. All patients had received prior anthracycline therapy.

- In the pazopanib treated patients, full (within 5% of baseline LVEF) or partial recovery (defined as above the LLN and more than 5% from the baseline LVEF) occurred in 9 patients (while continuing pazopanib or after discontinuation of pazopanib). Seven patients had insufficient follow up data to document recovery (this includes patient 300 described below).
- Three patients developed symptomatic LVEF decline manifesting as cardiac failure. The clinical synopses of the three patients are presented below. Patient 223, whose blood pressure was appropriately managed with antihypertensive medication and dose reduction of pazopanib was able to benefit from therapy for a prolonged period of time. In contrast, Patient 300 who developed a Grade 4 event, had hypertension that was not adequately controlled and the dose of pazopanib was not reduced despite protocol guidelines. This suggests that the risk of cardiac dysfunction could be mitigated with LVEF and blood pressure monitoring, control of hypertension, and interruption/reduction of pazopanib.
    - Patient 103 was a 55-year-old male with past medical history which included Grade 2 hypertension. The subject was a non-smoker with a baseline LVEF of 62%. The patient developed Grade 1 dyspnea 5 days and 45 days after initiating pazopanib with the latter episode continuing for duration of the study. On study day 8, the patient's BP (mean) was noted to be 154/112. Amlodipine was initiated; however, the dose of pazopanib was not adjusted (800 mg daily) during the entire study period despite the dyspnea attributed to cardiac dysfunction. On study day 94, the patient's LVEF was 52% (Grade 3 cardiac dysfunction with dypsnea) and blood pressure at that time was 115/85 mmHg. His LVEF was 38% on study day 143 and pazopanib was permanently discontinued on study day 144 due to disease progression. An LVEF nadir of 35% was recorded on study day 155. The subject received no additional medications and the LVEF improved to 54% on study day 177.

- Patient 223 had no prior history of heart failure or hypertension at study entry. She developed Grade 3 left ventricular dysfunction 54 days after initiating pazopanib 800 mg daily. The event of congestive heart failure was associated with recent onset of hypertension. An echocardiogram revealed a LVEF of less than 25% (baseline LVEF was 53%). Following interruption of pazopanib, and the treatment of hypertension, LVEF improved to 55% and pazopanib treatment was resumed at a reduced dose of 600 mg, but was interrupted about 41 days later, when the patient's LVEF decreased to 30%, again associated with an increased blood pressure (BP). One week later, the patient was asymptomatic with a LVEF of 55% and BP of 100/60 mmHg. Pazopanib treatment was resumed at a further reduced dose of 400 mg, hypertension was controlled with anti-hypertensive therapy, and no recurrence of LVEF was reported for the remaining period on study (329 days).
- Patient 300 had a medical history of hypertension, coronary artery disease, diabetes mellitus and hyperlipidemia. The patient developed hypertension requiring adjustment of anti-hypertensive medication, however, the blood pressure continued to be elevated. The dose of pazopanib was maintained at 800 mg daily. The patient subsequently developed Grade 4 congestive heart failure and was withdrawn from study in relation to this event. The congestive heart failure improved with medical intervention. A reduction of LVEF was documented at the time of the event; however, there were no further follow up LVEF assessments after the patient was transferred to hospice and until the patient's death from progressive disease.

Hypertension and/or the requirement of new anti-hypertensive medication and/or dose modifications of anti-hypertensive therapies were noted in 14 of the 16 patients on pazopanib with LVEF decline. Hypertension and the resultant increased cardiac afterload may, in turn, exacerbate subclinical left ventricular dysfunction in patients exposed to anthracyclines. This hypothesis is supported by the fact that the myocardial dysfunction, which developed in some patients on pazopanib, was manageable by the control of blood pressure and dose modifications of pazopanib. Monitoring of LVEF, rigorous control of blood pressure and pazopanib dose modification are therefore recommended for all patients treated with pazopanib with risk factors for myocardial dysfunction (e.g., prior anthracycline treatment).

Table 28 Cardiac and Vascular Events (VEG110727 and Across STS Studies Safety Population)

Treatment and Category		Maximum Grade		
	Any Grade	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)
VEG 110727 (N=363)				
Placebo, N=123				
Any non-vascular cardiac events	16 (13)	1 (<1)	0	0
Arrhythmia	11 (9)	1 (<1)	0	0
Myocardial Dysfunction	6 (5)	0	0	0
Any VTE	3 (2)	1 (<1)	2 (2)	0
PE	1 (<1)	0	1 (<1)	0
DVT	1 (<1)	0	1 (<1)	0
Other thrombosis	1 (<1)	1 (<1)	0	0
Pazopanib, N=240				
Any non-vascular cardiac events	34 (14)	6 (3)	1 (<1)	1 (<1)
Arrhythmia	15 (6)	3 (1)	0	1 (<1)
Myocardial Dysfunction	21 (9)	3 (1)	1 (<1)	0
Any VTE	13 (5)	5 (2)	1 (<1)	2 (<1)
PE	3 (1)	0	1 (<1)	2 (<1)
DVT	7 (3)	3 (1)	0	0
Other thrombosis	3 (1)	2 (<1)	0	0
Integrated STS studies (N=382)				
Any non-vascular cardiac events	43 (11)	6 (2)	1 (<1)	1 (<1)
Arrhythmia	24 (6)	3 (<1)	0	1 (<1)
Myocardial Dysfunction	21 (5)	3 (<1)	1 (<1)	0
Any VTE	21 (5)	7 (2)	6 (2)	2 (<1)
PE	8 (2)	0	6 (2)	2 (<1)
DVT	10 (3)	4 (1)	0	0
Other thrombosis	4 (1)	3 (<1)	0	0

4.4.2.1.1. Arrhythmias

The percentage of STS patients with cardiac arrhythmia AEs from the integrated pazopanib dataset was 6%. The incidence of AEs of QT prolongation for pazopanib-treated STS patients was 1%, and Grade 3 QT prolongation occurred in both the STS and RCC populations at <1%. There were no reports of AEs of torsades de pointes, or sudden death in the STS patients. It should be noted that ECG interval measurements were not recorded on the VEG110727 and VEG20002 CRFs.

4.4.2.1.2. Arterial Embolic and Thrombotic Events

In the Phase III study, 5 (2%) patients in the pazopanib arm, and no patients in the placebo arm, experienced arterial embolic and thrombotic events: 4 patients experienced Grade 1 to Grade 3 myocardial ischemic events, and one patient experienced a Grade 4 cerebrovascular accident 85 days following the last dose of pazopanib that resolved 4 days later. In the Phase II study, there were 2 on-therapy arterial thromboembolic events: one patient had Grade 3 coronary artery disease, and one patient had a Grade 4 thrombosis of a mechanical aortic valve.

4.4.2.1.3. Venous Embolic and Thrombotic Events

In the Phase III study, 13 patients (5%) in the pazopanib arm and 3 patients (2%) in the placebo arm experienced on-therapy or post therapy venous thromboembolic events. Grade 3 events were reported in 5 patients (2%) in the pazopanib arm and one patient (<1%) in the placebo arm. Three patients on pazopanib experienced PEs (Grade 4 or 5 events). Two of the 3 patients with PE, experienced fatal thromboembolic AEs of PE considered unrelated to study treatment by the investigator; both of these events were seen in association with disease progression. In the third patient with a PE in the pazopanib arm, this was an incidental asymptomatic finding at a tumor assessment showing progressive disease. In the placebo arm, one patient experienced a PE.

In the Phase II study, 8 (6%) patients reported on-therapy venous VTEs. All events were non-fatal; 5 events of PE, one inferior vena cava thrombosis and 3 DVTs were reported. Of the 5 events of PE, two were diagnosed in association with progressive disease and three were asymptomatic events diagnosed either at scheduled tumor assessments or by chest CT scan upon diagnosis of a DVT.

The exposure adjusted rate of venous VTEs in VEG110727 was 10.03 events per 100 PY (95% CI: 4.58, 15.48) for patients on pazopanib and 7.97 events per 100 PY (95% CI: 0, 16.98) for patients on placebo. The exposure adjusted rate of VTE was 9.84 events per 100 PY (95% CI: 5.63, 14.05) for the integrated STS population. The exposure adjusted rate of PE was similar in the placebo (2.66 events per 100 PY; 95% CI: 0, 7.86) and pazopanib arms (2.31 events per 100 PY; 95% CI: 0, 4.93) in VEG110727.

Overall, the exposure adjusted rates of VTE do not support an increase of these events with pazopanib treatment in STS, but the exposure adjusted rates in both placebo and pazopanib treated patients in the STS integrated dataset are higher than those seen in the RCC population previously studied.

4.4.3. Hemorrhagic Adverse Events

4.4.3.1. Hemorrhagic Events

The rate of all grades of hemorrhage was higher in the pazopanib arm (22%) as compared with placebo (8%); however, the rates of Grade 3 or Grade 4 hemorrhagic events were 1% or <1% and were similar between the treatment arms. No Grade 5 events were reported. The most common categories of hemorrhage in the placebo and pazopanib arms

respectively were epistaxis (2% vs. 8%), mouth (0 and 3%) and anal hemorrhage (0 and 2%).

For the integrated STS dataset, using the predefined hemorrhagic event MedDRA terms for analysis, hemorrhagic events were reported by 75 (20%) patients for all grades, 4 (1%) patients for Grade 3, and 3 (<1%) for Grade 4; rates comparable to the Phase III individual study data. No fatal events were reported.

4.4.4. Pneumothorax

Necrosis of peripherally located pulmonary or pleural lesions in response to active therapy is postulated to be responsible for pneumothorax development in STS patients. Patients with STS responding to anti-cancer therapy may therefore be at higher risk of pneumothorax [Hoag, 2010]. Since pneumothorax is a potential complication from sarcoma, the incidence of this AE was evaluated in the STS studies.

In the Phase III study, 8 (3%) of pazopanib-treated patients reported on-therapy AEs of pneumothorax vs. none in the placebo arm. Overall, for both STS studies, 15 (4%) of the 382 pazopanib-treated STS patients experienced pneumothorax. Ten cases were Grade 1 or 2 in severity with 5 cases of Grade 3 or 4 pneumothorax (one case was upgraded following clinical cut-off). At the time of clinical cut-off, 9/15 (60%) patients had recovered from the pneumothorax event, an additional 2 recovered with sequelae, and 4 patients had the event reported as ongoing. Of the 5 cases of Grade 3 or 4 pneumothorax, recovery with sequelae was documented in 3 patients and full recovery in 2 patients. The median time to first pneumothorax event was 40 days, with a large range of 12 to 614 days.

In contrast to the STS population, only one of 290 (<1%) patients treated with pazopanib in the pivotal RCC study developed a pneumothorax. The increased risk of pneumothorax in the STS population is likely due to response to active treatment with pazopanib in a patient population at risk for this event.

4.4.5. Safety data from other clinical studies and post marketing report

Review of the Pharmacovigilence database that collects SAE reports from pazopanib clinical trials and from spontaneous safety reports (post marketing reports) revealed no new safety concerns. The frequency of previously identified SAE were consistent with that reported in the Votrient® prescribing information for RCC and the sNDA for STS.

It is recognized that hepatic failure is an adverse reaction of particular concern with the use of pazopanib. Therefore, potential cases of hepatic failure across the entire clinical trial experience with pazopanib were evaluated and described below.

A search of GSK's safety database identified 34 reports containing at least one AE term (MedDRA preferred terms hepatic failure, hepatorenal failure, hepatotoxicity, hepatic function abnormal, hepatic necrosis and hepatocellular injury), and an additional 150 reports from a broader search using a modified hepatic disorders standardised MedDRA query. Three fatal cases were identified in which hepatic failure related to pazopanib cannot be excluded (one described in Section 4.4.1.1 above, and two described in

previous documents [Pazopanib ODAC Briefing Document, 2009]. Other than these three cases, comprehensive medical review did not identify any additional cases meeting the definition of acute hepatic failure (liver injury without pre-existing cirrhosis; disease of <26 weeks duration; coagulopathy [INR>1.5] and any degree of encephalopathy, generally accompanied by markedly elevated liver chemistries). The majority of these reports were confounded by one or more factors including limited clinical information, progression of underlying disease, concurrent medical conditions, and the use of other potentially hepatotoxic medications. Possible drug-induced liver failure related to pazopanib was documented in 3 out of 4,115 (0.07%) patients who have received pazopanib in clinical trials.

For completeness, 64 cases fulfilling the same search criteria were identified from the post-marketing experience with pazopanib. Medical review of these reports for the presence of criteria for the definition of acute hepatic failure revealed one case in which hepatic failure related to pazopanib cannot be excluded.

4.4.6. Risk Management Plan

The Risk Management Plan focuses on the prescribing information to aid in the indentification and management of specific toxicities, including the newly indentified toxicities myocardial dysfunction, VTE and pneumothorax. A medication guide will fulfill the purpose of highlighting risks to patients. Routine pharmacovigilence will continue to monitor for changes in the safety profile.

4.5. Safety Discussion

VEG110727 is the first Phase III placebo controlled study in STS. This study allowed for robust characterization of the safety profile of pazopanib in the context of the disease. Pazopanib treatment in patients with STS was associated with toxicities that were predominantly mild to moderate in severity and were generally reversible upon interruption, dose reduction or discontinuation of therapy. Rare but severe AEs previously described with pazopanib in the setting of RCC were observed at a similar frequency in STS patients. The overall safety profile in the pazopanib-treated STS patients (VEG20002 and VEG110727) is generally consistent with the Votrient® Prescribing Information for RCC with a few exceptions. Three new safety signals (myocardial dysfunction, venous thromboembolic events, and pneumothorax) were identified in the STS population and are described below.

Myocardial dysfunction

The clinical and subclinical cardiotoxicity associated with anthracyclines is well recognized. As a result LVEF monitoring at baseline and every 12 weeks was instituted in VEG110727. Myocardial dysfunction was predominantly due to asymptomatic LVEF decline and this is in keeping with the literature on VEGF TKI [Vaklavas, 2010]. None of the events were fatal. Although a direct cardiotoxic affect cannot be excluded, nonclinical studies did not reveal any direct cardiotoxicity from pazopanib [French, 2010]. Hypertension and the resultant increased cardiac afterload may exacerbate LVEF in patients previously exposed to anthracyclines. This hypothesis is supported by the fact that the majority of patients with documented LVEF decline had hypertension and/or the

requirement of new anti-hypertensive medication. Patients who continued on pazopanib were able to be managed by either pazopanib dose interruption or reduction and control of hypertension. Therefore, monitoring of LVEF, along with rigorous control of blood pressure and modification of pazopanib dosing are recommended in the proposed labelling guidelines (Warnings and Precautions Section) for patients at risk of myocardial dysfunction (e.g., prior therapy with anthracyclines).

Venous Thromboembolic Events

Venous thromboembolic events occurred at a higher rate in the pazopanib arm compared with placebo. The exposure adjusted rate of VTEs in the pazopanib and placebo arms were similar indicating that the higher number of events in the pazopanib arm may be explained by the longer treatment period compared to patients in the placebo arm. Two patients on pazopanib experienced fatal VTEs which were confounded by co-existing medical conditions including progressive disease. VTE is a recognized complication of malignancy, although reported rates of VTE vary markedly [Khorana, 2009]. Despite this an increased rate of VTE with pazopanib in STS cannot be completely ruled out and is therefore, addressed in the proposed labeling update (Warnings and Precautions Section).

Pneumothorax

Pneumothorax is a recognized complication in patients with sarcoma [Hoag, 2010]. The majority of cases reported were low grade. In addition to the increased risk of spontaneous pneumothorax with sarcomas, pooled data from one study showed that one-half of patients with sarcoma received doxorubicin-based chemotherapy prior to their pneumothorax [Le Cesne, 2000]. Necrosis of peripherally located pulmonary or pleural lesions in response to active therapy is postulated to be responsible for pneumothorax development. Pneumothorax is addressed in the proposed labelling (Adverse Reaction Section) for this indication.

Management of toxicities

Pazopanib has a well characterized safety profile. The toxicities reported with pazopanib are ones that are familiar to oncologists. These toxicities can usually be managed with appropriate monitoring and prompt intervention. The current prescribing information addresses many of the toxicities reported in the STS studies, while the proposed updates to the Votrient® Prescribing information for this indication will expand on these toxicities and provide guidance on new toxicities observed in the STS population.

5. EFFICACY AND SAFETY OF PAZOPANIB IN THE CONTEXT OF COMMONLY USED CHEMOTHERAPIES FOR STS

Patients with metastatic STS are treated with chemotherapy agents including doxorubicin, ifosfamide, gemcitabine, docetaxel and trabectedin based on limited data. Pazopanib was investigated in patients who had received prior chemotherapy. To place the benefit and risk in the context of chemotherapy, albeit comparing cross-study, the

efficacy and safety of pazopanib compares favorably to chemotherapy agents as described below.

The evidence for the use of chemotherapy agents in non-GIST STS is largely based on Phase II clinical trials. Few Phase III and no placebo-controlled trials have been conducted to evaluate the true benefit of chemotherapy in prolonging PFS or OS. The efficacy and safety of these agents in representative Phase II and III studies is summarized in Table 29. The median PFS for monotherapy cytotoxic agents ranges from 2.2 months to 3.5 months. The median PFS for pazopanib of 4.6 months was observed in patients who had progressed on, or following, many of these chemotherapies and was retained irrespective of the number of prior agents.

Common to most cytotoxic agents used in STS are severe myelosuppression (anemia, neutropenia, thrombocytopenia) and associated complications, gastrointestinal toxicities (nausea, vomiting, diarrhea, mucositis), fatigue, and alopecia. Myelosuppression of Grade 3 and 4 is rare with pazopanib. In addition, each of the agents has specific toxicities. Examples of these toxicities include cardiomyopathy which can be irreversible [Casper, 1991]; hemorrhagic cystitis, neurotoxicity, and urotoxicity (hematuria, hemorrhagic cystitis, nephrotoxicity with ifosfamide; liver toxicity and rhabdomyolysis with trabectedin. The myocardial dysfunction observed with pazopanib is manageable with dose modifications and control of hypertension. Toxicities such as neurotoxicity and urotoxicity have not been associated with pazopanib.

In addition, all of the commonly prescribed chemotherapies are administered intravenously, and carry the added safety risks of thrombophlebitis, extravasation, and infection, as well as the notable inconvenience for patients and caregivers. Oral administration of pazopanib is convenient for patients and permits rapid dosing changes for toxicity.

Table 29 Selected Chemotherapy Study Results in STS

Study Treatment	Objective Response Rate [95% CI]	Median Progression Free Survival [95% CI]	Median Overall Survival [95% CI]	Histology Type	Main Toxicities
Doxorubicin 1st line 75 mg/m² IV bolus; every 3 weeks (n=110)	11.8% [CI not specified]	2.52 months [1.8 - 3.24 months]	12 months [9.96 – 17.4 months]	Leiomyosarcoma (31%) Synovial sarcoma (9%) Other and unclassified (60%)	Myelosuppression, alopecia, nausea, vomiting and stomatitis [Lorigan, 2007]
Ifosfamide 1st line 9g/m² over 3 day continuous infusion (n=102)	8.4%	3 months [2.52 - 3.72 months]	10.92 months [9.24 – 14.52 months]	Leiomyosarcoma (31%) Synovial sarcoma (8%) Other and unclassified (60%)	Neutropenia, febrile neutropenia, thrombocytopenia, nausea, vomiting, alopecia, and neurotoxicity & encephalopathy. [Lorigan, 2007]
3 g/m² x 3day (n=105)	5.5%	2.16 months [1.68 - 2.88 months]	10.92 months [9.72 – 13.32 months]		
Gemcitabine (900 mg/m² on Day 1 and Day 8) q 3 weeks, plus Docetaxel (100 mg/m² on Day 8) every 3 weeks (n=73)	16%	6.2 months	17.9 months	Leiomyosarcoma (40%) Others (60%)	Gem+Doc: thrombocytopenia (requiring platelet transfusion), febrile neutropenia, pulmonary fatigue; myalgia or muscle weakness
Gemcitabine 1200 mg/m² IV over 120 mins on Day 1 and Day 8, every 3 weeks (n=49)	8%	3.0 months	11.5 months	Leiomyosarcoma (18%) Others (82%)	Gem: thrombocytopenia anemia (requiring blood transfusions) [Maki, 2007]

Study Treatment	Objective Response Rate [95% CI]	Median Progression Free Survival [95% CI]	Median Overall Survival [95% CI]	Histology Type	Main Toxicities
2nd line+ Dacarbazine (DTIC) 1200 mg/m² IV infusion every 3 weeks (n=52)	25% [14, 39%]	2 months	8.2 months	Leiomyosarcoma (31%) Liposarcoma (17%) Undifferentiated pleomorphic (15%) Synovial (10%) Misc. sarcoma (27%)	Leucopenia, neutropenia, thrombocytopenia, anemia, asthenia, nausea, vomiting, diarrhea, stomatitis [Garcia-del-Muro, 2011]
Gemcitabine 1800 mg/m² plus DTIC 500 mg/m² every 2 weeks (n=57)	49% [36, 63%]	4.2 months	16.8 months	Leiomyosarcoma (28%) Liposarcoma (18%) Undifferentiated pleomorphic (19%) Synovial (11%) Misc. sarcoma (25%)	
Trabectedin (Prior anthracycline and ifosfamide) 1.5 mg/m² as a 24-hour every 3 weeks (n=132)	4.0% [1.1-9.9%]	3.5 months [2.0-4.5 months]	16.7 months [12.2-NR]	Leiomyosarcoma (66%) Liposarcoma (34%)	Q3wk 24h dose: ALT elevation; neutropenia, AST elevation, dyspnea, fatigue, nausea, vomiting, febrile neutropenia, CPK elevations, rhabdomyolysis [Yondelis EPAR, 2007]
0.58 mg/m² weekly as a 3 hour for 3 weeks of a 4 week cycle (n=134)	1.0% [0.0-5.5%]	2.1 months [1.9-3.4 months]	11.8 months [8.9-14.9 months]		

Abbreviations: IV: intravenous; PS: performance status; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatinine phosphokinase; MFH: malignant fibrous histiocytoma

6. BENEFIT RISK ASSESSMENT

6.1. Therapeutic Justification

In the randomized double-blind placebo-controlled Phase III trial (VEG110727), pazopanib has demonstrated a clinically meaningful and highly statistically significant improvement in PFS in a patient population that has been heavily pre-treated with chemotherapy. The OS result favors pazopanib although it is not statistically significant. The safety profile of pazopanib is well characterized and thus patients can be monitored. Most toxicities can be addressed with dose modification or appropriate intervention. Metastatic STS that has progressed following chemotherapy is a clear unmet medical need and pazopanib provides a new treatment option for these patients. Key efficacy and safety considerations are summarized below.

6.2. Benefits

The efficacy and safety of single agent pazopanib in patients with recurrent and bulky metastatic STS was demonstrated in the Phase III pivotal study VEG110727. This is the first Phase III study to be conducted in heavily pre-treated patients with recurrent metastatic STS, and the only placebo controlled study in non-GIST STS. These data are supported by the Phase II study VEG20002.

Pivotal Study

- Pazopanib demonstrated a statistically significant and clinically meaningful increase in PFS compared to placebo, unprecedented as a single agent in heavily pre-treated patients with rapidly progressive metastatic non-GIST STS. The 3 month median advantage of pazopanib in PFS time is noteworthy given the very short median PFS time in the placebo arm (pazopanib 4.6 months vs. placebo 1.6 months).
- The robustness of the PFS benefit is evidenced by consistent results seen across all 10 pre-specified sensitivity analyses and all subgroup analyses including the US population.
- Improvement in PFS with pazopanib was independent of number of prior chemotherapy agents.
- The OS result numerically favored pazopanib; however, the result was not statistically significant.
- Given that median OS in the placebo arm was 10.7 months, the actual power of this study to detect a 3-month benefit in OS with pazopanib, a clinically meaningful effect of the same magnitude observed in PFS, was less than 50%. A trial adequately powered (80% power) to detect a 3 month OS benefit, would require a sample size in excess of 750 patients which would be impractical for the specific subtypes of STS included in VEG110727.
- Higher rates of objective responses and stable disease were observed in the pazopanib arm compared to the placebo arm. Tumor shrinkage was observed at a higher rate with pazopanib across all tumor subgroups.

- A modest decline from baseline in the Global Health Status/Quality of Life (QoL) summary scale was observed in each of the treatment arms with no clinically or statistically significant differences between the two arms. The QoL analysis was limited by the restriction of data collection to the first 12 weeks on study and only prior to disease progression, the higher drop-out rate in the placebo arm (due primarily to disease progression), and the lack of QoL instruments validated for STS.
- Based on comparisons to published studies and recognizing the caveats of cross-study comparisons, the pazopanib efficacy demonstrated in this first ever Phase III study conducted in a heavily pre-treated population appears to be commensurate with or more favorable than doxorubicin or other single agent chemotherapies in less heavily pre-treated STS patients.

Supportive Study

Efficacy data in the pivotal study are supported by the efficacy results of the Phase II study VEG20002.

In VEG20002 antitumor activity with pazopanib (>40% progression-free survival rate at Week 12) was demonstrated in leiomyosarcoma, synovial sarcoma, and "other STS" strata. These were the subgroups that were evaluated in VEG110727 Phase III study. The adipocytic sarcoma stratum did not meet the primary endpoint in VEG20002 and was therefore not investigated in the Phase III study.

6.3. Risks

The placebo arm of the VEG110727 study provided an opportunity for a robust evaluation of the safety profile of pazopanib in the context of the underlying disease. The vast majority of AEs observed with pazopanib are those that are common to the class of VEGF-TKI.

- The most common AEs reported in the pazopanib arm were fatigue, diarrhea, nausea, weight decreased, hypertension, decreased appetite, hair color changes and vomiting. The most frequent AEs which occurred at a higher rate in the pazopanib arm compared to placebo (based on relative risk) were hair color changes, alopecia, skin disorder, dysguesia, hypertension, diarrhea, stomatitis, weight decrease. Most events were Grade 1/2 and few led to permanent discontinuation.
- The most common SAEs associated with pazopanib included dyspnea, transaminase increase, hemoglobin decrease, pneumothorax and embolism (VTE). Fatal SAEs were reported at a similar rate in both arms; the majority of fatal events in the pazopanib arm were attributed to complications from disease progression. One patient in the pazopanib arm died of multi-organ failure/possible drug-induced liver injury (described below).
- Hepatoxicity is of concern for VEGF-TKI including pazopanib. Transaminase elevations were common but reversible in the majority of patients. The frequency, severity and time course are consistent with that reported in the Votrient® Prescribing information. As over 90% of all transaminase elevations occur in the first 18 weeks of treatment, frequent monitoring during this period allows for early

identification and intervention. One case of severe drug-induced liver injury which was fatal was reported in the STS population. In the overall pharmacovigilence database, fatal hepatic events potentially attributable to pazopanib were rare (0.07%).

- New AEs which were identified in the STS population were myocardial dysfunction, VTE and pneumothorax .
    - LVEF decline was asymptomatic in the majority of patients and improvement was observed in all cases where follow up measures were obtained. The majority of patients with cardiac dysfunction had documented hypertension; control of hypertension by dose interruption/reduction and/or antihypertensive medications was generally effective in managing the cardiac dysfunction.
    - Excess VTE were observed on pazopanib compared to placebo in the integrated STS analysis. The exposure adjusted rates for VTE were not significantly different between the pazopanib and placebo arms of Study VEG110727, and between the integrated pazopanib-treated STS population and the placebo arm. Rare but fatal events of pulmonary embolism were observed.
    - Pneumothorax, is a known complication in patients with STS, particularly those who have received active therapy. A higher rate of pneumothorax was observed in the pazopanib arm compared to placebo. No fatalities were associated with pneumothorax and these events were reversible in the majority of patients.

Pazopanib has a well characterized and manageable toxicity profile in heavily pretreated patients with recurrent metastatic STS. The safety profile of pazopanib compares favorably to commonly used cytotoxic chemotherapies. Oral administration of pazopanib is convenient for patients and permits rapid dose adjustments for toxicity.

6.4. Overall Benefit-Risk

Soft tissue sarcomas are rare and orphan diseases which accounts for less than 1% of all cancers. Approximately 50% of patients with STS develop metastatic disease. Recurrent metastatic disease is characterized by bulky tumors that involve multiple organs and impinge on vital structures. Rapid progression of the disease leads to increased morbidity. Patients with metastatic STS are treated with sequential chemotherapies. The use of these chemotherapies is based largely on limited data from single arm or randomized Phase II studies. Despite these therapies, progressive disease is inevitable and constitutes an area of unmet medical need for new and effective therapies that could benefit these patients.

To address this unmet need, the efficacy and safety of pazopanib was investigated in a well conducted, randomized double-blind placebo controlled Phase III trial in patients with bulky metastatic STS who had progressed on or after prior chemotherapy. This is the first Phase III trial to be conducted in heavily pre-treated patients with recurrent, metastatic STS. It was designed in collaboration with the EORTC SBSTG, a premier academic group of sarcoma investigators, and US sarcoma experts. This trial demonstrated a clinically and statistically significant improvement in PFS with pazopanib compared to placebo. Sarcoma experts consider the 3 month median benefit in PFS as clinically compelling, especially in a patient population with bulky and rapidly progressive disease; the latter being evidenced in the placebo arm. Importantly, the PFS

benefit with pazopanib was observed irrespective of the extent of prior chemotherapy treatment.

The OS result favored pazopanib, although it was not statistically significant. The actual power of the study to detect a 3-month benefit in OS with pazopanib (commensurate with the PFS benefit observed in this trial) was less than 50%. A trial adequately powered to detect a 3 month OS benefit, would require a sample size in excess of 750 patients which would be impractical for the specific subtypes of STS included in VEG110727.

The benefits observed must be weighed against pazopanib-induced risks. The risks associated with pazopanib have been well characterized through a large clinical development program, and through post-marketing experience with RCC. The safety profile of pazopanib in STS patients is generally consistent with the Votrient® Prescribing Information for RCC. Three new safety signals: myocardial dysfunction, venous thromboembolic events and pneumothorax were identified. STS patients may be predisposed to these toxicities. Myocardial dysfunction in these patients, all exposed to prior anthracycline, was predominantly due to asymptomatic decline in LVEF. Symptomatic LVEF decline was generally reversible if managed appropriately, as evidenced in the pivotal study. With baseline and periodic LVEF monitoring, and prompt and effective management of hypertension, this toxicity can be mitigated. Venous thromboembolic events are a well known complication of cancer, and the exposure adjusted rates are higher in STS compared with RCC irrespective of treatment. Although a causal relationship between VTE events and pazopanib is questionable, guidance for this AE has been included in the proposed labeling. Pneumothorax is a recognized but rare complication of STS which may occur spontaneously or following active therapy. Awareness of this rare complication would allow patients and healthcare providers to detect this complication and intervene appropriately.

The pazopanib risk management plan focuses on the prescribing information to aid in the identification and management of specific toxicities including newly identified toxicities. A medication guide will fulfill the purpose of highlighting risks to patients. Routine pharmacovigilence will continue to monitor for changes in safety profile.

Albeit comparing across studies, the efficacy and safety profile of pazopanib in heavily pre-treated patients appears favorable when compared with published data on chemotherapies in either treatment naïve or less heavily pre-treated patients with STS.

The magnitude of benefit, coupled with the well characterized and generally manageable safety profile of pazopanib in patients with recurrent metastatic STS fulfils an unmet medical need. GSK and experts in STS believe that the benefit:risk of pazopanib is favorable and represents a valuable treatment option for patients with this disease.

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