Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Pazopanib hydrochloride

Proprietary Product Name: Votrient

Sponsor: GlaxoSmithKline Australia Pty Ltd

**Date of CER: December 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

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# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| TKI | tyrosine kinase inhibitor |
| VEGFR | vascular endothelial growth factor receptor |
| PDGFR | platelet derived growth factor receptor |
| ARCC | advanced renal cell cancer |
| SAE | serious adverse event |
| VTE | venous thromboembolism |
| TE | thromboembolic |

# 1. Introduction and clinical rationale

This submission seeks approval for an additional indication for pazopanib for the treatment of patients with advanced (unresectable and/or metastatic) soft tissue sarcoma (STS) who received prior anthracycline treatment or for patients who are unsuited for such therapy.

Pazopanib is an orally administered potent multi-target tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, platelets derived growth factor (PDGFR) alpha and beta and stem cell factor receptor (c-KIT). Pazopanib is presently approved for the treatment of advanced and/or metastatic renal cell carcinoma (ARCC). The proposed additional indication is for the treatment of patients with advanced (unresectable and/or metastatic) soft tissue sarcoma who received prior anti-cancer therapy or for patients who were unsuited for such therapy.

Pazopanib as indicated above is a potent TKI and despite heterogeneity of various soft tissue sarcomas these tumours have been shown to have a commonality in that high levels of VEGF gene expression have been observed in many STS sub-types. Furthermore circulating VEGF levels are higher in patients with advanced STS and are associated with the histologic grade of the tumour. Other mediators of angiogenesis such as PGDGF have also been shown to be expressed in STS and are correlated with higher tumour grade and increased cell-proliferation. Accordingly this represents an appropriate rationale for evaluation of tyrosine kinase inhibitors in the treatment of advanced stage STS.

# 2. Contents of the clinical dossier

## 2.1. Scope of the clinical dossier

This submission contains the appropriate materials in regards to module 1 and module 2 including relevant clinical overview, summary of clinical efficacy and summary of clinical safety as well as literature references. Module 5 contains full reports in relation to the two principal studies for assessment, namely the pivotal Phase III randomised control trial, study VEG110727 and a supportive Phase II trial, study VEG20002. There is also an additional study examining thromboembolic events in STS patient study WEUSRTP4987.

## 2.2. Paediatric data

While no specific data is provided in this submission regarding paediatric data, comments in the application indicate that earlier results of juvenile toxicity studies in modules 2 and 4 indicate that there is an action of pazopanib which severely affects organ growth and maturation during early post-natal development. Accordingly a warning is proposed to be included in the proposed Product Information that pazopanib should not be given to paediatric patients younger than two years of age.

## 2.3. Good clinical practice

All aspects of good clinical practice have been observed.

# 3. Pharmacokinetics

Full pharmacokinetic data for pazopanib after single and repeated oral dose administration for patients with cancer were provided in the original regulatory submission in relation to advanced stage RCC.

Additional pharmacokinetic data for pazopanib in adult subjects with STS after repeated oral doses of pazopanib are provided in the supportive study VEG20002 which is a Phase II multicentre open label non-randomised study evaluating the therapeutic activity, safety and tolerability of pazopanib in subjects with four of the most common types of soft tissue sarcoma including leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and other eligible types of STS who had relapsed following standard therapies or for whom no standard therapy existed.

Patients received oral pazopanib 800 mg once daily until disease progression or unacceptable drug related events, any recurrent illnesses preventing further drug administration or subject refusal. Pazopanib dose reductions were allowed during the study. Serial blood samples for analysis of plasma pazopanib were collected on the day 29 visit. Blood samples for the determination of the trough plasma pazopanib concentrations were also collected prior to administration of study drug at day 57 and day 85 visits.

A total of 142 patients were entered into this Phase II study and 74 of these patients had pharmacokinetic measurements undertaken suitable for analysis. Plasma pazopanib concentrations on the day 29 visit are summarised in Table 1.

**Table 1. Summary of plasma pazopanib concentrations at Day 29 visit in subjects with STS (VEG20002)**

| | | Day 29 Plasma Pazopanib Concentration (µg/mL) | |
|---|---|---|---|
| Time (h) | N | Median (range) | Mean (SD) |
| 0 (predose) | 74 | 33.2 (5.43 - 104) | 37.1 (21.1) |
| 1 – 2 | 73 | 42.7 (0 - 109) | 42.0 (21.6) |
| 3 – 4 | 77 | 46.2 (0 - 131) | 48.6 (23.5) |
| 6 – 8 | 74 | 43.8 (0 - 106) | 45.3 (22.4) |

Data from earlier studies VEG10003 and VEG102616 demonstrated that trough plasma pazopanib concentrations associated with one half of the maximum effect in two concentration - effect relationships were similar being 21.3 µg/mL and 15.2 µg/mL demonstrating that there is a consistent inhibition of VEGF receptors in patients with cancer when plasma pazopanib concentrations are maintained above these concentrations. Accordingly the data presented in Table 1 are consistent with this.

Steady state trough (pre-dose) plasma pazopanib concentrations and the number of patients with concentrations associated with biologic effects, namely at least 20 µg/mL are indicated in Table 2. The difference between the mean pre-dose plasma pazopanib concentration on day 29 and day 85 was <5%.

**Table 2. Summary of the predose plasma pazopanib concentrations and the number of subjects with predose plasma pazopanib concentrations ≥ 20 µg/mL in subjects with STS (VEG20002)**

| Visit | N | Predose Concentration (µg/mL) | | Number (%) of Subjects with Predose conc ≥ 20 µg/mL |
|---|---|---|---|---|
| | | Median (range) | Mean (SD) | |
| Day 29 | 74 | 33.2 (5.43- 104) | 37.1 (21.1) | 55 (74%) |
| Day 57 | 74 | 33.1 (0 – 89.1) | 36.1 (18.5) | 61 (82%) |
| Day 85 | 58 | 33.1 (3.87 – 88.6) | 36.0 (19.0) | 46 (79%) |

Data Source: VEG20002 Table 13.1 and Table 13.3

To evaluate results across the studies it is noted an identical blood sampling scheme was used in the Phase II study of pazopanib in patients with renal cell carcinoma, namely VEG102616 and present Phase II study VEG20002.

Observed plasma pazopanib concentration/time data from the patients in the STS study at the day 29 clinic visit and from patients in the RCC study at the week 4 clinic visit are displayed together in the dossier. These data demonstrated that the mean plasma pazopanib concentrations from study VEG20002 were greater than the mean values from study VEG102616 at all time-points at which the blood samples were obtained. The differences between the mean plasma pazopanib concentrations in patients with STS and patients with RCC ranged from approximately 8-29%. However only one concentration at the 3-4 hour time interval and three concentrations at the 24 hour post-dose (pre-dose sample) time point at the day 29 clinic visit for subjects with STS were greater than the range of values collected at the

same time-points at the week 4 clinic visit from subjects with RCC. These results therefore suggest that there was no marked difference in the pazopanib pharmacokinetics between patients with STS and those patients with RCC.

***Comment:***

This data from the Phase II study VEG20002 demonstrates the plasma pazopanib concentration were maintained above the level associated with biologic effects consistent with VEGFR inhibition in more than 70% of patients for whom data were available similar to those observed in renal cell carcinoma in study VEG102616. These results therefore indicated that pazopanib 800 mg once daily is an appropriate monotherapy dose for patients with STS and provides optimal biologic effect associated with VEGFR inhibition and clinical effects.

# 4. Pharmacodynamics

No new data regarding pharmacodynamics is provided in this submission.

# 5. Dosage selection for the pivotal studies

The data indicated in the pharmacokinetic section regarding study VEG20002 in patients with advanced stage STS who received pazopanib in a dose of 800 mg daily demonstrates that the pazopanib 800 mg once daily dosage is an appropriate monotherapy for patients with STS and provides optimal biologic effects associated with VEGFR inhibition and clinical effects. Accordingly a dose of 800 mg pazopanib per day represents an appropriate dosage selection for the pivotal studies.

# 6. Clinical efficacy

The primary evidence to support the clinical efficacy of pazopanib in advanced STS is provided by the pivotal Phase III study VEG110727. Supportive data is provided from the Phase II open-label study VEG20002. Clinical design features, study population and efficacy endpoints are summarised in Table 3.

**Table 3. Overview of studies evaluating the efficacy of pazopanib in STS**

| Study | VEG110727 | VEG20002 |
|---|---|---|
| Level of Evidence | Pivotal | Supportive |
| Critical Design Features | Phase III<br>Randomized (2:1)[a]<br>Double-blind<br>Placebo-controlled | Phase II<br>Non-randomized<br>Open-label<br>Single-arm |
| 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<br>Disease progression on or after anthracycline-based regimen<br>WHO PS 0 or 1<br>-Leiomyosarcoma<br>-Synovial sarcoma<br>-Other types of STS (excluding GIST and adipocytic STS) | 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<br><br>WHO PS 0 or 1<br>-Leiomyosarcoma<br>-Synovial sarcoma<br>-Adipocytic tumors<br>-Other types of STS (excluding GIST). |
| Number of subjects | 369 subjects<br>Pazopanib: 246<br>Placebo: 123 | 142 subjects |
| Efficacy endpoints<br>Primary<br><br>Secondary | PFS by independent radiologist<br><br>OS (principal);<br>ORR;<br>Duration of response, Time to response | PF rate at Week 12 by peer[b] and investigator review<br>PFS<br>OS<br>ORR<br>Duration of response, Time to response |
| Module location | m5.3.5.1 | m5.3.5.2 |

Data source: VEG110727 Protocol, Reporting and Analysis Plan (RAP), Table 6.0000, VEG20002 Protocol, RAP Table 6.0000

GIST: gastrointestinal stromal tumor; OS: overall survival; ORR: overall response rate; PF: progression-free; PFS: progression-free survival; PS: performance status; STS: soft tissue sarcoma; WHO: World Health Organization

a. 2:1 randomization of pazopanib: placebo.

b. Peer Review: Subjects who were alive and assessed by the investigator as CR, PR or SD at Week 12 also had their scans reviewed by peers at Erasmus University Medical Center in Rotterdam.

Note: Translational Research was conducted in VEG110727 and VEG20002, but data and results are not included in this submission.

## 6.1. Pivotal Study VEG110727

### 6.1.1. Study design, objectives, locations and dates

Study VEG110727 was a pivotal Phase III randomised double blind placebo controlled multicentre international study conducted by the EORTC in collaboration with Glaxo Smith Kline.

The primary objective of the study was to evaluate and compare progression free survival (PFS) in pazopanib vs placebo treated patients. The principal secondary objective was to evaluate and

compare overall survival (OS) in the two treatment arms. Other secondary objectives were to evaluate PFS in the three histology sub-types, ie leiomyosarcoma, synovial sarcoma and other STS eligible histolgies recruited onto study. Also 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.

Key eligibility criteria for patients were to have histological evidence of high or intermediate grade malignancy STS and confirmed disease progression as determined by the RECIST criteria compared with a prior disease assessment within six months or 12 months for those who had only prior systemic adjuvant therapy; metastatic STS with a maximum of four prior lines of systemic therapies for advanced disease of which no more than two lines were combination regimens and protocol specified criteria for acceptable organ function. All patients were required to have had disease progression on or after an anthracycline based regimen, disease progression on or after available standard chemotherapies except if medically contraindicated or refused; 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.

A centralised panel of pathologists determined the specific histological types of STS. Tumour types eligible included fibroblastic; so called fibrohistiocytic, leiomyosarcoma; malignant glomus tumours; skeletal muscle sarcomas, vascular sarcomas; uncertain differentiated sarcomas including synovial sarcomas but excluding chondrosarcomas, Ewing's tumours and primitive neuroectodermal tumours; malignant peripheral nerve sheet tumours; undifferentiated soft tissue sarcomas not otherwise specified. Ineligible sarcomas included adipocytic of all subtypes; all rhabdomyosarcomas that were not alveolar or pleomorphic; chondrosarcomas; osteosarcomas, Ewing's tumours and PNET tumours; GIST tumours; dermatofibromatosis sarcoma protuberans; inflammatory myofibroblastic sarcomas; malignant mesotheliomas and mixed mesodermal tumours of the uterus.

All patients required a WHO performance status of 0 or 1.

Stratification factors in relation to randomisation included performance status and number of lines of prior therapy. Patients were then centrally randomised in a 2:1 ratio of pazopanib vs placebo. Patient were to receive pazopanib in a dose of 800 mg daily on a continuous basis and continued on study drug until disease progression, death, unacceptable toxicity or withdrawal of consent.

Visits occurred every four weeks for the first 12 weeks of treatment followed by visits every eight weeks. Radiological assessments were performed for all patients at baseline and then every four weeks until week 12 and every eight weeks thereafter until progression. Clinical assessment for safety occurred at baseline every four weeks until week 12 and every eight weeks after week 12. Patients who discontinued study drug prior to disease progression were to continue disease assessments according to predefined schedules. All patients were followed for survival until death due to any cause or withdrawal of consent.

### 6.1.2. Efficacy variables and outcomes

Disease was assessed by measurement of target lesions, non-target lesions and identification of new lesions using RECIST criteria.

The primary efficacy endpoint of progression free survival is defined as the interval between the date of randomisation and the earliest date of either disease progression or death due to any cause. The principal secondary endpoint of overall survival was defined as the time from date of randomisation until date of death due to any cause.

In relation to statistical methods the primary endpoint of PFS had a trial power to detect a 37% decrease in the hazard ratio, ie a hazard ratio of < or = 0.63 corresponding to an increase from

2.2 to 3.5 months in the median PFS. A total of 224 PFS events were required for detecting the targeted difference with a 90% power and 5% two-sided alpha level.

Overall survival was powered to detect a 33% decrease in the death hazard ratio < or = 0.67 corresponding to an increase from eight to 12 months in median OS. The overall power for this endpoint was 80% based on 206 death events.

PFS and OS were summarised using Kaplan-Meier survival curves to compare between treatment arms and the final analysis using a stratified log rank test.

Various pre-specified sensitivity analyses were undertaken in relation to PFS and these are summarised in Table 4.

**Table 4. Summary of analyses of PFS – Primary and sensitivity analyses (VEG110727)**

| Analysis | Population | Assessed by: | Statistical Analysis | Adjusted for: | Additional Unique Features of Analysis |
|---|---|---|---|---|---|
| Primary analysis | ITT | Independent reviewer | Stratified log rank test; Pike estimator | Randomization strata | |
| Sensitivity analysis 1 | Per Protocol | Independent reviewer | Stratified log rank test; Pike estimator | Randomization strata | |
| Sensitivity analysis 2 | ITT | Independent reviewer | Log rank test; Pike estimator | Unadjusted | |
| Sensitivity analysis 3 | ITT | Investigator | Stratified log rank test; Pike estimator | Randomization strata | |
| Sensitivity analysis 4 | ITT | Investigator | Log rank test; Pike estimator | Unadjusted | |
| Sensitivity analysis 5 | ITT | Investigator | Stratified log rank test; Pike estimator | Randomization strata | Includes symptomatic progressions as an event for subjects who have symptomatic progression without later having radiologic documented progression |
| Sensitivity analysis 6 | ITT | Independent reviewer | Stratified log rank test; Pike estimator | Randomization strata | No censoring for extended loss to follow-up |
| Sensitivity analysis 7 | ITT | Independent reviewer | Stratified log rank test; Pike estimator | Randomization strata | Subjects treated as progression at the next scheduled visit if investigator calls progression and the independent review would lead to censoring |
| Sensitivity analysis 9 | ITT | Independent reviewer | Stratified log rank test; Pike estimator | Randomization strata | Subjects censored if study medication stopped without radiologically documented progression |
| Sensitivity analysis 10 | ITT | Independent reviewer | Cox proportional hazards model | Randomization strata | |
| Sensitivity analysis 11 | ITT | 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 |

Data Source: VEG110727 RAP
ITT: Intent-to-Treat population; WHO PS: World Health Organization Performance Status

A variety of sub-groups were explored in the analysis of PFS data by Kaplan-Meier analysis including histological types, performance status, number of prior lines of therapy, age, race, gender, recruitment region and tumour grade at initial diagnosis.

Reviewing the results of study VEG110727 a total of 369 patients with STS were enrolled onto study between the 6th October 2008 and 26th February 2010. Clinical cut-off date for analysis was the 22nd November 2010.

The intent to treat population (ITT) included 246 patients receiving pazopanib and 123 receiving placebo. One patient on the placebo arm and 18 patients in the pazopanib arm remained on study treatment at the time of clinical cut-off. Most patients who had received placebo discontinued study treatment due to progressive disease being 96% compared to 68% of patients who received pazopanib.

As of the clinical cut-off date 58% of all patients randomised had died, 63% in the placebo arm and 56% in the pazopanib arm. Some 38% of patients remained ongoing on study, 34% placebo and 40% pazopanib.

Efficacy analyses were undertaken on the ITT population comprising all 369 patients allocated to the arm randomised.

Demographic and disease characteristics were comparable between the treatment arms. The median age of all patients was 55 years with 59% of patients female, 72% white and 23% Asian. Baseline disease characteristics were comparable between the treatment arms as indicated. The agreement between the independent radiologist and the investigator assessments on the presence of measurable disease, at baseline was 95%. Lung was the most common site in 80%

of subjects of tumour involvement. The number of disease sites and times since last progression were comparable between the treatment arms.

The most common disease sites of origin were lower extremity, thoracic and retroperitoneal region. Slightly more patients on the placebo arm had high-grade disease being 73% than patients on the pazopanib arm being 65%.

All patients had received extensive systemic anticancer therapy prior to study. The most common prior systemic therapy was doxorubicin which was given to 98% of patients in both treatment arms. The frequency of prior surgery and prior radiotherapy was similar between the treatment arms.

Regarding post treatment anticancer therapy administered as of the clinical cut-off date: post-treatment anticancer therapy was received by a greater proportion of patients in the placebo arm being 72% than the pazopanib arm being 54%. The median duration of follow up for patients with radiologic progression until the clinical cut-off date for the placebo treated arm being 6.8 months with a range of 0.1-21.7 months compared with the pazopanib arm being 4.37 months with a range of 0-19.7 months.

Reviewing the analysis of the primary efficacy endpoint, in relation to the independent radiological assessment of PFS. In the ITT population a statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm. The median PFS in the placebo arm was seven weeks with 95% CI 4.4, 8.1 and the pazopanib arm was 20 weeks with 95% CI 17.9, 21.3 with a corresponding HR of 0.35 and a P value <0.001.

In each of the 10 pre-specified sensitivity analyses, PFS was longer in the pazopanib arm compared to the placebo arm and corresponding HR were statistically significant with a P value <0.001 and consistent with the primary analysis.

Several post-hoc sensitivity analyses were also performed and in each case PFS is longer in the pazopanib arm compared with the placebo arm and the corresponding HR was statistical significant with P<0.001 similar to each other.

Reviewing the PFS by investigator assessment the median PFS in the placebo arm was 6.6 weeks and 20.1 weeks in the pazopanib arm with an HR 0.39 and P<0.001. Again these results were consistent with the primary analysis.

After conditioning for the stratification factors, pazopanib treatment was still statistically significant in the model with an HR 0.32 and P<0.001. In addition the co-variate of performance status was statistically significant with an HR 0.76 and a P 0.025 with a longer PFS in patients with a baseline WHO performance status of zero compared to those with a performance status of 1. With the statistically significant factors of treatment and baseline performance status in the model there was no statistically significant effect according to whether patients had received 01 or >2 lines of prior systemic therapy for advanced disease with a P value 0.268.

Reviewing sub-group analyses of PFS in relation to tumour histology, the improvement in median PFS and HR with pazopanib compared to placebo was noted in each of the histology sub-groups and was consistent with the overall population.

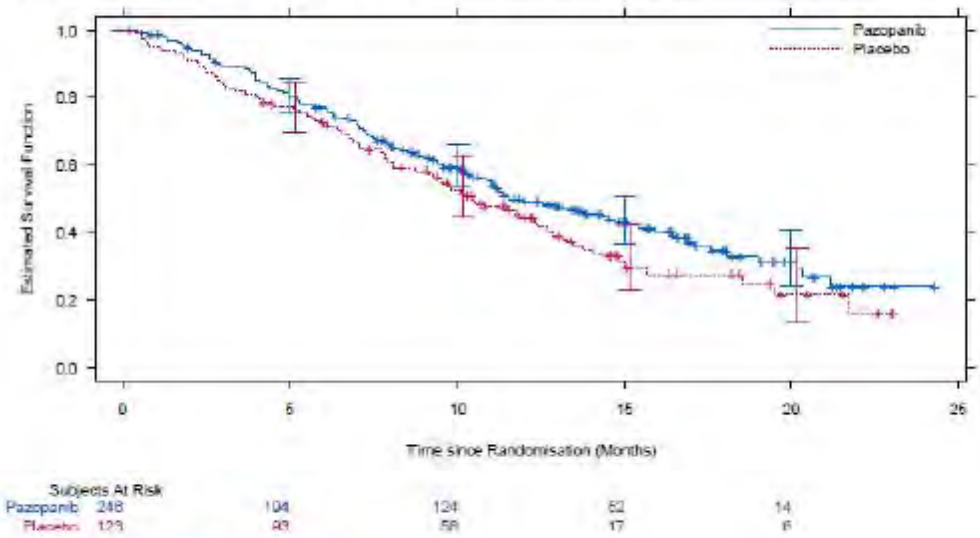
In relation to prior lines of therapy, geographical location of enrolment, tumour grade, these again significantly favoured the pazopanib therapy.

Again improvement in PFS and HR with pazopanib compared with placebo was noted in the sub-groups related to age, gender and race.

The principal secondary efficacy endpoint was that of overall survival and an interim overall survival analysis was conducted with 215 or 77% of the 279 required death events had occurred in the study which related to 58% of all patients on study. As of the clinical cut-off date of 22nd November 2010, 78 placebo patients or 63% had died and 137 of pazopanib patients or 56% had died. The median overall survival in the placebo arm was 10.4 months compared with

11.9 months with an HR 0.82 and a P value 0.156. These results did not reach the pre-specified level of significance. The Kaplan-Meier curves for overall survival are given in Figure 1:

**Figure 1. Kaplan-Meier curves overall survival curves (VEG110727, ITT population)**




Data Source: VEG110727 Figure 17.4000
Note: 95% confidence interval bands are shown for each treatment.

Some influence on this interim overall survival data maybe as a result of an imbalance in the anticancer therapy following discontinuation of study drug as in the placebo arm 89 or 72% of patients received post-study drug anticancer therapy compared with 132 or 54% of patients in the pazopanib arm. All further therapy was with agents other than pazopanib which was not offered for patients who previously were on placebo.

Results of pre-specified sensitivity analyses was consistent with the principal analyses of overall survival with estimated hazard ratios ranging from 0.63 – 0.82. Similarly sub-group analyses by the various sub-groups such as tumour histology, prior lines of therapy, baseline performance status and extent of initial disease all failed to reveal significant differences in overall survival data.

In relation to other secondary efficacy endpoints in terms of overall response rate by independent radiology 11 or 4% of patients and by investigator assessment 23 or 9% of patients in the pazopanib arm experienced confirmed partial remission. There were no responses in the placebo arm. Other secondary endpoints such as time to response and duration of response were only applicable to the pazopanib arm and therefore were not considered to be of real value in the assessment of outcomes in this study. It is noted that the median time to partial response for pazopanib patients was 8.4 weeks whereas duration of response was 38.9 weeks by independent radiologist and 32.1 weeks by investigator assessment.

***Comment:***

The data from this quite robust study has clearly indicated a significant advantage in terms of progression free survival for those patients receiving pazopanib as second or later line therapy in the patients with advanced stage STS. This result was applicable across the various histological sub-types as well as other stratification factors and also applicable in relation to appropriate sensitivity and sub-group analyses. It is noteworthy that despite this benefit overall survival analyses did not show a significant difference for the pazopanib vs placebo arms. Certainly the differences in terms of proportion of patients receiving subsequent therapy may have an influence on this but at this time the level of benefit for pazopanib appears to be modest. Certainly there would be value for the evaluation of pazopanib as an earlier treatment in patients who have advanced and metastatic STS.

## 6.2. Supportive Study VEG20002

## 6.3. Study design, objectives, locations and dates

The supportive trial VEG20002 was a Phase II multicentre open-label non-randomised study conducted by the EORTC and supported by Glaxo Smith Kline. The purpose of the study was to evaluate the activity and tolerability of pazopanib in patients with relapsed or refractory STS for whom no standard therapy existed. The patients entered onto study received oral pazopanib at a dose of 800 mg once daily until disease progression, unacceptable drug related events, intercurrent illnesses preventing further drug administration or subject refusal.

The study enrolled patients into four different strata based on the WHO classification of STS, namely leiomyosarcoma; adipocytic tumours, including liposarcoma, de-differentiated, myxoid-round cell, pleomorphic, mixed type and not otherwise specified; synovial sarcoma; other types of high or intermediate grade malignant STS.

Eligibility criteria also included those who had relapsed or were refractory and incurable by surgery or radiotherapy, had tumour progression as determined by RECIST criteria with a prior disease assessment during the past six months, when eligible for chemotherapy or had more than one combination therapy or two single-agent chemotherapy agents for advanced disease, had a WHO performance status of 0 or 1 and adequate organ function.

Thirty-seven patients could be recruited into each stratum in two stages, 17 patients in the first stage and 20 in the second. The treatment plan included, treatment following the first 17 patients for 12 weeks and if there were three or fewer patients who exhibited stable disease a partial response or complete response this stratum was closed to further enrolment. If >3 patients had at least stable disease then the stratum was continued to a total of 37 patients.

Histological tumour types were initially determined by a local pathologist and subsequently reviewed by a central pathology panel.

Following the first stage of study sufficient responses were seen in the leiomyosarcoma, synovial sarcoma and other types of STS, therefore patients with these types of sarcoma were enrolled in the second stage of the trial.

### 6.3.1. Efficacy variables and outcomes

The primary efficacy endpoint was progression free rate at week 12 and was defined as the number of patients with at least stable disease or better over the total number of patients based on the disease evaluation at 12 weeks after the start of treatment determined by appropriate scans and tumour measurements. A central radiology panel reviewed all scans.

Secondary efficacy endpoints included progression free survival, overall survival, overall response rate, time to response and duration of response.

A total of 142 patients with STS were enrolled into the study between the 26th October 2005 and the 15th October 2009. Clinical cut-off date for analyses was the 20th August 2010. Information on subject disposition is provided in the submission.

Efficacy analysis was conducted on the ITT population which comprised 138 patients as four were considered unevaluable for response as they did not meet eligibility criteria. The median age for all patients on trial was 51 years with a range of 18-79 years with 50% of patients being male and 48% of patients with WHO performance status of 0 and 51% with WHO performance status 1. Data were provided on the breakdown of the various soft tissue sarcoma types in the four strata analysed, summary of disease site of origin, and summary of tumour grade by histology.

Only two patients had not received prior chemotherapy and a total of 105 patients had received chemotherapy for advanced disease with 71 receiving one line of combination chemotherapy and 34 at least two lines of single agent chemotherapy.

Patients who discontinued study treatment could go on to receive other anticancer therapies and as of the clinical cut-off date 80% or 56% had received at least one other anticancer therapy post-study drug discontinuation of which 66 of these patients received chemotherapy.

Reviewing results of the primary efficacy endpoint of progression free rate at 12 weeks for the stage I of study 5/19 patients with leiomyosarcoma, 9/16 patients with synovial sarcoma and 11/28 patients with other STS experienced either partial response or stable disease. The number of progression free subjects at week 12 exceeded the predefined threshold, that is, at least 3/17 patients for these three strata and therefore were open for further enrolment.

In the adipocytic stratum at week 12, 2/17 patients experienced stable disease and this did not meet the prerequisite progression free rate. Stratum was closed to further enrolment. It is of note that on central pathology review two patients from the other STS stratum were subsequently classified as having adipocytic sarcoma and had achieved stable disease. Therefore a total of 19 patients were assigned to the adipocytic stratum and entered the study.

For stage II evaluation additional 22, 21 and 15 patients were enrolled in the leiomyosarcoma, synovial sarcoma and other STS strata respectively and the progression free rate at 12 weeks for the combined stage I and stage II is given in Table 5. Overall a total of 4% of patients achieved partial remission, a further 37% stable disease.

**Table 5. Summary of progression-free rate at 12 weeks (RECIST criteria) Primary analysis (VEG20002, ITT population)**

| Category | Leiomyo-sarcoma[b] N=41 | Adipocytic sarcoma[b] N=19 | Synovial sarcoma[b] N=37 | Other STS[b] N=41 | Total N=138 |
|---|---|---|---|---|---|
| **Response at Week 12, n (%)[a]** | | | | | |
| Complete Response (CR) | 0 | 0 | 0 | 0 | 0 |
| Partial Response (PR) | 1 (2) | 0 | 4 (11) | 1 (2) | 6 (4) |
| Stable Disease (SD) | 16 (39) | 5 (26)[c] | 14 (38) | 16 (39) | 51 (37) |
| Progressive Disease (PD) | 19 (46) | 13 (68) | 15 (41) | 21 (51) | 68 (49) |
| Unknown[d] | 2 (5) | 0 | 0 | 1 (2) | 3 (2) |
| Missing[e] | 3 (7) | 1 (5) | 4 (11) | 2 (5) | 10 (7) |
| **Progression-free Rate** | | | | | |
| CR+PR+SD, n (%) | 17 (41) | 5 (26) | 18 (49) | 17 (41) | 57 (41) |
| (90% CI) | (28.4, 55.5) | (11.0, 47.6) | (34.3 , 63.2) | (28.4, 55.5) | (34.2, 48.7) |
| p-value[f] | 0.003 | 0.653 | <0.001 | 0.003 | <0.001 |

Data Source: VEG20002 Table 7.1000

a. Response at Week 12 is from the peer radiology review, if conducted. Otherwise the response is from the investigator review.
b. Histology assessment based on Central Pathology determination when tissue was available.
c. One subject was enrolled at the same time as the decision was made to stop enrolment into Stage 2 and 2 subjects (Subjects 93 and 137) were reclassified from "other" STS to the adipocytic stratum after enrollment to this stratum had ended.
d. Subjects with a response of unknown did not have a known response per RECIST at Week 12.
e. Subjects with a response of missing did not have a post-baseline disease assessment.
f. p-value = the strength of evidence to reject the null hypothesis of the PF rate being equal to 20% with an alpha level of 0.10.

Reviewing the secondary efficacy endpoints in relation to progression free survival, the mean progression free survival for the overall ITT population was 12.1 weeks. The median overall survival in the overall ITT population was 10.6 months. Median overall survival ranged from 6.5 months in the adipocytic stratum to 11.7 months in the leiomyosarcoma stratum.

The overall response rate, defined as the number of patients who experienced a confirmed complete or partial response by investigator assessment, was 8 or 6% with all responses being partial responses.

The median time to response for the eight patients who had achieved partial response was 18 weeks, with a range of 79-169 days. The median duration of response was 33.6 weeks with a range from 165-508 days.

***Comment***

These data show a modest level of response to pazopanib in these patients. The most sensitive sub-groups being leiomyosarcoma and synovial sarcoma patients. It is noteworthy that progression free survival for these two groups of patients was similar to that observed in the pivotal trial. This therefore lends some degree of support to the data from the principal study.

# 7. Clinical safety

## 7.1. Studies providing evaluable safety data

This review of safety for those patients receiving pazopanib for the treatment of advanced stage soft tissue sarcoma arise from the two principal studies presented in this submission, namely the pivotal study VEG110727 and the supportive trial VEG20002.

A total of 382 patients who received pazopanib in these two studies provide the safety data evaluated. In the main the safety data is presented as an integrated evaluation of these two studies with certain elements of the pivotal trial emphasised. The safety population was all patients who had received at least one dose of investigational agent.

Data from the therapy period is defined as the time from the first dose of randomisation medication to 28 days post last dose of medication. The safety data for the pivotal study is based on the clinical cut-off date of 22nd November 2010 and for the supportive study 20th August 2010.

Adverse events were defined in the protocol as any untoward medical occurrence temporally associated with the use of medicinal product whether or not considered related to medicinal product. Adverse events were reported by investigators and graded according to NCI criteria. Standard definitions were utilised for indications of serious adverse events.

At the time of data evaluation some 95% of patients had discontinued therapy in the pivotal study VEG110727 and some thirty-four or 14% had discontinued pazopanib because of toxicity related to the study drug.

## 7.2. Patient exposure

In relation to exposure to pazopanib for the two trials the median time on study treatment for pazopanib treated patients in the pivotal study was 19.36 weeks or approximately 4.5 months while the median length of exposure to study drug was 12.9 weeks or approximately three months for the supportive trial. Overall there was a median exposure to pazopanib of 3.6 months with a range of 0-53 months.

Demographic and baseline disease characteristics for the two studies have previously been presented in the *Efficacy* sections, above. Integrated summary of the data for the two safety populations was provided. It is noted that tumour grade, the most common locations of disease and the number disease sites were all comparable between the pivotal study and the integrated data set. The most common tumour sub-types being leiomyosarcoma in 39% of patients and synovial sarcoma in 16%.

## 7.3. Frequent adverse events

Reviewing the common adverse events observed across the integrated study data these demonstrated the most frequent adverse events for patients receiving pazopanib included fatigue, diarrhoea, nausea, decreased weight, hypertension and decreased appetite. The overall summary of adverse events noted regardless of relationship to investigational product was

provided. The majority of these events were reported at grade I or II in intensity. The overall incidence of adverse events with a maximum severity of grade III or higher was 58% which was a little lower than that of the pivotal study with a 62% incidence of grade III and higher events. Grade V or fatal events were reported for 13 pazopanib treated patients, eight from the pivotal study and five from the supportive study.

It is noted that some aspects of adverse events reported in the patients with STS differed from those reported earlier in the studies with renal cell carcinoma. Namely there was an increased incidence of fatigue and asthenia and nausea and decreased weight for those patients with STS compared to the renal cell carcinoma patients. The differences were however relatively minor.

## 7.4. Treatment related adverse events

Reviewing treatment related adverse events across the STS studies the most frequent on-therapy adverse events considered related to study treatment by the investigator were similar to those for the pivotal study again emphasising diarrhoea, fatigue, nausea, hypertension, hair colour changes, decreased appetite and decreased weight.

## 7.5. Deaths

Reviewing deaths which occurred in the two studies. In the pivotal trial death was reported in 134 patients in the pazopanib arm (56%) with a primary cause of death being progression of disease in 122 of these patients and deaths due to adverse events were noted in five patients in the pazopanib arm. For the integrated data for the two studies a total of nine patients had an adverse event of toxicity or cause unknown listed as the primary cause of death.

Reviewing fatal serious adverse events. In the pivotal study nine fatal serious adverse events were reported by eight or 3% of patients in the pazopanib arm. One of these was considered related to disease progression and of the remaining seven patients who experienced eight fatal serious adverse events a possible relationship to pazopanib treatment was noted in one patient with multi-organ failure but no other events were considered treatment related. An additional patient in the supportive study had death reported as a fatal adverse event but the death occurred more than six months after discontinuation of study drug and therefore was not reported in the clinical data base. Cause of death was considered to be pneumonia following earlier disease progression.

## 7.6. Serious adverse events

Reviewing the overall incidence of serious adverse events across the integrated data set this was documented in 37% of patients which was similar to that observed in the pivotal study in which 41% of patients developed serious adverse events. The most frequent serious adverse events regardless of relationship included embolism, dyspnoea, pneumothorax, elevation of liver enzymes, decreased Hb, fatigue, vomiting and chest pain. Of 140 patients with any SAE 82 of these experienced events considered at least possibly related to study drug by the investigator.

It is noted that this overall incidence of serious adverse events for the STS data set of 37% is somewhat higher than that observed from the three pivotal renal cell carcinoma studies previously reported with an overall incidence of SAEs of 27%. This may have some relationship to the extensive prior therapy of the patients with STS and associated co-morbidities.

## 7.7. Discontinuation and withdrawals due to adverse events

Reviewing adverse events leading to investigational product discontinuation or withdrawal from study, the data is only available from the pivotal trial. Adverse events leading to

discontinuation of pazopanib occurred in 20% of patients in VEG1102727. It is of note that of the 48 patients who were reported as having an adverse event leading to permanent discontinuation of study drug, 12 of these also had documented disease progression. The most common adverse events leading to discontinuation of pazopanib included elevated hepatic enzymes ALT, dyspnoea, left ventricular dysfunction, fatigue, hypertension and vomiting.

This was comparable to that reported earlier for renal cell carcinoma patients with the most common reason for treatment discontinuation in this group being diarrhoea, elevation of hepatic enzyme ALT, asthenia/fatigue and hepatotoxicity.

## 7.8. Dose reductions and interruptions due to adverse events

In relation to adverse events requiring dose reduction for the pivotal study this occurred in 32% of patients. The most frequent reasons being fatigue, hypertension, diarrhoea and nausea. This compares to renal cell carcinoma studies in which hypertension and diarrhoea were the most common reasons.

Dose interruptions occurred in 50% of patients receiving pazopanib in the pivotal study with the most frequent reasons again being fatigue, hypertension, nausea and diarrhoea. This is similar to that reported for renal cell carcinoma patients with the most frequent reasons for dose interruption being diarrhoea and hypertension.

## 7.9. Adverse events of special interest

A number of adverse events of special interest were selectively evaluated on the basis of prior experience with pazopanib including assessment of liver chemistry abnormalities known and adverse events, hypertension, cardiac and vascular events including venous thromboembolic events, haemorrhagic events, pneumothorax, thyroid function abnormalities, bowel perforations and enteral fistula and proteinuria. Assessment was also made in relation to pneumothorax, myocardial dysfunction and venous thromboembolism.

### 7.9.1. Hepatic effects.

In relation to hepatic dysfunction, assessment of liver chemistry abnormalities was reviewed in relation to the pivotal study and across the two pivotal trials. Bilirubin and ALT elevations were seen in 5% and 18% of pazopanib treated patients in the pivotal study. A total of 13 or 5% of pazopanib treatment patients experienced ALT elevations >8 times the upper limit of normal and of these five patients had elevations >20 times the upper limit of normal. It is noteworthy that ALT elevations tended to be significant higher when they were associated with AST elevations indicating a pattern of hepatocellular injury as opposed to a mixed or cholestatic pattern. It is noted that only one patient who died of multi-organ failure associated with major hepatic dysfunction deceased as a direct relationship to pazopanib induced liver dysfunction. Two patients who had evidence of elevated liver enzymes whose treatment was interrupted with subsequent improvement in liver enzymes were then re-challenged with further elevation. Two other patients however whose liver function improved after dose interruption resumed therapy without adverse effect.

It is worth commenting that one further patient apart from that discussed above died of features consistent with liver failure but had confounding other clinical factors including massive pulmonary embolus, progressive disease and possible influence of concurrent medications.

In summary it would certainly appear that there is definite evidence of a potential hepatic dysfunction associated with pazopanib administration requiring appropriate monitoring and relevant dose interruption or cessation according to liver function disturbances developing.

Further review of hepatic enzyme abnormalities indicated that grade III and grade IV shifts in these enzymes were more frequent among pazopanib patients compared to placebo. The majority of these elevations were noted in the first 18 weeks of treatment with pazopanib 18 or 92.9% of patients whose hepatic enzyme elevations >3 times the upper limit of normal occurred.

### 7.9.2. Hypertension

Reviewing the incidence of hypertension across the STS studies, this was evaluated by analysing the time to first baseline elevation of systolic blood pressure of at least 150mmHg or diastolic blood pressure of at least 100mmHg. Hypertension was reported as an adverse event in 42% of patients in the two studies which compared with a 47% incidence of hypertension in the renal cell carcinoma studies. Grade III hypertension across the studies was documented in 7% of patients. There was no incidence of hypertensive crisis. Three patients discontinued because of an adverse event of hypertension. Hypertension led to dose reductions in 7% and interruptions in 10%.

### 7.9.3. Cardiac effects

Reviewing myocardial dysfunction, this was noted to occur in the pivotal study in 9% of patients on pazopanib with the majority of these events of lower grade toxicity and reported left ventricular dysfunction based on a decline in LVEF assessments. Four patients in the pazopanib arm or 2% had grade III or IV toxicity. Symptomatic left ventricular decline was reported in two of these patients. No fatal events were reported.

A total of eight serious adverse events related to cardiac disorders were reported in the pivotal study, for patients on pazopanib, five of which were listed as ventricular dysfunction and the remaining three as cardio-respiratory arrests. One of these three was in a patient who had a pulmonary embolus, another a myocardial infarction and the third a malignant pericardial effusion. Of the five patients with left ventricular dysfunction as a serious adverse event, three resolved on treatment interruption but two following treatment withdrawal had dysfunction which did not resolve. It is noteworthy that all of these patients had received anthracyclines which may have contributed.

In relation to cardiac arrhythmias, in the pivotal study the incidence of patients reporting cardiac arrhythmias was 6% for those receiving pazopanib and of these five or 2% experienced QT prolongation of any grade with two patients reporting grade III events with a QTc >500msecs without associated arrhythmia. There was one fatal event in the pazopanib arm that could potentially have been associated with arrhythmia in a patient with a fatal event “not otherwise specified” who died at home.

This incidence is similar to that reported in the earlier renal cell carcinoma studies.

### 7.9.4. Venous thromboembolic events

In relation to venous embolic and thrombolic events in the pivotal study 13 patients or 5% receiving pazopanib experienced on therapy or post-therapy venous thromboembolic events. More specifically ten of these 13 patients developed venous thrombosis including DVT, vena cava thrombosis and vascular graft thrombosis without reports of associated pulmonary embolus, and three patients on pazopanib experienced pulmonary emboli. Two patients experienced fatal thromboembolic adverse events of pulmonary embolus considered unrelated to study treatment by investigator as both events were seen in association with disease progression. In a third patient with pulmonary embolism there was associated finding of tumour which subsequently was assessed as disease progression.

In the supportive study eight patients reported on therapy VTE events all of which were non-fatal, five were pulmonary emboli, one inferior vena cava thrombosis and three DVTs. Two of these events were associated with progressive disease but the others were documented during the course of planned evaluations. When these events were compared to placebo patients in the

pivotal study and exposure adjusted venous thromboembolic events analysed for both treatment arms, the overall exposure adjusted rate of VTE do not support increase of these events of pazopanib treated patients with STS but the exposure adjusted rates in both placebo and pazopanib treated patients in the STS integrated data set are higher than those seen in the renal cell carcinoma population.

### 7.9.5. Arterial thromboembolic events

In relation to arterial embolic and thrombotic events in the pivotal study five patients in the pazopanib arm experienced arterial embolic and thrombotic events. Four experienced grade I – grade III myocardial ischemia and one experienced grade IV thrombovascular accident 85 days from the last dose of pazopanib. In the supportive study there were two on-therapy arterial thrombotic events, one being a grade III coronary artery disease and one a grade IV event of thrombosis with a mechanical aortic valve.

These rates for arterio-thromboembolic events are similar to that reported for renal cell carcinoma patients.

### 7.9.6. Haemorrhagic events

In relation to haemorrhagic events in the pivotal study: the rate of all grades of haemorrhage was higher in the pazopanib arm being 22% compared to placebo 8% but the incidence of grade III or IV haemorrhage events were 1% for pazopanib.

Epistaxis, mouth and anal haemorrhage were the most common categories of haemorrhage. Two patients experienced grade IV haemorrhage, one an intra-abdominal bleed considered possibly related to study treatment and the other an intra-cranial haemorrhage possibly related to study treatment. Again these data were consistent with that observed for renal cell carcinoma patients.

### 7.9.7. Pneumothorax

In relation to pneumothorax an incidence of 3% was observed in the pivotal study involving eight patients on pazopanib. Overall for both STS studies, 15 or 4% of the 382 patients experienced pneumothorax, 11 were reported as serious adverse events and seven considered possibly related to study treatment. It is postulated that this may be due to necrosis of peripheral sarcoma lesions within the lung. The median time to first pneumothorax was 40 days, ranging from 12-614 days. Pneumothorax led to permanent discontinuation of study drug for one patient in the pivotal trial who experienced a grade IV pneumothorax. Three other cases were grade III and the remainder grade I and II.

It is noteworthy that the incidence of pneumothorax in the renal cell carcinoma population was considerably lower increasing the likelihood of this relating to necrosis of lung lesions in the STS population.

### 7.9.8. Thyroid abnormalities

In relation to thyroid function abnormalities across the STS studies, 15 pazopanib treated patients experienced concomitant elevations in TSH and decreases in T4 which were consistent with hypothyroidism. Laboratory evidence of hyperthyroidism was confirmed in five patients in the pazopanib arm all from the pivotal study. The rates of thyroid function abnormalities based on laboratory data were shown. These data are consistent with those reported from the renal carcinoma studies.

### 7.9.9. Bowel perforations and enteral fistula

In relation to bowel perforations and enteral fistula, a total of four or 1% of patients in the two STS studies experienced bowel perforation or fistula. All of these patients had known abdominal metastases at study entry and for two of the patients the perforations were shown that these developed at the site of metastatic lesions. One of these events led to peritonitis which was fatal

and the other resolved following surgery. Of the two patients with fistula, one had a fistula at baseline and another developed this during study, both fistulae ultimately resolved. These data are again consistent with that previously reported in renal cell carcinoma patients.

#### 7.9.10. Proteinuria and renal effects

In relation to proteinuria which is a recognised adverse event with tyrosine kinase inhibitor agents, proteinuria for the STS studies was reported as an adverse event in two patients, one being grade I and one grade II. In addition a grade IV nephrotic syndrome with occurrence of a serious adverse event of increased urine protein/protein creatinine ratio was reported resulting in discontinuation from study. The incidence of proteinuria in the STS population is a little lower than that seen in the renal carcinoma population.

### 7.10. Laboratory tests

#### 7.10.1. Haematology

Reviewing clinical laboratory evaluations: in relation to haematological assessments in the pivotal study, haematological shifts from baseline were mostly grade I or grade II for both arms of study and increases of any grade were comparable for pazopanib and placebo. Grade IV anaemia occurred in four patients. One was related to bleeding from a wound site. Shifts in lymphocyte levels were similar between treatment arms with 10% of patients on pazopanib experiencing grade III lymphocytopenia. Grade IV thrombocytopenia affected two patients on pazopanib both of which were considered related to disease progression.

Across the STS studies it is noted that three patients experienced grade IV thrombocytopenia being an additional patient from the supportive trial. None of these were considered related to pazopanib treatment.

#### 7.10.2. Other clinical chemistry

Reviewing chemistry assessments from the pivotal study, shifts from baseline data showed that most shifts were mild in grade with few grade III or IV shifts reported for any parameters. The reports of any grade shift for creatinine or potassium were comparable between the placebo and pazopanib arms.

Shifts in glucose representing hypo and hyperglycaemia and shifts in sodium reported high rates for pazopanib patients although these were mild in grade.

Hypokalaemia had grade III levels reported for six patients and one patient experiencing grade IV hypokalaemia on the pazopanib arm of therapy. These data are similar to those of the renal cell carcinoma patients.

### 7.11. Vital signs and electrocardiograph

In relation to vital signs data, this is only available from the pivotal study. It is noted that 83% of patients receiving pazopanib maintained heart rate within the normal range. Any other changes in heart rate were essentially similar between the pazopanib patients and those on placebo. This is similar to the renal cell carcinoma data where few changes in the heart rate were noted.

In relation to ECG changes in the pivotal study, post-baseline six patients in the pazopanib arm experienced abnormal and clinically relevant changes on ECG including grade III QTc prolongation for two patients, tachycardia for two patients, one of which were considered related to ventricular ectopics. Cardiac ischaemia with T-wave and QRS abnormalities were noted in two patients.

## 7.12. Subgroup analyses

Reviewing adverse events in relation to age, there was no evidence that the overall incidence of adverse events differed between those of <65 years vs those >65 years. Similarly the overall incidence of grade III/IV/V events was comparable between the age groups. Only differences noted were a slightly higher incidence of diarrhoea, vomiting and arterial embolism for the younger patients whereas the older sub-group experienced a higher incidence of fatigue, hypertension and decreased appetite and liver enzyme elevations. There were no real differences in the incidence and severity of adverse events between males and females in the two STS studies.

In relation to race, adverse events of hair colour changes, exfoliative skin rash were more frequent among Asian patients being 30% compared to 16% for white patients.

## 7.13. Post-marketing safety data

Based on the standard daily dose of 800 mg per day the estimated cumulative worldwide post-marketing exposure for pazopanib to the 31st December 2010 was 999.1 patient years. There were 1242 spontaneous adverse events from 361 patients reported. It is noteworthy that a total of 16 reports of fatal outcomes were documented with 13 related to malignancy progression, two due to renal failure and one myocardial infarction. The precise relationship to therapy was not determined.

It is also noted that a total of 32 spontaneous reports were related to hepatic dysfunction, the precise relationship to therapy again too difficult to define.

Of the 46 spontaneous reports of hypertension reported, none were associated with hypertensive crises. Other events reported including cardiac arrhythmias, myocardial dysfunction, myocardial infarction and ischaemia, haemorrhagic events and arterial thrombotic events were reported on occasion at an incidence essentially similar to that reported for the STS studies.

### 7.13.1. Study GSK-WEUSRTP4987 - thromboembolic events

Because of earlier reporting of thromboembolic events in the pazopanib soft tissue sarcoma clinical trial programme a study based on SEER medicare data was undertaken to assess the incidence in patients over the age of 65 years with a diagnosis of STS who had follow up of at least 12 months from diagnosis. There were 3480 STS patients included in the analysis and the unadjusted rates of TE events before and after STS diagnosis. For all TE events the incidence rate in the 12 months after STS diagnosis was higher than in the 12 months before STS diagnosis. The most pronounced increase in rates after diagnosis was seen in pulmonary embolism and DVT. Rates of TE events before and after STS diagnosis were also evaluated for each individual TE event by demographic characteristics. In general the pattern of occurrence by age, race and sex were similar before and after STS diagnosis, however one important pattern emerged in the rates of OTEs before and after STS diagnosis with difference more marked for African/American patients than for white patients, being 3.5 vs 1.7 relative ratio.

Patients with a history of a TE event of interest in the 12 months before STS diagnosis had a substancially a higher rate of that same TE event in the 12 months after STS. Patients with a history of TE during the three months before diagnosis were in the even more pronounced risk of a TE event after STS diagnosis if they had had that same event in the three months prior to diagnosis. In particular a history of PE was very strongly associated with PE after STS diagnosis. Review of history of cardiovascular disease before diagnosis with STS was also evaluated and shown that it was not strongly associated with an increased rate of TE events after STS diagnosis as history of a specific event. It is noted STS patients with advanced or regional staged cancer had 1.4-2.1 times higher rate of TE events in the 12 months after diagnosis than STS patients with localised disease. Results were similar for venous and arterial outcomes. Stages

did not seem to be a particularly strong driver for the risk of TEs after STS diagnosis. Rate of events for TE for STS patients by chemotherapy status was similar across all outcomes except for DVT which was 1.7 times higher for those patients on chemotherapy than those without chemotherapy.

The incidence proportion of TE events in the 12 months after STS diagnosis were DVT 10.6%, PE 3%, PVT 0.1%, OTE 3.1% etc. In general half of all TE events regardless of type occurred within the first 90 days after STS diagnosis.

These data have therefore shown that there is a higher rate of all TE events after STS diagnosis compared to before diagnosis. This has been particularly related to an incidence of DVT and PE. Over half of the TE events occurred in the first 90 days after STS diagnosis and patients with a recent history of TE event had substantially higher rates of TE events after STS diagnosis than those without.

### 7.14. Summary and conclusions on safety

The safety data presented from the two study populations with advanced stage STS treated with pazopanib essentially show toxicities similar to that previously observed in studies with renal cell carcinoma. These included fatigue, diarrhoea, nausea, decreased weight and hypertension. More serious toxicities such as hepatotoxicity, arterial thromboembolic events, haemorrhagic events, bowel perforations and fistulae have been previously identified as has also myocardial dysfunction. Only a small proportion of these adverse events reached grade III or IV in intensity including a small number of cases of fatigue, hypertension, dyspnoea and diarrhoea.

The incidence of more significant toxicities including hepatotoxicity previously well described among the renal cell carcinoma patient population demonstrated a somewhat similar incidence in these STS studies with these two patients dying with hepatic failure in conjunction with other clinical events.

The incidence of myocardial dysfunction appeared to be perhaps a little higher in these studies which may relate to the previous exposure to antrhacyclines for the vast majority of these patients. Nevertheless there is a requirement for careful monitoring of these patients with appropriate evaluations of LVEF both at baseline and regular intervals throughout treatment thereafter.

The increased of incidence of venous thromboembolic phenomena in this STS population appears in part to be related to the overall general medical condition of the patient population but nevertheless certainly in patients with advanced stage STS caution is required in the administration of pazopanib and for appropriate monitoring. The new signal of pneumothorax appears to be a phenomena associated with necrosis of tumour nodules with the lung but again requires relevant monitoring.

In summary the overall safety profile of pazopanib in this STS patient population appears to be generally manageable with relevant monitoring and early intervention as required.

# 8. Clinical questions

There were no outstanding questions at this time.

# 9. Benefit-risk assessment

## 9.1. Assessment of benefits

Data provided from the pivotal study VEG110727 in patients with advanced metastatic STS of various histological sub-types who had previously received at least one line of chemotherapy in the advanced disease setting demonstrates pazopanib results in a statistically significant improvement in progression free survival compared to placebo. The study was generally well conducted and quite robust in terms of numbers entered onto trial. The spectrum of sarcomas evaluated was relatively broad with evidence of worthwhile benefit being observed across the various histological sub-types. There was significant improvement in progression free survival supported by a modest but definite response rate together with significance in duration of response. There was however an insignificant difference in overall survival data for the two groups of patients. This may in part be due to the somewhat higher proportion of patients in the placebo group receiving subsequent treatment following progression but nevertheless is indicative of the fact that pazopanib in this setting exerts a modest degree of benefit. Nevertheless as these patients were heavily previously treated and there is a paucity of agents available for the management of STS it seems appropriate to support pazopanib as a new agent for the treatment of advanced stage STS.

In regards to the proposed indication for patients with advanced soft tissue sarcoma and not stating specific histological sub-type is supported by the evidence of the pivotal study in which the various histologic sub-types evaluated all showed benefit in terms of significant improvement in progression free survival.

In regards to the supportive trial this provides limited evidence of further benefit for pazopanib but nevertheless the time to disease progression in this study was comparable to that from the pivotal trial thereby supporting the data. It is worth commenting that as a result of this study, patients with adipocytic tumours were excluded from the pivotal study. Nevertheless review of the data for the adipocytic tumour type would suggest that there is modest responsiveness in these patients and therefore this evaluator does not see any particular reason to exclude them for potential benefit from a trial of pazopanib.

## 9.2. Assessment of risks

The overall safety profile of pazopanib demonstrated from the two STS trials is generally comparable with that previously observed in patients with advanced stage renal cell carcinoma for which pazopanib has now been approved for usage. The overall incidence of adverse effects including the most common including fatigue, diarrhoea, nausea, decreased weight and hypertension were most often grades I and II with limited numbers of more severe grades. The more significant toxicities including hepatotoxicity, myocardial infarction and venous thromboembolism certainly warrant careful monitoring but nevertheless in general terms relevant management should minimise major adverse sequelae.

The new safety signals arising from the studies of the STS patients in relation to increased incidence of venous thromboembolism and pneumothorax as well as a clearer understanding of the potential for myocardial dysfunction are all clearly signalled in the Product Information with appropriate caution being advised as a result.

## 9.3. Assessment of benefit risk balance

The benefits observed from the pivotal trial together with the data from the supportive study have certainly indicated a significant benefit in terms of progression free survival for pazopanib in patients with advanced and heavily previously treated soft tissue sarcoma. The benefit seems

to range across all the relevant histologic sub-types. The degree of benefit observed is modest but nevertheless as the patient population was heavily previously treated this nevertheless still represents evidence of worthwhile benefit warranting appropriate consideration for inclusion of pazopanib in the treatment armamentarium of advanced stage soft tissue sarcoma. The safety profile observed from these studies is generally commensurate with that seen from earlier trials and also the same levels of severity. The new safety signals of pneumothorax and an increased incidence of venous-thromboembolism have been clearly delineated and relevant statements made in the revised Product Information section.

In relation to an earlier agent trabectedin being evaluated and rejected for treatment of patients with STS the evaluation demonstrates that the level of benefit for trabectedin in STS was very small and the overall spectrum of toxicities associated with trabectedin considerable. Accordingly the benefit risk balance was insufficient to support its recommendations. This evaluator does not consider that the evidence from trabectedin has an adverse influence on that related to pazopanib which has shown a somewhat greater degree of benefit and most importantly a lesser range and extent of adverse effects.

Accordingly this reviewer considers the benefit risk balance is supportive of approval of pazopanib for the treatment of patients with advanced stage soft tissue sarcoma.

# 10. Recommendation regarding authorisation

On the basis of the evaluation discussed above this evaluator considers that it is appropriate to support approval for the additional indication for pazopanib for the treatment of patients with advanced (unresectable and/or metastatic) soft tissue sarcoma who have received prior anthracycline treatment or for patients who are unsuited for such therapies.

# 11. Addendum to the evaluation

## 11.1. Quality of Life evaluation

In the pivotal study VEG110727 Quality of Life assessments were undertaken utilising a global health status-quality of life summary scale for each of the treatment arms. This involved assessment of this questionnaire at three assessment time points at weeks 4, 8 and 12. Assessment was made based on decline from baseline over these three time points of assessment. As indicated in Table 6 below, assessment at week 4 was acceptable with a >80% response rate for the two arms but by week 8 the proportion of patients responding in the placebo arm particularly was declining as a result of progressive disease excluding these patients.

**Table 6 Completion rates for EORTC-QLQ-C30 as a percentage of randomised subjects and of available subjects at each assessment timepoint (ITT population)**

| Assessment timepoint | Placebo (N=123) | | | Pazopanib (N=246) | | |
|---|---|---|---|---|---|---|
| | n available to complete assessment n who completed assessment | % of randomized subjects | % of available subjects who completed assessment | n available to complete assessment n who completed assessment | % of randomized subjects | % of available subjects who completed assessment |
| Screening | 123<br>119 | 97% | 97% | 246<br>237 | 96% | 96% |
| Week 4 | 113<br>98 | 80% | 87% | 231<br>198 | 80% | 86% |
| Week 8 | 74<br>58 | 47% | 78% | 186<br>156 | 63% | 84% |
| Week 12 | 45<br>35 | 28% | 78% | 153<br>135 | 55% | 88% |

Data Source: Table 13.1200

Analyses of change from baseline for the global health status scale showed a numerically greater decline for pazopanib than placebo although the difference was not statistically significant at any of the time points that are indicated in Table 7 and Figure 2.

**Table 7. Summary of Mixed-Model Repeated Measures Analysis for Change from Baseline in Global Health Status/HRQoL Scores (ITT population)**

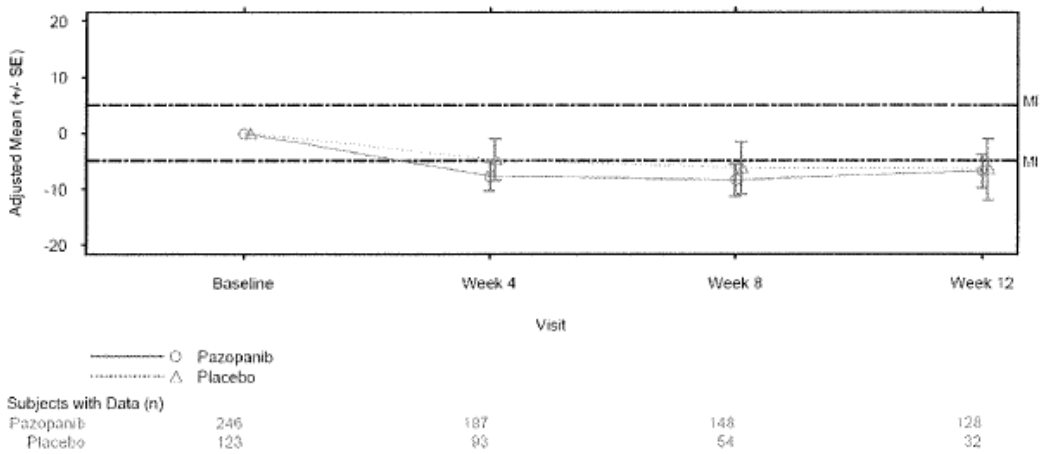
| Change from Baseline to | | Placebo (n=123) | Pazopanib (n=246) |
|---|---|---|---|
| Week 4 | n | 93 | 187 |
| | Adjusted Mean (SE) | -4.75 (1. 937) | -7.69 (1.361) |
| | Diff vs. Placebo | -2.937 | |
| | 95% CI | -7.593, 1.719 | |
| | p-value | 0.215 | |
| Week 8 | n | 54 | 148 |
| | Adjusted Mean (SE) | -6.24 (2.387) | -8.38 (1.489) |
| | Diff vs. Placebo | -2.145 | |
| | 95% CI | -7.690, 3.399 | |
| | p-value | 0.447 | |
| Week 12 | n | 32 | 128 |
| | Adjusted Mean (SE) | -6.45 (2.819) | -6.77 (1.492) |
| | Diff vs. Placebo | -0.324 | |
| | 95% CI | -6.613, 5.966 | |
| | p-value | 0.919 | |

Data Source: Table 13.2000

Abbreviations: 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 subject. Unstructured covariance matrix was used.

**Figure 2. Mixed-Model Repeated Measures Analysis of Change from Baseline for EORTC-QLQ-C30 Global Health Status/QoL Score (ITT population)**




Data Source: Figure 23.1000
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 subject. Unstructured covariance matrix was used.

Most notable was the fact that the areas of difference occurring in this global health scale assessed particularly related to a greater degree of fatigue, nausea, vomiting, appetite loss and diarrhoea in patients receiving pazopanib which may be expected in view of the nature of the adverse effect profile for this agent.

A second quality of life assessment was undertaken utilising EQ-5D evaluation which was undertaken at screening and at week 4. As indicated in Table 8, changes from baseline showed decline in both pazopanib and placebo groups for the EQ-5D index again showed some favouring of placebo over pazopanib but the results were not statistically significant.

**Table 8. Analysis of Change from Baseline for EQ-5D Utility and Thermometer (VAS) Scores (ITT population)**

| Change from baseline to | Treatment Group | n[a] | Adjusted mean[b] | S.E. | Difference vs. Placebo | 95% CI for treatment difference | P-value |
|---|---|---|---|---|---|---|---|
| Utility Score Week 4 | Placebo | 94 | -0.04 | 0.024 | | | |
| | Pazopanib | 184 | -0.04 | 0.017 | 0.006 | (-0.053, 0.064) | 0.850 |
| Thermometer Score (VAS) Week 4 | Placebo | 89 | -2.85 | 1.731 | | | |
| | Pazopanib | 173 | -5.21 | 1.242 | -2.358 | (-6.553, 1.837) | 0.269 |

Data Source: Table 13.4000 and 13.4100
a. n= number used in analysis
b. Adjusted for baseline score

***Comment:***

The data from these quality of life analyses are limited in their value partly because of the significant proportion of patients receiving placebo who did not undergo assessment on weeks 8 and 12 because of progressive disease thereby reducing the potential utility of this assessment. Certainly a greater decline in quality of life seen with patients receiving pazopanib in the assessment relates to side-effects associated with pazopanib therefore might be

anticipated. Nevertheless these changes appear to be relatively small and it was the opinion of the investigators that they were not clinically significant.

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