24 May 2012
EMA/408292/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Votrient

(pazopanib)

Procedure No.: EMEA/H/C/001141/II/0007

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name Votrient

Procedure No. EMEA/H/C/001141/II/0007

Marketing authorisation holder (MAH): Glaxo Group Ltd.

Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxo Group Ltd. submitted to the European Medicines Agency on 07 July 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Votrient	Pazopanib	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1 of the SmPC in order to extend the indication of Votrient for the treatment of patients with advanced Soft Tissue Sarcoma (STS). Related changes were proposed to SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.3. The Package Leaflet was proposed to be updated accordingly.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Jens Ersbøll

Co-Rapporteur: Barbara van Zwieten-Boot

1.2. Steps taken for the assessment

Submission date:	07 July 2011
Start of procedure:	24 July 2011
Rapporteur's preliminary assessment report circulated on:	20 September 2011
Co-Rapporteur's preliminary assessment report circulated on:	27 September 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 October 2011
MAH's responses submitted to the CHMP on:	17 February 2012
Rapporteur's and Co-rapporteur's joint preliminary assessment report on the MAH's responses circulated on:	30 March 2012
Rapporteur's and Co-rapporteur's joint final assessment report on the MAH's responses circulated on:	17 April 2012
2nd Request for supplementary information and	19 April 2012

extension of timetable adopted by the CHMP on:	
MAH's responses submitted to the CHMP on:	20 & 24 April 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	8 May 2012
Rapporteur's final assessment report on the MAH's responses circulated on:	22 May 2012
CHMP opinion:	24 May 2012

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006, the application included an EMA decision (P/4/2011) on the agreement of a paediatric investigation plan (PIP01-09). At the time of submission of the application, the PIP (P/4/2011) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Additional data / Market exclusivity

The applicant requested consideration of one year data/market exclusivity in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

Scientific Advice

The applicant received Scientific Advice from the CHMP on the 13th of December 2007. The Scientific Advice pertained to clinical aspects of the dossier.

2. Scientific Discussion

2.1 Introduction

Soft Tissue Sarcoma (STS) is a rare, heterogeneous group of connective tissue cancers originating from mesenchymal cells and their precursors. There are multiple histopathological subtypes of STS. Current conventions often group these subtypes under the general rubric of "STS" for the purpose of treatment, although new treatment options are increasingly directed more specifically at individual histopathological subtypes.

STS accounts for less than 1% of all new malignancies in adults, and 2% of total cancer-related mortality [Fletcher, 2002; Altekruse, 2009].

Surgery is usually the first line of management for localized STS. Standard treatment is generally a wide surgical excision or even more radical surgery of the primary tumour combined with adjuvant radiotherapy in selected cases. The addition of post-operative radiotherapy may reduce the rate of local recurrence [Leibel, 1982].

Optimal local treatment of STS tumours does not prevent the occurrence of distant metastases in many patients, especially those with high-grade tumours. STS metastasizes primarily to the lungs, but also to liver, bone and other organs, depending on the subtype. Conventional cytotoxic chemotherapy is widely used in the treatment of locally advanced (unresectable) and metastatic STS. With the exception of the chemosensitive small round cell tumours such as Ewing's sarcoma family of tumours and rhabdomyosarcoma, as well as osteosarcomas, some of which are potentially curable even when metastatic, virtually all other patients with metastatic STS are destined to die from their disease no matter how aggressive their management [Kriekelis, 2010].

Treatment options for second line treatment usually comprise (previously un-used) ifosfamide or, sometimes, dacarbazine. Other options include pegylated doxorubicin, epirubicin, taxanes or gemcitabine. Combination regimens (frequently involving doxorubicin or gemcitabine) are considered when the clinical condition of the patient as well as the histology of the tumour provides arguments for such choice.

Pazopanib monohydrochloride is an orally bioavailable multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR) -1 and -3, the stem cell factor receptor (c-Kit), interleukin-2 inducible T-cell kinase (ITK), leukocyte-specific protein tyrosine kinase (Lck), and the transmembrane CSF1 receptor tyrosine kinase (c-Fms). The recommended dose of pazopanib is 800 mg once daily.

Votrient (pazopanib) was first authorised in the EU on 04 June 2010. Based on available data at the time of the application, pazopanib was granted a conditional marketing authorisation as monotherapy for the treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

Glaxo Group Ltd submitted an application for a type II variation in July 2011 to extend the indication of Votrient for the treatment of patients with advanced STS and proposed to add the following wording in the current indication:

"Votrient is indicated for the treatment of patients with advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy, or for patients who are unsuited for such therapy.
The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma."

With the MAH's response to the second RSI (request for supplementary information), the proposed indication has been amended as follows:

Votrient is indicated for the treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

Efficacy and safety has only been established in certain STS histological tumour subtypes (see section 5.1)*''.*

2.2 Quality aspects

No new data related to pharmaceutical quality were submitted with this variation application, which is considered acceptable.

2.3 Non clinical aspects

2.3.1 Introduction

The non-clinical studies submitted by the MAH included a liposarcoma xenograft study, an in vitro transport study, an oral 8 day toxicity study in rats and three toxicity studies in juvenile rats.

2.3.2 Pharmacology

The effect of pazopanib on growth of human liposarcoma (SW-872) has been examined in xenograft in severe combined immunodeficiency (SCID) Mice.

SCID mice (10♂/group) were inoculated with human liposarcoma cells. When the tumour volume reached about 100 – 200 mm^3, the mice were treated orally with pazopanib (100 mg/kg/day once daily or 30, 100 mg/kg/day twice daily) for 21 days.

When compared to the vehicle control, pazopanib significantly inhibited the tumour growth from day 8 until the end of treatment (measured as both tumour volume and weight) for all three treatment regimes. Reductions in body weight were observed in all dose groups starting on Day 3, although body weight gain was evident from Day 8. Mice dosed pazopanib at 100 mg/kg BID showed stabilization in body weight reduction after Day 12. At Day 22, body weight was lowest in the animals dosed pazopanib at 100 mg/kg BID. Doses of 30 mg/kg BID or 100 mg/kg pazopanib QD or BID significantly inhibited tumour growth in a dose-dependent manner, starting from Day 8. At Day 21, inhibition at 30 mg/kg BID or 100 mg/kg pazopanib QD or BID was 52, 49 and 67%, respectively (data not shown).

2.3.3 Pharmacokinetics

An *in vitro* study using sandwich-cultured rat or human hepatocytes was conducted to investigate the inhibition of the sodium-taurocholate co-transporting polypeptide (NTCP) and bile salt export pump (BSEP) by pazopanib and its metabolites GSK1268992 and GSK1268997. The three compounds had minimal effects on taurocholate disposition in human hepatocytes. In rat hepatocytes, all three compounds reduced taurocholate uptake by approximately 33-44% at 30 µM (data not shown).

2.3.4 Toxicology

Repeat-dose toxicity

The hepatotoxicity of pazopanib was evaluated in an investigative study (RD2010-00192) conducted in Sprague Dawley SD rats (6♂/group) following 8-days of oral dosing of the monohydrochloride salt of pazopanib (500 mg/kg/day expressed as parent compound). The following endpoints/parameters were evaluated: clinical observations, body weights, food consumption measurements, clinical chemistry results (from pre-treatment Days 2, 4 and 8), microscopic observations (three lobes of the liver), hepatic gene expression analysis (lateral lobe), and toxicokinetics (treated animals only). The findings are summarised in Table 1.

Table 1. Summary of study RD2010-00192

Study ID/ GLP status/ Duration	Species/ Sex/Number/Group/ Dose/Route	Major findings
RD2010-00192/ Non-GLP/ 8-days	SD mice/ 6/♂/group and 3/♂ (TK)/ 500 mg/kg/day PO (BID by gavage)	**500:** Food consumption ↓ (up to 14%) *Clinical chemistry*: ↑ ALT, AST and total bilirubin (1.4 to 2.8-fold); ↑ GLDH (1.7 to 8.6); ↑ total bile acids (up to 1.86-fold, Day 8 only) *Microscopic:* Arteriopathy

ALT - Alanine aminotransferase, AST - Aspartate aminotransferase, GLDH - Glutamate dehydrogenase, TK – Toxicokinetics

Based on the results, mild elevations in alanine aminotransferase, aspartate aminotransferase, total bilirubin, glutamate dehydrogenase, and total bile acids occurred in rats given 500 mg/kg/day. There were no histopathology findings in hepatocytes or biliary epithelium to correlate with the clinical chemistry findings. However, vascular effects were observed in intrahepatic branches of the hepatic artery and arterioles near the liver hilus in all rats given 500 mg/kg/day.

The toxicokinetic data of study RD2010-00192 and the comparison with toxicokinetic parameters in human are summarised in Table 2.

Table 2. Toxicokinetic data of study RD2010-00192 and comparison toxicokinetic parameters in Human

Study ID/ GLP status/ Duration	Daily Dose	Animal TK		Animal: Human XXX Exposure Multiple[a]	
RD2010-00192/ Non-GLP/ 8-days	500 mg/kg/day	C_{max} 92 µg/mL	AUC 1279 µg.h/mL	C_{max} 2.3	AUC 1.97

[a] Using a steady state AUC of 648 µg.h/mL and C_{max} of 40 µg/mL.

Reproduction toxicity

The MAH has conducted three juvenile repeat-dose toxicity studies to support ongoing clinical development of pazopanib in children with soft tissue sarcoma. The studies are summarised in Table 3.

Table 3. Summary of three juvenile repeat-dose toxicity studies.

Study ID/ GLP status/ Duration	Species/ Sex/Number/Group/ Dose/Route	Major findings
2010n106398/ Non-GLP/ PP Day 9 to 21, PP Day 9 to 35 or PP Day 21 to 35	SD rats/ 6 pups/sex/group **(no control group)**/ 30, 300, 1000 mg/kg/day PO once daily, 0.3, 3 mg/kg/day PO once daily, or 30, 300, 1000 mg/kg/day PO once daily (gavage)	**PP Day 9 to 21 ≥30:** Mortality, ↓ body weight gain **PP Day 9 to 35 3:** *Macroscopic observations*: Bilateral broken incisors (1/12 animals) **PP Day 21 to 35 ≥300:** ↓ Body weight gain

Study ID/ GLP status/ Duration	Species/ Sex/Number/Group/ Dose/Route	Major findings
20100106400/ Non-GLP/ PP Day 9 to 14	SD rats/ 7 pups/sex/group 10, 100 mg/kg/day PO once daily (gavage)	**≥10:** ↓ Body weight gain *Clinical chemistry*: ↑ ALT (up to 5.7-fold), ↑ bilirubin (up to 4.3) *Microscopic observations*: Minimal to mild vesicular vacuolation of hepatocytes; Degenerative changes in the kidney **100:** Mortality *Clinical chemistry*: ↑ AST (up to 3.4-fold), ↑ serum urea (up to 2.2-fold), ↑ BUN *Macroscopic observations*: Absence of milk in stomach and opaque white fluid accumulation in the abdominal cavity *Microscopic observations*: Glomerulopathy
20100106399/ GLP/ PP Day 21 to 62 with 4-weeks recovery	SD rats/ 10 non-littermates/sex/group/ 10, 30, 300->100 mg/kg/day PO one daily (gavage)	**≥10:** ↓ Body weight gain (up to 40% at the high dose); ↓ food consumption *Macroscopic observation*: ↓ femur length (up to 18%) **≥30:** *Macroscopic observations*: Broken incisors (nearly in all animals); overgrown or loose teeth *Microscopic observations*: Growth plate hypertrophy associated with thinning of cortical and trabecular bone (femur and tibia); depletion of globule leukocytes within the mucosal epithelium of the trachea; incisor teeth degeneration; **300->100[a]:** *Clinical chemistry*: ↑ ALT (2.6-fold); ↑ total bilirubin (1.6-fold); ↑ cholesterol (1.5-fold, ♂); ↑ triglyceride (1.8-fold, ♀); ↓ albumin; ↓ total protein; ↓ creatinine (♀) *Urinalysis*: ↓ urine total protein (55%, ♂); urine glucose (64%) *Haematology*: ↑ Neutrophils (up to 2.8-fold); ↑ monocyte (up to 2.4-fold, ♀); Red cell distribution width, mean cell volume and mean cell haemoglobin (up to 1.4-fold) *Microscopic observations*: Partial physeal closure and clinical/subclinical fractures of the mid to distal tibia; Adrenal necrosis and adrenal cortical angiectasis; duct dilation and acute inflammation of Brunner's glands and ampulla dilation in the duodenum; mixed cell inflammation and duct dilation in the pancreas; hypertrophy of the epiphyseal growth plate in the sternum; foreign material consistent with drug substance within macrophages in the medulla of mesenteric lymph nodes; hyperplasia of the mucous secreting cells in the pyloric region of the stomach; acinar hypoplasia in the mammary gland (♂ only); decreased secretory content in the prostate; hypocellularity of germinal epithelium in the testis; epididymis hypospermia; mucification of the vaginal mucosa with acute/suppurative inflammation; Hindlimb fractures (♂) **300:** Mortality; body weight loss; impaired gait *Macroscopic observations*: Fractured hindlimbs (♂) **Recovery:** **≥30:** Partial recovery from body weight gain; ↓ food consumption *Macroscopic observations*: Broken upper incisor (1/10); ↓ femur length (up to 22%) *Microscopic observations*: Bone thinning; tibial fractures (♂); Retention of cartilage in the trabeculae and cortex of long bones; **300->100[a]:** *Microscopic observations*: Adrenal necrosis; ↑ partial physeal closure and clinical/subclinical fractures of the mid to distal tibia; foreign material consistent with drug substance within macrophages in the medulla of mesenteric lymph nodes; partial recovery of spermatogenesis and prostate secretory content; partial recovery of dental changes and onset of remodelling of tooth roots

ALT - Alanine aminotransferase, AST - Aspartate aminotransferase, BUN – Blood urea nitrogen, PP – Postpartum

[a] Due to mortality and marked decreases in body weight gain among the group, the 300 mg/kg/day group was given a drug holiday for 4 days and resumed dosing at 100 mg/kg/day for the study duration.

2.3.5 Ecotoxicity/environmental risk assessment

An updated ERA has been submitted by the MAH as part of this application.

- **Phase I**

$PEC_{surfacewater}$

Based on the maximum daily dose of 800 mg/day, the MAH has calculated $PEC_{surfacewater}$ values using both the default Fpen of 0.01 and a refined Fpen. Using the default Fpen of 0.01, the $PEC_{surfacewater}$ becomes 0.4 µg/L, which is well above the action limit of 0.01 µg/L. When an Fpen based on the prevalence of RCC (3.12×10^{-4}) is used, the $PEC_{surfacewater}$ becomes 0.12 µg/L. Assuming all patients are treated with the prescribed dose for 365 days/year, results in a $PEC_{surfacewater}$ with the same value. When an Fpen based on the estimated yearly consumption (4.46×10^{10} mg/year) and the defined daily dose (DDD, 1250 mg) is used, the $PEC_{surfacewater}$ becomes 0.08 µg/L.

PBT assessment

The MAH has performed an OECD 302C test and OECD 107 test in order to determine the inherent biodegradability and the log Kow for pazopanib, respectively. Pazopanib was determined to be not inherently biodegradable and is thus considered a potential persistent substance. Using the currently reported log Kow values the ion-corrected low Dow of pazopanib was determined to be 2.26, 3.33 and 3.92 at pH 5, 7 and 9, respectively.

Phase II

The results for the phase II-Tier A assessment for pazopanib are summarized in table 4:

Table 4. Phase II assessment for pazopanib

Test	Result	PNEC
Activated Sludge Respiration Inhibition Test	EC_{50} = 1,000 mg/L NOEC = 1,000 mg/L	PNECmicro-organisms = 100,000 µg/L
Inhibition of Growth to the Alga *Desmodesmus subspicatus*, OECD 201	EC50 >0.42 mg/L[a] NOEC = 0.42 mg/L[a]	
Acute Toxicity to *Daphnia magna*, OECD 202	EC_{50} (48 hours) > 2.50 mg/L[a] NOEC (48 hours) = 2.50 mg/L[a]	
Reproduction study with *Daphnia magna*, OECD 211	EC_{50} (immobilisation) > 0.50 mg/ L[a] EC_{50} (reproduction) = 0.28 mg/ L[a] LOEC(reproduction) = 0.50 mg/ L[a] NOEC(reproduction) = 0.15 mg/ L[a]	PNECwater = 15 µg/L PNECgroundwater = 15 µg/L
Fish ELS Toxicity Test, *Pimephales promelas*, OECD 210	LOEC > 0.30 mg/L NOEC = 0.30 mg/L	

[a] Based on geometric mean measured concentrations:

The $PEC_{groundwater}$ is based on the $PEC_{surfacewater}$. Using the $PEC_{surfacewater}$ of 4 µg/L based on a worst case scenario, the $PEC_{groundwater}$ becomes 1 µg/L.

$PEC_{surfacewater}/PNEC_{micro\text{-}ogranisms}$ = 4 µg/L / 100,000 µg/L = 4.0×10^{-5}. This ratio is lower than the trigger ratio of 0.1.

$PEC_{surfacewater}/PNEC_{water}$ = 4 µg/L / 15 µg/L = 0.27. This ratio is lower than the trigger ratio of 1.

$PEC_{groundwater}/PNEC_{groundwater}$ = 1 µg/L / 15 µg/L = 0.067. This ratio is lower than the trigger ratio of 1.

In addition, based on the reported Koc value of 2.35, studies for the terrestrial environment are not necessary.

2.3.6 Discussion on non-clinical aspects

The MAH has submitted one *in vivo* pharmacodynamic study, one *in vitro* pharmacokinetic study, one investigative repeat-dose toxicity study and three juvenile repeat-dose toxicity studies.

The liposarcoma xenograft study supports the use of pazopanib in the treatment of sarcoma malignancies. However it should be noted that the predictive value of mouse xenograft models for clinical efficacy is rather limited.

Two studies (one in vitro kinetic study and one 8 days repeated-dose toxicity) were performed to elucidate the possible mechanism involved in the hepatotoxicity seen in clinical and non-clinical studies. Neither study provided evidence about the mechanism involved in the hepatic enzyme alterations observed following pazopanib treatment.

In juvenile toxicity studies, when rats were dosed from day 9 post partum through day 21 postpartum, pazopanib caused mortalities and abnormal organ growth/maturation in kidney, lung, liver and heart, at a dose approximately 0.1 times the clinical exposure based on AUC in adult humans. When rats were dosed from day 21 post partum to day 62 post partum, toxicologic findings were similar to adult rats at comparable exposures. Human paediatric patients are at increased risk for bone and teeth effects as compared to adults, as these changes, including inhibition of growth (shortened limbs), fragile bones and remodelling of teeth, were present in juvenile rats at ≥ 10 mg/kg/day (equal to approximately 0.1-0.2 times the clinical exposure based on AUC in adult humans. The section 5.3 of the SmPC has been updated to include the above information on juvenile toxicity studies.

An update of the original environmental assessment taking into account both indications (the metastatic renal cell carcinoma and soft tissue sarcoma) has been provided by the MAH.

Overall the ERA is considered acceptable. However the CHMP recommended the MAH to perform a water sediment study (OECD 308) to determine the effects on sediment organisms. Furthermore, using the currently reported log Kow values the ion-corrected low Dow of pazopanib was determined to be 2.26, 3.33 and 3.92 at pH 5, 7 and 9, respectively. Based on that, the CHMP recommended the MAH to perform a bioconcentration study (OECD 305).

2.4 Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.1 Pharmacokinetics / Pharmacodynamics

Pharmacokinetic data was collected in supportive Phase II study VEG20002. Serial blood samples for analysis of plasma pazopanib were collected at the Day 29 visit. A blood sample for analysis of plasma pazopanib was also collected prior to pazopanib administration on Days 57 and Day 85. The results are presented in Table 5.

Table 5. Summary of the Predose Plasma Pazopanib Concentrations

Visit	n	Predose(µg/mL) Concentration		Number (%) of Subjects with Predose conc ≥ 20 µg/mL
		Mean (SD)	Median (range)	
Day 29	74	37.1 (21.1)	43.8 (5.43 - 104)	55 (74%)
Day 57	74	36.1 (18.5)	33.1 (0 – 89.1)	61 (82%)
Day 85	58	36.0 (19.0)	33.1 (3.87 – 88.6)	46 (79%)

2.4.2 Conclusion on Clinical Pharmacology

The difference between the mean pre-dose plasma pazopanib concentrations on Day 29 and Day 85 was less than 5%. Although the data presented regarding the PK of pazopanib in STS are limited, no difference in pazopanib plasma concentrations evaluated at the same time points were observed between STS and RCC patients. Moreover, the pazopanib plasma concentrations measured in study VEG20002 employing pazopanib 800 mg once daily were ≥20 g/ml in more than 70% of patients. This threshold concentration has been correlated with pharmacodynamic markers such as hypertension and soluble VEGFR2 inhibition, and with efficacy in RCC.

2.5 Clinical efficacy

The data in the current application are mainly from a multicentre, randomised, double-blind, placebo-controlled phase III trial (VEG110727) comparing pazopanib to placebo in patients with metastatic STS with confirmed disease progression during or following therapy. It is supported by data from a phase II study (VEG20002) of pazopanib in advanced and/or metastatic STS that was refractory or relapsed. A summary of both pivotal and supportive studies is presented in Table 6.

Table 6. Summary of clinical studies

Study	VEG110727	VEG20002
Level of Evidence	Pivotal	Supportive
Critical Design Features	Phase III / Randomised (2:1) Double-blind / Placebo-controlled	Phase II/ Non-randomised Open-label/ 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 Disease progression on or after anthracycline-based regimen WHO PS 0 or 1 -Leiomyosarcoma -Synovial sarcoma -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 WHO PS 0 or 1 -Leiomyosarcoma -Synovial sarcoma -Adipocytic tumours -Other types of STS (excluding GIST).
Number of subjects	369 subjects Pazopanib: 246 / Placebo: 123	142 subjects
Primary Efficacy endpoints Secondary Efficacy endpoints	PFS by independent radiologist OS (principal); ORR; Duration of response, Time to response	PF rate at Week 12 by peer and investigator review PFS OS ORR Duration of response, Time to response

2.5.1 Main study

VEG110727 study

This was a Phase III, randomised, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of pazopanib compared to placebo in patients with STS whose disease had progressed during or following prior chemotherapy.

Methods

Study Participants

The study population included patients with histological evidence of high or intermediate grade malignant STS, or cytological evidence in case of presence of multiple metastases. Low grade tumours were allowed provided there was evidence of disease progression.

Eligible histology subtypes included fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumours), so-called fibrohistiocytic (pleomorphic malignant fibrous histiocytoma (MFH), giant cell MFH, inflammatory MFH), leiomyosarcoma, malignant glomus tumours, skeletal muscles (pleomorphic and alveolar rhabdomyosarcoma), vascular (epithelioid hemangioendothelioma, angiosarcoma), sarcoma of uncertain differentiation as well as synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma, malignant peripheral nerve sheath tumours, and undifferentiated soft tissue sarcomas not otherwise specified (NOS).

Excluded were chondrosarcoma and ewing tumours / primitive neuroectodermal tumour (PNET). Histology subtypes also not considered eligible were adipocytic sarcoma (all subtypes), all rhabdomyosarcoma that were not alveolar or pleomorphic, chondrosarcoma, osteosarcoma, Ewing tumours / PNET, gastrointestinal stromal tumours (GIST), dermofibromatosis sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma, mixed mesodermal tumours of the uterus.

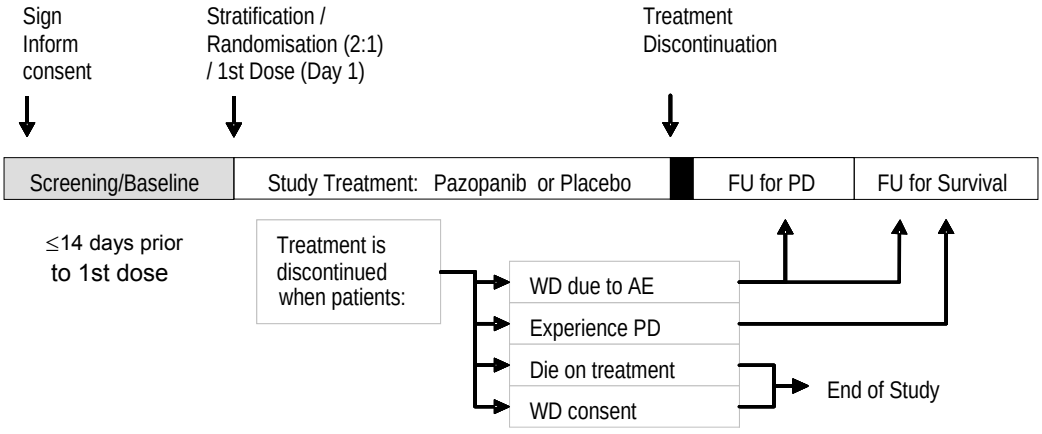
In addition, all patients needed to have metastatic and not only locally advanced disease, World Health Organization (WHO) performance status 0-1, and to have progressed after no more than 4 prior treatments (2 in case of combination treatments) for advanced disease.

All patients had to be pre-treated with anthracycline or not to be suitable for such treatment. QT corrected for heart rate (QTc) <480 msec at baseline as well as left ventricular ejection fraction (LVEF) within the normal range >50%) was requested, as well as adequate bone marrow, lever and renal function.

Treatments

Eligible patients were first stratified according to the following factors: a) WHO performance status: 0 vs. 1 and b) number of prior lines of systemic treatment for advanced disease: 0, 1 vs. 2+. Patients were then centrally randomised 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. The design of the study is presented in Figure 1.

Figure 1. Design of study VEG110727



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

Objectives

The primary objective of the study was to evaluate and compare progression free survival (PFS) (by independent radiology review) in pazopanib-treated versus placebo-treated patients.

Secondary objectives were to evaluate and compare overall survival (OS) in the two treatment arms**,** 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 (ORR), to compare the two treatment arms for time to response (TTR) and duration of response (DR), and to assess safety and tolerability.

Outcomes/endpoints

Primary efficacy endpoint

Progression-free survival, defined as the interval between the date of randomisation and the earliest date of either disease progression or death due to any cause.

Secondary efficacy endpoints

Overall survival, defined as the time from date of randomisation until date of death due to any cause.

Other secondary endpoints

PFS in the 3 histology types (leiomyosarcoma, synovial sarcoma and other eligible histologies).

ORR defined as the percentage of patients who achieved either confirmed complete response (CR) or partial response (PR).

Time to response, defined for the subset of patients who achieved a confirmed CR or PR, defined as the time from date of randomisation until date of first documented evidence of CR or PR (whichever status is recorded first).

Duration of response, defined for the subset of patients who achieved a confirmed CR or PR, defined as the time from date of first documented evidence of CR or PR until date of either the first documented sign of progressive disease (PD) or death due to any cause. Patients who have neither died nor progressed will be censored at the date of the last adequate radiologic assessment.

Safety and tolerability endpoints included evaluation of adverse events (AEs), serious adverse events (SAEs) and changes from baseline in vital signs (including WHO performance status (PS)), laboratory parameters and LVEF.

Exploratory endpoints

Changes in quality of life (QoL) from baseline, as assessed by the Quality of Life Questionnaire (QLQ)-C30 and EQ-5D.

Sample size

The primary endpoint is PFS and the trial was powered to detect at least a 37% decrease in the hazard rate (HR) (HR less than or equal to 0.63) corresponding to an increase from 2.2 to 3.5 months in median PFS. A total of 224 PFS events were required for detecting the targeted difference with 90% power and a 5% two-sided alpha level. For OS, the trial was powered to detect a 33% decrease in the death hazard rate (HR less than or equal to 0.67) corresponding to an increase from 8 to 12 months in median OS. The overall power on this endpoint was 80% based on 206 death events.

After observing a higher than expected recruitment rate, the expected sample size was increased to 360 patients in a period of 22 months. At the time of this decision, approximately 130 patients were recruited, and there was no access to unblinded data. The median assumptions for PFS and OS 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. Increasing the number of required events (deaths) to 279 provides 90% power to detect a HR of less than or equal to 0.67 for the OS endpoint.

Randomisation

Eligible patients were first stratified according to PS (0 vs. 1) and number of prior lines of systemic treatment for advanced disease: 0, 1 vs. 2+. Patients were then randomised in the placebo and treatment arms using a permuted blocks randomisation technique.

Blinding

The study was double-blind.

Statistical methods

Two analyses were planned in this study. The first planned analysis of the study was when the final event goal (274 events) for PFS endpoint had occurred, and mature OS data (70% of the required death events) was available for an interim OS analysis. The final analysis on OS occurred when at least the required number of death events (279) for the OS analysis accrued.

Primary efficacy analysis of PFS

The primary PFS analysis occurred after 1) at least 274 PFS events (progression or death by any cause) documented, 2) at least 195 deaths documented, 3) all subjects have been followed for at least 3 months after randomisation

The primary analysis evaluated PFS within the Intent-to-Treat (ITT) population (all randomised subjects were analyzed in the arm they were allocated by randomisation). This analysis was performed using the data from the independent radiological review of the various scans from the disease assessments.

Sensitivity analyses of PFS

Ten pre-specified sensitivity analyses were performed for PFS as described in Table 7.

Table 7. Summary of analysis of PFS – Primary and sensitivity analysis (VEG 110727)

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

Subgroup analyses of PFS

The following subgroups were explored in the analysis of PFS data by Kaplan-Meier analysis, log rank analyses with adjustment for stratification factors of baseline WHO PS and number of prior lines of systemic therapy for advanced disease: Histology types (leiomyosarcoma, synovial or "other" STS histologies), baseline WHO PS: 0 vs. 1, number of prior lines of therapy for advanced disease (0, 1 vs. 2+), age: older or younger than 65 years, race (White vs. Asian/Other), gender, recruitment region: US, EU/Australia and Japan/Korea, standard of care in each region at the time of starting the study and tumour grade at initial diagnosis (post-hoc analysis).

Post-hoc analyses

Post-hoc analyses of PFS were conducted by the same method as many of the other sensitivity analysis, i.e., a log rank analyses with adjustment for stratification factors of baseline WHO PS and number of prior lines of systemic therapy for advanced disease.

Results

Participant flow

A total of 369 patients with STS were enrolled into the study. At the time of clinical cut-off, 1 patient in the placebo arm and 18 patients in the pazopanib arm remained on study treatment. Most patients (96%) who received placebo discontinued study treatment due to PD, as compared to 68% of patients who received pazopanib. The other most common reasons patients in the pazopanib arm discontinued treatment were toxicity related to study drug (14%) and subject refusal/patient decision (5%).

The participant flow is displayed in Table 8.

Table 8. Participant flow (VEG110727 ITT)

Participant flow	**Number (%) of Subjects**	
	Placebo (N=123)	**Pazopanib (N=246)**
Treatment status		
Discontinued study treatment	122 (>99)	228 (93)
On study treatment	1 (<1)	18 (7)
Primary reason for discontinuation of study treatment		
Reasons not associated with AEs or toxicities		
Progression of disease/relapse/clinical progression/death due to PD	118 (96)	168 (68)
Protocol violation	0	3 (1)
Lost to follow-up	0	0
Study closed/terminated	0	0
Subject's refusal/subject's decision	1 (<1)	13 (5)
Missing	0	0
Discontinuations due to toxicities/AEs/or death (not due to PD)		
Toxicity related to the study drug (or toxic death)	1 (<1)	34 (14)
Adverse event not related to the study drug	2 (2)	6 (2)
Intercurrent death (not due to malignant disease or toxicity)	0	3 (1)
Other	0	1 (<1)

Recruitment

A total of 369 subjects with STS were enrolled into the study at 72 centres in 13 countries between 06 October 2008 and 26 February 2010.

Conduct of the study

The original protocol was approved on 23 June 2008 and has been amended twice as follows:

Amendment 1 (19 June 2009): Selection criteria were modified to: allow alveolar or pleomorphic rhabdomyosarcoma, to exclude patients with nervous system metastases or leptomeningeal tumour spread, with known intraluminal metastatic lesions in gastrointestinal system with increased risk of bleeding, with history of coronary artery bypass graft surgery within the last 6 months and with endobronchial lesions and/or infiltrations of major pulmonary vessels. In addition one of the major changes was the increase in sample size from 255 to 360 patients. Finally, PFS analysis would not occur until 3 months from the last patient first visit and the required number of death events for the interim OS analysis (195 deaths) had occurred.

Amendment 2 (21 June 2010): The majority of patients in the study had received prior anthracycline-containing chemotherapy which poses a significant risk for cardiac dysfunction. Since decreases in LVEF were reported in some patients participating in the study, additional data were to be obtained on cardiac risk factors and prior treatments. Additional guidance on the management of LVEF changes and cardiac dysfunction was provided. A description of additional data that were to be collected for cardiac events and clarification on the timing of LVEF, thyroid stimulating hormone, and free T4 evaluations was provided.

Baseline data

Baseline demographic characteristics of the patients in the pivotal study are presented in Table 9.

Table 9. Summary of Demographic characteristics (VEG110727 ITT)

	Placebo (N=123)	Pazopanib (N=246)	Total (N=369)
Age (yrs)	n=123	n=246	n=369
Mean	51.7	54.0	53.2
SD	13.77	14.92	14.57
Median	51.0	56.0	55.0
Min.	18	20	18
Max.	78	83	83
Sex, n (%)	n=123	n=246	n=369
Female	69 (56)	147 (60)	216 (59)
Male	54 (44)	99 (40)	153 (41)
Weight (kg)[a]	n=121	n=237	n=358
Mean	75.0	71.5	72.7
SD	17.23	16.88	17.05
Median	73.0	69.0	70.8
Min.	40	41	40
Max.	124	134	134
Ethnicity, n (%)	n=123	n=246	n=369
Hispanic or Latino	7 (6)	13 (5)	20 (5)
Not Hispanic or Latino	115 (93)	228 (93)	343 (93)
Unknown	1 (<1)	5 (2)	6 (2)
Race, n (%)	n=123	n=246	n=369
African American/African Heritage	2 (2)	4 (2)	6 (2)
American Indian or Alaska Native	0	1 (<1)	1 (<1)
Asian - Central/South Asian Heritage	2 (2)	0	2 (<1)
Asian - East Asian Heritage	7 (6)	24 (10)	31 (8)
Asian - Japanese Heritage	16 (13)	31 (13)	47 (13)
Asian - South East Asian Heritage	2 (2)	2 (<1)	4 (1)
White - Arabic/North African Heritage	2 (2)	1 (<1)	3 (<1)
White - White/Caucasian/European Heritage	89 (72)	174 (71)	263 (71)
Mixed Race	1 (<1)	0	1 (<1)
Unknown	2 (2)	9 (4)	11 (3)

The disease characteristics at baseline are displayed in Table 10:

Table 10. Baseline Disease characteristics (VEG110727 ITT)

	Placebo (N=123)	Pazopanib (N=246)	Total (N=369)
Measurable disease at baseline by investigator[a], n (%)			
No	0	1 (<1)	1 (<1)
Yes	123 (100)	245 (>99)	368 (>99)
Measurable disease at baseline by independent review[b], n (%)			
No	5 (4)	8 (3)	13 (4)
Yes	118 (96)	234 (95)	352 (95)
Unknown	0	4 (2)	4 (1)
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)
Locations of disease[a], n (%)			
Lung	100 (81)	196 (80)	296 (80)
Other site	33 (27)	93 (38)	126 (34)
Abdominal cavity	40 (33)	66 (27)	106 (29)
Liver	37 (30)	66 (27)	103 (28)
Lymph node	31 (25)	54 (22)	85 (23)
Bone	26 (21)	45 (18)	71 (19)
Pleural effusion	14 (11)	15 (6)	29 (8)
Retro-intra abdominal	7 (6)	15 (6)	22 (6)
Lower extremity	4 (3)	15 (6)	19 (5)
Skin	5 (4)	9 (4)	14 (4)
Thoracic	6 (5)	8 (3)	14 (4)
Visceral gynaecological	2 (2)	9 (4)	11 (3)
Ascites	3 (2)	6 (2)	9 (2)
Trunk	2 (2)	5 (2)	7 (2)
Upper extremity	3 (2)	3 (1)	6 (2)
Head and neck	1 (<1)	2 (<1)	3 (<1)
Time since initial diagnosis (months)	n=123	n=240	n=363
Min., Max.	2, 330	2, 232	2, 330
1st quartile	15.7	14.5	15.4
Median	27.0	26.6	26.7
3rd quartile	40.8	46.1	44.9
Time since last progression (months)[c]	n=123	n=240	n=363
Min., Max.	0, 3	0, 11	0, 11
1st quartile	0.3	0.3	0.3
Median	0.6	0.7	0.6
3rd quartile	1.0	1.1	1.1

Leiomyosarcoma was the most common tumor subtype (n=158), followed by Synovial sarcoma (n=38), Undifferentiated pleomorphic sarcoma (n=31), and Undifferentiated sarcoma NOS (n=20). The most common disease sites of origin were lower extremity, thoracic, and retro-intra abdominal region.

Patients received extensive systemic anti-cancer therapy prior to study entry, which are described in Table 11.

Table 11. Prior Cancer therapy (VEG110727 ITT)

Prior anti-cancer therapy	Number (%) of Subjects		
	Placebo (N=123)	Pazopanib (N=246)	Total (N=369)
Systemic therapy	123 (100)	246 (100)	369 (100)
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)
Type of systemic therapy			
Doxorubicin	121 (98)	242 (98)	363 (98)
Ifosfamide	93 (76)	164 (67)	257 (70)
Docetaxel	35 (28)	69 (28)	104 (28)
Gemcitabine	42 (34)	85 (35)	127 (34)
Trabectedin (Yondelis)	22 (18)	38 (15)	60 (16)
mTOR inhibitors	3 (2)	11 (4)	14 (4)
Other	53 (43)	105 (43)	158 (43)
Surgery	114 (93)	224 (91)	338 (92)
Radiotherapy	75 (61)	128 (52)	203 (55)
Other therapy	15 (12)	11 (4)	26 (7)

Numbers analysed

The number of patients included in each analysis population is summarised in Table 12.

Table 12. Analysis population

	Number (%) of Subjects		
	Placebo (N=123)	Pazopanib (N=246)	Total (N=369)
Intent-to-treat (ITT)	123 (100)	246 (100)	369 (100)
Leiomyosarcoma	49 (40)	109 (44)	158 (43)
Synovial sarcoma	13 (11)	25 (10)	38 (10)
Other STS histologies	61 (50)	112 (46)	173 (47)
Per-protocol[a]	108 (88)	213 (87)	321 (87)
Safety	123 (100)	240 (98)	363 (98)

Outcomes and estimation

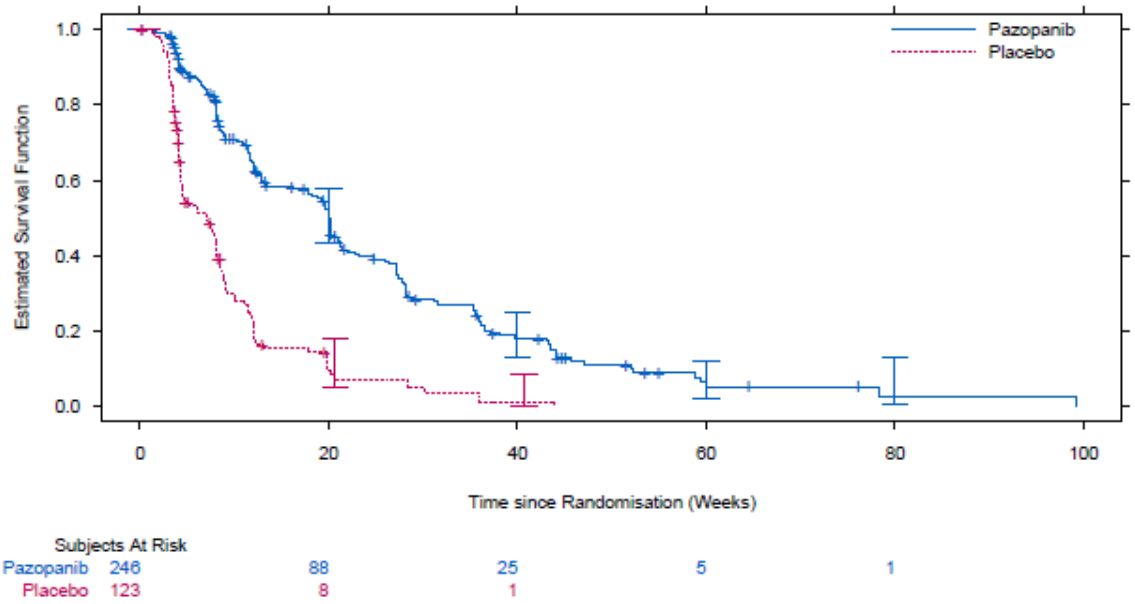
Primary endpoint: PFS

The results of the PFS in the ITT population (cut-off date 22 November 2010) are presented in Table 13 and the Kaplan-Meier curve in Figure 2.

Table 13. Independent Radiologist-assessed Progression-free Survival (ITT population)

	Placebo (N=123)	Pazopanib (N=246)
Subject Classification, n (%)		
Progressed or died (event)	106 (86)	163 (66)
Censored, follow-up ended	16 (13)	73 (30)
Censored, follow-up ongoing	1 (1)	10 (4)
Kaplan-Meier Estimate for PFS (weeks)		
1st quartile (95% CI)	3.9 (3.6, 4.1)	8.3 (8.1,1 1.4)
Median (95% CI)	7.0 (4.4, 8.1)	20.0 (17.9, 21.3)
3rd quartile (95% CI)	11.4 (8.9, 12.1)	35.6 (28.1, 38.1)
Adjusted hazard ratio[e](95% CI)	0.35 (0.26, 0.48)	
Stratified log-rank p-value	<0.001	

Figure 2. Kaplan-Meier graph of PFS per Independent Radiologist Assessment (ITT population)



Secondary endpoint: OS

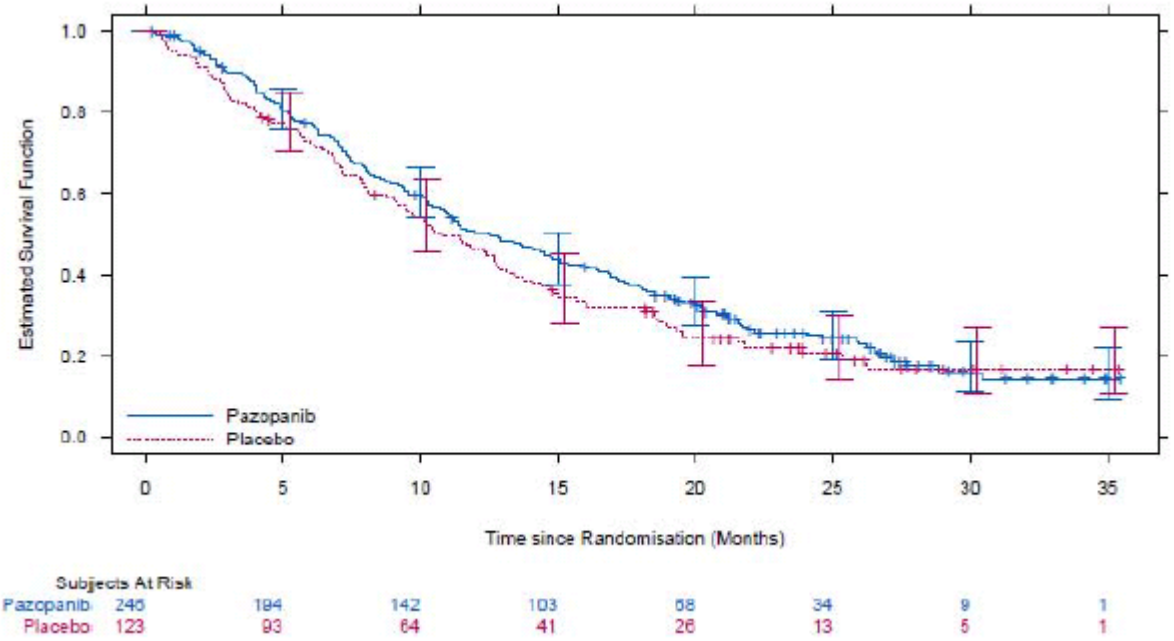
The efficacy results of OS for the updated analysis of 24 October 2011 are summarised in the following Table 14, and Figure 3.

Table 14. Summary of final analysis of Overall Survival (ITT population)

	Placebo (N=123)	Pazopanib (N=246)
Subject 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 PS 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 3. Kaplan-Meier Overall Survival Curves (ITT Population)



Secondary endpoint: ORR

The results of ORR are displayed in Table 15.

Table 15. 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	

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 subject 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.

Secondary endpoint: Duration of response

The results of the duration of response are detailed in Table 16.

Table 16. Duration of response-Independent Radiologist and Investigator Assessment (RECIST Criteria) (ITT Population)

	Pazopanib	
	Independent (N=246)	Investigator (N=246)
Subject classification[a]		
N	11	23
Progressed or died, n (%)	6 (55)	17 (74)
Censored, follow-up ended	1 (9)	1 (4)
Censored, follow-up ongoing	4 (36)	5 (22)
Duration of response (weeks)[b]		
1st quartile (95% CI)	22.6 (8.3, 38.9)	17.1 (15.9, 28.1)
Median (95% CI)	38.9 (16.7, 40.0)	32.1 (22.6, 44.0)
3rd quartile (95% CI)	40.0 (24.1, NC)	44.0 (32.1, 64.1)

a.The duration of response will be restricted to the subgroup of the population who experience a confirmed response (Complete Response or Partial Response) during the study.
b Duration of response is defined as the time from the first documented evidence of Complete Response or Partial Response until the first documentation of disease progression or death due to any cause, whichever occurs first.

Exploratory endpoints

EORTC QLQ-30

Completion rates for the QLQ-C30 for each treatment group were 78% or greater for subjects remaining in the study, with a higher rate of dropout on the placebo arm. This resulted in relatively fewer QoL assessments available at Weeks 8 and 12, for the placebo arm (47 and 28%) than the pazopanib arm (63 and 55%). The Mixed-Model Repeated Measures (MMRM) analyses of change from baseline in Global Health Status/QoL showed a numerically greater decline for pazopanib, but no statistically significant differences were observed in this analysis between pazopanib and placebo, across each of the 3 assessment time points.

There were noticeable differences between the treatment groups in mean change from baseline for several symptom scales across assessment time points, in particular these symptoms include: fatigue, nausea and vomiting, appetite loss, and diarrhea with subjects; the results suggest that these symptoms were worse on pazopanib (data not shown)

EQ-5D

Completion rates for the EQ-5D for each treatment group across each assessment time point were 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 Thermometer (VAS). Although results from an analysis of change from baseline adjusted for baseline score for EQ-5D VAS numerically favoured placebo, the results from these analyses did not show any statistically significant differences between treatment groups (data not shown).

Ancillary analyses

The MAH submitted a large number of ancillary analyses. The results of the PFS and OS in subgroups with different STS histology and the results of the pre-planned sensitivity analysis are presented in Tables 17, 18 and 19 respectively.

Table 17. Summary of PFS by STS histology subgroups-Independent Radiologist (ITT population)

	Placebo (N=123)	Pazopanib (N=246)
Leiomyosarcoma		
Subject Classification, n (%)	n=49	n=109
Progressed or died (event)	42 (86)	73 (67)
Censored, follow-up ended	7 (14)	33 (30)
Censored, follow-up ongoing	0 (0)	3 (3)
Median PFS in weeks (95% CI)	8.1 (7.6, 9.3)	20.1 (13.3, 23.1)
HR (95%CI)	0.37 (0.23, 0.60)	
Stratified log-rank p-value	<0.001	
Synovial sarcoma		
Subject Classification, n (%)	n=13	n=25
Progressed or died (event)	13 (100)	17 (68)
Censored, follow-up ended	0 (0)	6 (24)
Censored, follow-up ongoing	0 (0)	2 (8)
Median PFS in weeks (95% CI)	4.1 (3.7, 8.9)	17.9 (8.9, 27.1)
HR (95%CI)	0.43 (0.19, 0.98)	
Stratified log-rank p-value	0.005	
"Other" STS		
Subject Classification, n (%)	n=61	n=112
Progressed or died (event)	51 (84)	73 (65)
Censored, follow-up ended	9 (15)	34 (30)
Censored, follow-up ongoing	1 (2)	5 (4)
Median PFS in weeks (95% CI	4.3 (4.0, 7.9)	20.1 (13.0, 27.1)
HR (95%CI)	0.39 (0.25, 0.60)	
Stratified log-rank p-value	<0.001	

Table 18. Summary of OS by STS histology subgroups-Independent Radiologist (ITT population)

	Placebo (N=123)	**Pazopanib** (N=246)
Leiomyosarcoma	n=49	n=109
Median OS in months (95% CI[a])	14.1 (11.8, 18.5)	16.7 (12.6, 19.0)
HR[be](95% CI)	0.84 (0.56, 1.26)	
P value (two-sided)	0.363	
Synovial sarcoma	n=13	n=25
Median OS in months (95% CI[a])	21.6 (6.6, 25.4)	8.7 (5.7, 14.6)
HR[be](95% CI)	1.62 (0.79, 3.33)	
P value (two-sided)	0.115	
"Other" STS	n=61	n=112
Median OS in months (95% CI[a])	9.5 (7.1, 10.7)	10.3 (8.0, 13.6)
HR[be](95% CI)	0.84 (0.56, 1.21)	
P value (two-sided)	0.325	

a. Confidence intervals for quartiles are estimated using the Brookmeyer-Crowley method.
b. Hazard ratios are estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio is adjusted for WHO PS and number of prior lines of systemic treatment.
Note: These analyses mirror the primary analysis except that they are based on the individual Intent-to-treat population of leiomyosarcoma, synovial sarcoma and "other" STS.

Table 19. Pre-planned Sensitivity Analysis

Pre-planned Sensitivity Analysis, Number and Description	Placebo (N=123)	Pazopanib (N=246)
1: PP population	n=108	n=213
Median PFS in weeks (95%CI)	7.6 (4.6, 8.6)	20.1 (18.1, 21.3)
HR (95%CI), p-value	0.37 (0.27, 0.51), <0.001	
2: unadjusted for stratification factors		
Median PFS in weeks (95%CI)	7.0 (4.4, 8.1)	20.0 (17.9, 21.3)
HR (95%CI), p-value	0.35 (0.26, 0.48), <0.001	
3: investigator assessment		
Median PFS in weeks (95%CI)	6.6 (4.4, 8.1)	20.1 (18.9, 24.9)
HR (95%CI), p-value	0.39 (0.30, 0.52), <0.001	
4: investigator assessment unadjusted for stratification factors		
Median PFS in weeks (95%CI)	6.6 (4.4, 8.1)	20.1 (18.9, 24.9)
HR (95%CI), p-value	0.39 (0.29, 0.52), <0.001	
5: investigator assessment including clinical progressions		
Median PFS in weeks (95%CI)	6.6 (4.4, 8.1)	20.0 (16.1, 20.7)
HR (95%CI), p-value	0.42 (0.31, 0.55), <0.001	
6: without censoring for PD/death after extended period of inadequate assessment		
Median PFS in weeks (95%CI)	7.0 (4.4, 8.1)	20.0 (17.3, 21.0)
HR (95%CI), p-value	0.35 (0.26, 0.48), <0.001	
7: with adjustment for earlier investigator assessments of progression		
Median PFS in weeks (95%CI)	7.6 (4.6, 8.1)	17.9 (12.1, 20.1)
HR (95%CI), p-value	0.38 (0.29, 0.51), <0.001	
9: censoring subjects who permanently stopped IP prior to radiological progression		
Median PFS in weeks (95%CI) (weeks)	7.0 (4.4, 8.1)	20.1 (19.6, 26.0)
HR (95%CI), p-value	0.33 (0.24, 0.46), <0.001	
10: Cox regression adjusted for stratification factors		
Treatment HR[b] (95%CI), p-value	0.32 (0.24, 0.41), <0.001	
11: Cox regression stepwise selection of covariates baseline WHO PS selected from covariates evaluated (baseline WHO PS, number of prior lines of systemic treatment for advanced disease, age, gender, race, metastatic disease and histology types)	n=121	n=233
Treatment HR[b] (95%CI), p-value	0.31 (0.24, 0.41), <0.001	

The MAH has performed a "worst case time-to-treatment-failure analysis" where an event was defined as the earliest of progression or death in the placebo arm and as the earliest of progression, death, withdraw from study drug or withdraw from study (regardless of reason) in the pazopanib arm. Also the MAH conducted the analysis on the 3 major histology groups (leiomyosarcoma, synovial sarcoma and the group designated as "other") according to the requested specifications on 'worst case' analysis. Both analyses confirmed a PFS improvement for the pazopanib treated patients (data not shown).

Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

Clinical studies in special populations performed across trials (pooled analyses AND meta-analysis)

N/A

Supportive study

VEG20002

This was a Phase II, multi-centre, open-label, non-randomised study designed to evaluate the activity and tolerability of pazopanib in patients with relapsed or refractory STS, for whom no standard therapy existed. Patients received oral pazopanib, 800 mg once daily, until disease progression, unacceptable drug-related events, intercurrent illnesses preventing further drug administration, or patient refusal. The study included a screening/baseline period, an open-label treatment period, and a post-treatment follow-up visit. The study enrolled patients into 4 different strata based on the WHO classification of STS: leiomyosarcoma (uterine, skin or non organ origin), adipocytic tumours, synovial sarcoma, and other types of high or intermediate grade malignant STS.

The key eligibility criteria were: patients with high or intermediate grade of STS that was relapsed or refractory and incurable by surgery or radiotherapy, tumour progression per RECIST v1.0 compared with a prior disease assessment during the past 6 months, ineligible for chemotherapy or not more than 1 combination therapy or 2 single chemotherapy agents for advanced disease, WHO PS of 0 or 1, and protocol-specified criteria for adequate organ function.

The primary endpoint was progression-free (PF) rate at Week 12, defined as a binary endpoint with "success" equal to the number of patients with CR, PR or stable disease (SD)/ total number of patients based on the disease evaluation performed 12 weeks after the start of treatment. The secondary endpoints were PFS, OS, ORR, Time to response, and Duration of response.

Thirty-seven patients could be recruited into each stratum in two stages: 17 patients in the first stage and 20 patients in the second stage. After treating and following 17 patients for 12 weeks, sufficient responses were seen in leiomyosarcoma, synovial sarcoma and other types of STS ("other" STS); therefore patients with these types of sarcoma were enrolled into the second stage of these strata.

A total of 142 patients with STS were enrolled into the study. The 142 patients consisted of 41 patients with leiomyosarcoma, 19 patients with adipocytic sarcoma, 37 patients with synovial sarcoma, and 41 patients with "other" STS.

Results

The key efficacy data from the supportive study VEG20002 is summarized in Table 20.

Table 20. Key Efficacy Data from Supportive Study VEG20002 (ITT Population)

Endpoints	Leiomyo-sarcoma N=41	Adipocytic sarcoma N=19	Synovial sarcoma N=37	Other STS N=41	Total N=138
Progression-free Rate at Week 12[a] - Peer + Investigator Assessment[b]					
CR+PR+SD, n (%) (90% CI) p-value[c]	17 (41) (28.4, 55.5) 0.003	5 (26) (11.0, 47.6) 0.653	18 (49) (34.3, 63.2) <0.001	17 (41) (28.4, 55.5) 0.003	57 (41) (34.2, 48.7) <0.001
Progression-free Survival (weeks) – Investigator Assessment					
Median (90% CI)[d]	17.2 (12.0, 24.1)	11.1 (7.1, 11.9)	23.4 (11.7, 29.3)	14.0 (12.0, 36.3)	12.1 (12.0, 22.4)
Overall Survival (months)					
Median (90% CI)[d]	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)	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)

a. The CRF does not explicitly state which assessment is Week 12 for the investigator data. The analysis uses the first post-baseline assessment.
b. Scans assessed by investigator as CR, PR and SD were peer reviewed. Scans assessed by investigator as PD were not peer reviewed
c. p-value = the strength of evidence to reject the null hypothesis of PFrate being equal to 20% with an alpha level of 0.10.
d. Confidence intervals for quartiles were estimated using the Brookmeyer-Crowley method

2.5.2 Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy results are derived from the pivotal study VEG110727 (n=369) and the supportive VEG20002 study (n=142). The pivotal study was well conducted, with no problematic protocol amendments and relatively few protocol violations.

Efficacy data and additional analyses

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 7.0 weeks (95% CI: 4.4, 8.1) in the placebo arm and 20.0 weeks (95% CI: 17.9, 21.3) in the pazopanib arm, with a corresponding HR of 0.35 (95% CI: 0.26, 0.48; p<0.001) as assessed by IRC. The 13 weeks improvement in median PFS in the pazopanib arm as compared to placebo in the heavily pre-treated VEG110727 study population is statistically significant and exceeded the targeted improvement by over two-fold. Results of pre-specified and post-hoc analyses provide assurance as to the accuracy of PFS determinations. Factors which may have confounded PFS in favour of pazopanib including the schedule of disease assessment and off-schedule assessments were systematically evaluated and found to have little effect on the observed PFS HR. In all subgroup and sensitivity analyses, a very robust and consistent PFS benefit was found in favour of pazopanib. In addition, a "worst case time-to-treatment-failure analysis" confirmed a PFS improvement for pazopanib treated patients.

Although few objective responses by RECIST were observed with pazopanib in VEG110727 (no CRs and only very few PRs were seen), treatment with pazopanib almost doubled the occurrence of disease stabilisation (SD) which is also considered clinically relevant.

The final OS analysis from trial VEG110727 (N=369) showed no statistically significant difference between pazopanib and placebo. The HR only numerically favoured pazopanib (HR 0.87; 95% CI: 0.67, 1.12), and the p-value was not statistically significant (0.256). The trial was not adequately powered to show differences in OS of less than four months.

The synovial sarcoma histology subgroup only included 38 patients. This is why the efficacy results in this subgroup should be interpreted with caution taken into account the wide confidence intervals as well. It is acknowledged that the paradoxical adverse effect observed on the final median OS in the pazopanib arm as compared to the placebo arm could have arisen by chance, possibly due to the unusually long survival of patients on placebo in this small subgroup. For the above reasons, the results of the subgroup analyses for OS have been included in section 5.1 of the SmPC and this issue has been addressed in the RMP. Finally, due to the small numbers, the studied biomarkers and prognostic factors are unlikely to present an explanation for the observed phenomenon.

The possible rebound phenomenon -after stopping pazopanib- that might have influenced post-study survival - was investigated by the MAH. A rebound effect could explain the lack of OS benefit as observed also in the VEG110727 study. The Kaplan Meier estimate for survival post progression showed that (median) survival seemed reduced in the pazopanib arm.

No statistically significant difference in QoL was overall observed between treatment arms, but for certain specific symptoms (fatigue, nausea, vomiting, appetite loss, diarrhoea) the placebo arm was favoured in absolute numbers. No QoL data was collected after progression or study week 12. There was no indication that pazopanib had a negative impact on the PS of patients in an exploratory analysis.

Supportive study VEG20002 met its primary endpoint of a 12 week progression-free rate ≥ 40% in patients with leiomyosarcoma, synovial sarcoma and "other" STS treated with pazopanib, thus suggesting activity of the drug in these histological subgroups of STS. In contrast, the response observed in the adipocytic subgroup (2/17 patients with SD) did not meet the response criteria in order to warrant further enrolment. As a consequence, patients with liposarcoma have been excluded from the confirmatory VEG110727 study. In conclusion, no benefit of pazopanib in the adipocytic subgroup has been proven.

Based on the above and the inclusion criteria of both pivotal and supportive studies, the indication does not include patients with adipocytic sarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, GISTs, dermatofibrosarcoma protuberans, Ewing sarcoma/primitive neuroectodermal tumours, inflammatory myofibroblastic tumour, and malignant mesothelioma.

All 27 patients who were unsuited for prior chemotherapy for metastatic disease had received either neoadjuvant or adjuvant chemotherapy and progressed within 12 months. It is reasonable to include those patients in the trial and have them encompassed by the indication. Neither the pivotal trial nor the supportive data support the inclusion of patients too frail for mono-drug chemotherapy. Therefore the indication has been amended accordingly to include that "*patients who received only neo-adjuvant and/or adjuvant therapy should have progressed within 12 months".*

Very few samples have actually been available for biomarker investigations which is insufficient. The potential role of specific biomarkers for patient selection and/or monitoring of treatment is unknown. At present the MAH has no plans for further investigations on biomarkers as no studies in STS are ongoing. Future studies are still under consideration. In case the MAH engages in further studies in patients with STS, the CHMP recommended that the MAH includes pre-specified investigations on biomarkers and measures on quality of life/symptom control as exploratory endpoints.

2.5.3 Conclusions on clinical efficacy

The CHMP considered that both studies VEG110727 and VEG20002 provide robust evidence for clinically significant effects of second-line pazopanib treatment in patients with advanced Soft Tissue Sarcoma who have received prior chemotherapy.

2.6 Clinical safety

The safety population comprised all randomised subjects who receive at least one dose of investigational product (either pazopanib or placebo), and will be based on the actual treatment received if this differs from that to which the subject was randomised.

The safety database of pazopanib in patients with advanced STS includes data collected on 382 of which 240 patients enrolled in the pivotal VEG110727 phase III study, and 142 patients enrolled in the VEG20002 supportive phase II study.

The date of data cut-off was 22 November 2010 for the pivotal study and 20 August 2010 for the supportive study.

Patient exposure

In the pivotal VEG110727 trial 240 patients were treated with pazopanib (246 were randomised to pazopanib but 6 patients were excluded from the safety population as they did not receive the allocated treatment with pazopanib). The recommended dosage was 800 mg once daily. Patients stayed longer on treatment in the pazopanib arm (median: 19.36 weeks) compared to the placebo arm (8.14 weeks). The summary of exposure for the pivotal study is displayed in Table 21.

Table 21. Summary of Exposure to Study Treatment (Safety Population) for Study VEG110727

	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.	101.9	102.9
Daily dose (mg)		
Mean	788.41	700.35
SD	53.00	139.11
Median	800.00	794.21
Min.	407.0	249.4
Max.	800.0	800.0

In the uncontrolled, supportive VEG20002 trial 142 patients were treated with pazopanib at the same target dose. In the integrated analysis of the two studies in STS patients, the median time on pazopanib treatment was 3.6 months.

Adverse events

Common AEs

In the pivotal trial enrolling patients with STS, 99% of patients in the pazopanib arm and 89% of patients in the placebo arm reported AEs. The most common AEs in pazopanib-treated patients were fatigue (65%), diarrhoea (59%), nausea (56%), weight decreased (48%), hypertension (42%),

decreased appetite (40%) and hair colour changes (39%). In the placebo arm the most common AES were fatigue (48%), nausea (22%), tumour pain (21%), musculoskeletal pain (20%), decreased appetite (19%), dyspnoea (17%), constipation (17%) and diarrhoea (15%). In comparison, directly tumour-related symptoms and some constitutive symptoms occurred with a similar frequency in the pazopanib arm compared to the control arm (tumour pain: 29%, musculoskeletal pain: 23%, dyspnoea: 20%, constipation: 14%, pyrexia: 10%).

The same pattern was observed in the pooled analysis across STS studies (including the pivotal study + the supportive VEG20002 trial).

Severity of AEs

In pazopanib-treated patients 49% of patients reported an AE of grade 3 and 10% an AE of grade 4 severity. The most common grade 3 events were fatigue (13%), tumour pain (8%), hypertension (7%), decreased appetite (6%), dyspnoea (5%) and diarrhoea (5%). Severe events were also reported in the placebo arm ; 19% of placebo-treated patients reported a grade 3 event and 6% a grade 4 event. The most common grade 3 events in placebo-treated patients include tumour pain, dyspnoea and fatigue.

Treatment-related AEs

The treatment-related adverse reactions reported in both STS trials are detailed in Table 22.

Table 22. Treatment-related adverse reactions reported in STS trials (n=382)

System Organ Class	Frequency (all grades)	Adverse Reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations	Common	Gingival infection	4 (1 %)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very common	Tumour pain	121 (32 %)	32 (8 %)	0
Endocrine disorders	Common	Hypothyroidism	18 (5 %)	0	0
Metabolism and nutrition disorders	Very common	Decreased appetite	108 (28 %)	12 (3 %)	0
	Common	Dehydration	4 (1 %)	2 (1 %)	0
	Uncommon	Hypomagnesaemia	1 (< 1 %)	0	0
Psychiatric disorders	Common	Insomnia	5 (1 %)	1 (< 1 %)	0
Nervous system disorders	Very common	Dysgeusia[c]	79 (21 %)	0	0
	Very common	Headache	54 (14 %)	2 (< 1 %)	0
	Common	Peripheral sensory neuropathy	30 (8 %)	1 (< 1 %)	0
	Common	Dizziness	15 (4 %)	0	0
	Uncommon	Somnolence	3 (< 1 %)	0	0
	Uncommon	Paresthesia	1 (< 1 %)	0	0
	Uncommon	Cerebral infarction	1 (< 1 %)	0	1 (< 1 %)
Eye disorders	Common	Vision blurred	15 (4 %)	0	0
Cardiac disorders	Common	Left ventricular dysfunction	13 (3 %)	3 (< 1 %)	0
	Common	Bradycardia	4 (1 %)	0	0
	Uncommon	Myocardial infarction	1 (< 1 %)	0	0
Vascular disorders	Very common	Hypertension	152 (40 %)	26 (7 %)	0

System Organ Class	Frequency (all grades)	Adverse Reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
	Common	Venous thromboembolic event[d]	13 (3 %)	4 (1 %)	5 (1 %)
	Common	Hot flush	12 (3 %)	0	0
	Common	Flushing	4 (1 %)	0	0
	Uncommon	Haemorrhage	2 (< 1 %)	1 (< 1 %)	0
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	22 (6 %)	0	0
	Common	Dysphonia	20 (5 %)	0	0
	Common	Dyspnoea	14 (4 %)	3 (< 1 %)	0
	Common	Cough	12 (3 %)	0	0
	Common	Pneumothorax	7 (2 %)	2 (< 1 %)	1 (< 1 %)
	Common	Hiccups	4 (1 %)	0	0
	Common	Pulmonary haemorrhage	4 (1 %)	1 (< 1 %)	0
	Uncommon	Oropharyngeal pain	3 (< 1 %)	0	0
	Uncommon	Bronchial haemorrhage	2 (< 1 %)	0	0
	Uncommon	Rhinorrhoea	1 (< 1 %)	0	0
	Uncommon	Haemoptysis	1 (< 1 %)	0	0
Gastrointestinal disorders	Very common	Diarrhoea	174 (46 %)	17 (4 %)	0
	Very common	Nausea	167 (44 %)	8 (2 %)	0
	Very common	Vomiting	96 (25 %)	7 (2 %)	0
	Very common	Abdominal pain[a]	55 (14 %)	4 (1 %)	0
	Very common	Stomatitis	41 (11 %)	1 (< 1 %)	0
	Common	Abdominal distension	16 (4 %)	2 (1 %)	0
	Common	Dry mouth	14 (4 %)	0	0
	Common	Dyspepsia	12 (3 %)	0	0
	Common	Mouth haemorrhage	5 (1 %)	0	0
	Common	Flatulence	5 (1 %)	0	0
	Common	Anal haemorrhage	4 (1 %)	0	0
	Uncommon	Gastrointestinal haemorrhage	2 (< 1 %	0	0
	Uncommon	Rectal haemorrhage	2 (< 1 %	0	0
	Uncommon	Enterocutaneous fistula	1 (< 1 %	1 (< 1 %)	0
	Uncommon	Gastric haemorrhage	1 (< 1 %	0	0
	Uncommon	Melaena	2 (< 1 %)	0	0
	Uncommon	Oesophageal haemorrhage	1 (< 1 %	0	1 (< 1 %
	Uncommon	Peritonitis	1 (< 1 %	0	0
	Uncommon	Retroperitoneal haemorrhage	1 (< 1 %	0	0
	Uncommon	Upper gastrointestinal haemorrhage	1 (< 1 %	1 (< 1 %	0
	Uncommon	Ileal perforation	1 (< 1 %	0	1 (< 1 %
Hepatobiliary disorders	Uncommon	Hepatic function abnormal	2 (< 1 %)	0	1 (< 1 %
Skin and subcutaneous disorders	Very common	Hair colour change	93 (24 %)	0	0
	Very	Skin	80 (21 %)	0	0

System Organ Class	Frequency (all grades)	Adverse Reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
	common	hypopigmentation			
	Very common	Exfoliative rash	52 (14 %)	2 (< 1 %)	0
	Common	Alopecia	30 (8 %)	0	0
	Common	Skin disorder[c]	26 (7 %)	4 (1 %)	0
	Common	Dry skin	21 (5 %)	0	0
	Common	Hyperhydrosis	18 (5 %)	0	0
	Common	Nail disorder	13 (3 %)	0	0
	Common	Pruritus	11 (3 %)	0	0
	Common	Erythema	4 (1 %)	0	0
	Uncommon	Skin ulcer	3 (< 1 %)	1 (< 1 %)	0
	Uncommon	Rash	1 (< 1 %)	0	0
	Uncommon	Rash papular	1 (< 1 %)	0	0
	Uncommon	Photosensitivity reaction	1 (< 1 %)	0	0
	Uncommon	Palmar-plantar erythrodysaesthesia syndrome	2 (<1 %)	0	0
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain	35 (9 %)	2 (< 1 %)	0
	Common	Myalgia	28 (7 %)	2 (< 1 %)	0
	Common	Muscle spasms	8 (2 %)	0	0
	Uncommon	Arthralgia	2 (< 1 %)	0	0
Renal and urinary disorders	Uncommon	Proteinuria	2 (<1 %)	0	0
Reproductive system and breast disorder	Uncommon	Vaginal haemorrhage	3 (< 1 %)	0	0
	Uncommon	Menorrhagia	1 (< 1 %)	0	0
General disorders and administration site conditions	Very common	Fatigue	178 (47 %)	34 (9 %)	1 (< 1 %)
	Common	Oedema[b]	18 (5 %)	1 (< 1 %)	0
	Common	Chest pain	12 (3 %)	4 (1 %)	0
	Common	Chills	10 (3 %)	0	0
	Uncommon	Mucosal inflammation[e]	1 (<1 %)	0	0
	Uncommon	Asthenia	1 (< 1 %	0	0
Investigations[f]	Very common	Weight decreased	86 (23 %)	5 (1 %)	0
	Common	Ear, nose and throat examination abnormal[e]	29 (8 %)	4 (1 %)	0
	Common	Alanine aminotransferase increased	8 (2 %)	4 (1 %)	2 (< 1 %)
	Common	Blood cholesterol abnormal	6 (2 %)	0	0
	Common	Aspartate aminotransferase increased	5 (1 %)	2 (< 1 %)	2 (< 1 %)
	Common	Gamma glutamyltransferase increased	4 (1 %)	0	3 (< 1 %)
	Uncommon	Blood bilirubin increased	2 (<1 %)	0	0
	Uncommon	Aspartate aminotransferase	2 (< 1 %)	0	2 (< 1 %)
	Uncommon	Alanine aminotransferase	1 (< 1 %)	0	1 (< 1 %)

System Organ Class	Frequency (all grades)	Adverse Reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
	Uncommon	Platelet count decreased	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Electrocardiogram QT prolonged	2 (< 1 %)	1 (< 1 %)	0

The following terms have been combined:
[a] Abdominal pain, abdominal pain upper and gastrointestinal pain
[b] Oedema, oedema peripheral and eyelid oedema
[c] The majority of these cases were Palmar-plantar erythrodysaesthesia syndrome
[d] Venous thromboembolic events – includes Deep vein thrombosis, Pulmonary embolism and Thrombosis terms
[e] The majority of these cases describe mucositis
[f] Laboratory abnormalities were reported as adverse events less frequently by investigators than these abnormalities occurred as indicated by laboratory value tables. Certain laboratory abnormalities occurring in ≥ 15 % of patients who received pazopanib and more frequently than with placebo in the randomised controlled trial for the treatment of STS (VEG110727; N=240) include Leukopenia (All Grades-44 %; Grade 3-1 %, Grade 4-0 %), Neutropenia (All Grades-33 %; Grade 3-4 %, Grade 4-0 %), Thrombocytopenia (All Grades-36 %; Grade 3-3 %, Grade 4-< 1 %), ALT increased (All Grades-46 %; Grade 3-8 %, Grade 4-2 %), AST increased (All Grades-51 %; Grade 3-5 %, Grade 4-3 %), Albumin increased (All Grades-34 %; Grade 3-< 1 %, Grade 4-0 %), and Bilirubin increased(All Grades-29 %; Grade 3-1 %, Grade 4-0 %).

Adverse events of special interest

These include: Liver chemistry abnormalities and AEs, hypertension, cardiac and vascular events, pneumothorax, thyroid function abnormalities, bowel perforations and enteral fistulae and proteinuria.

Liver chemistry abnormalities and AEs

In study VEG110727 bilirubin (BIL) and alanine transaminase (ALT) elevations were reported in 5% and 18 % of pazopanib treated patients (compared with 2% and 5% patients treated with placebo), with ALT elevations >8x ULN in 13 (5%) pazopanib treated patients (versus 2 (2%) placebo treated patients). Six patients in the pazopanib arm experienced ALT elevations >20xULN: 3 patients had Grade 4 ALT elevations in association with fatal SAEs; all other 3 remaining patients recovered. The majority of ALT>3 ULN elevations (92.9%) are detected in the first 18 weeks of treatment with pazopanib.

Incidence and time to development of liver chemistry abnormalities is consistent with previous data in RCC.

'Possible Hy's Law Criteria' (defined as >3xULN ALT & >2x ULN BIL & <3xULN alkaline phosphatase (ALP) (or ALP missing)) were met by 4 patients in study VEG110727 and 1 patient in the VEG20002 study. In all these patients, there were confounding medical conditions at study entry: pre-existing biliary disease or elevated bilirubin, pre-existing drug-related liver disease or primary disease in the liver. For three of these patients, measurement of direct bilirubin was performed at the same time as the total bilirubin was measured. Two patients had hyperbilirubinemia predominantly unconjugated. Samples for UGT1A1 analysis were available for 2 of the 3 patients: one patient had the UGT1A1 TA6TA7 genotype and one patient had the UGT1A1 TA7TA7 genotype which may explain the hyperbilirubinemia. The liver chemistries recovered in 3 of the 5 patients, whereas recovery was not demonstrated in the other 2 patients. Another patient met Hy's law criteria; however, the laboratory values were only reported in the SAE form and not in the case report form. Symptoms consistent with liver failure were observed in two patients in study VEG110727 but also confounding clinical events; in one patient a potential contribution of pazopanib could not be excluded despite the confounding effects of concomitant moxifloxacin and extensive malignant disease. In the other patient disease progression, Grade 5 pulmonary embolus, and ischemic hepatitis were the causes of death. In VEG110727 study, another patient had ischemic hepatitis as a result of progressive disease with cardiac tamponade and extensive thrombosis, but no liver failure (no bilirubin elevation).

Across the STS integrated data (N=382), 54 (14%) patients had an elevation in ALT >3 x ULN. In an analysis performed overall liver enzymes elevations were reversible in 46/54 (85%) patients and ALT values recovered to Grade ≤1 (<2.5xULN). Based on previous data in RCC the recovery was documented in 91% of patients. The median time to recovery post study treatment interruption was 22 days (range 5-39 days). Among the remaining 8 patients (15%) who did not recover, 3 had no follow-up data and their liver events occurred after discontinuing study for either progressive disease or unrelated toxicity. Of the remaining 5 who did not recover, 4 patients with fatal AEs had ongoing liver dysfunction confounded by medical conditions and one patient was still on treatment at data cut-off.

Adaptation (defined as return to Grade 0 or baseline levels of ALT from >3xULN while exposed to study drug without any interruption) was experienced by 10 patients which remained on study drug despite elevations of ALT >3xULN (and <8xULN) and experienced adaptation while remaining on the same dose of pazopanib. The majority of these patients had a peak ALT ≤5xULN (8 of 10 patients). The median time to adaptation was 46 days (range of 8 to 168 days).

Re-challenge (restart of pazopanib at the same or reduced dose after interruption due to ALT ≥3xULN and subsequent recovery to Grade ≤ 1) was performed in 16 patients. Of these, 63% tolerated a re-challenge without recurrent ALT elevation and 38% had recurrent ALT elevations. None of the patients with a positive re-challenge had an adverse clinical outcome. The data reported in STS are consistent with prior experience in RCC where 31 patients were re-challenged, 65% tolerated a re-challenge and 32% had recurrent elevations, none with adverse clinical outcome.

Hypertension

In study VEG110727 on-therapy AEs of hypertension were reported in 101 (42%) patients in the pazopanib arm and 7 (6%) patients in the placebo arm, with Grade 3 hypertension observed in 7% (16 patients) and 0%, respectively. There were no reports of Grade 4 or Grade 5 hypertension. No SAEs of hypertension were reported in the study. However, in the pazopanib arm hypertension led to dose reductions in 7% of patients, drug interruptions in 10% of patients and permanent discontinuation in 3% of patients. No incidence of hypertensive crisis AE occurred across STS studies. Systolic blood pressure ≥ 150 mmHg was observed in 96 (40%) patients in the pazopanib arm (29 [12%] ≥ 170 mmHg) and 13 (11%) patients in the placebo arm. Diastolic blood pressure ≥ 90 mmHg was observed in 134 (56%) patients in the pazopanib arm (15 [6%] ≥110 mmHg) and 22 (18%) patients in the placebo arm.

These data are in line with prior experience with pazopanib in advanced RCC where 47% of patients experience hypertension of worsening of hypertension during treatment with pazopanib. Hypertension occurred early in the course of treatment for both RCC (88% within the first 18 weeks) and STS patients (40.1% by Day 9 and 90.1% within the first 18 weeks).

Cardiac and Vascular Events

a) Myocardial Dysfunction

Due to the potential prior exposure of STS patients to cardiotoxic therapy (i.e., anthracycline), LVEF monitoring was conducted at baseline in VEG20002 and at baseline and Week 12 in VEG110727 study (with later amendment for monitoring beyond Week 12), or as clinically indicated. Myocardial dysfunction was defined by development of 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).

In study VEG110727, the rate of AEs of myocardial dysfunction of any grade was higher in the pazopanib arm (9%) compared with placebo (5%) before adjusting for exposure. The exposure-

adjusted incidence rates (using a 100 patient-years rate) for myocardial dysfunction AEs of any grade were similar across the two arms of study VEG110727.

The majority of myocardial dysfunction events were mild or moderate in severity and were reported as left ventricular dysfunction based on decline in left ventricular ejection fraction assessments. In VEG110727 study 4 patients in the pazopanib arm (2%) had Grade ≥ 3 events; no fatal events were reported. All events in the placebo arm were of lower grade of severity.

Symptomatic left ventricular decline (congestive heart failure) was reported in 2 out of 382 patients (0.5 %) while asymptomatic decline was reported in the others. No fatal events were reported.

In VEG110727 study, an analysis of LVEF decline from baseline was conducted in patients with at least one post-baseline LVEF measurement. Data was available for 58% of patients in pazopanib arm and for 32% of patients treated with placebo. Among patients with on-therapy LVEF assessments, decreased LVEF was seen in 15/140 (11%) pazopanib-treated patients versus 1/39 (3%) placebo-treated patient. The 15 patients in the pazopanib arm who developed left ventricular systolic dysfunction (LSVD) all had a normal LVEF at baseline and they had all previously been exposed to an anthracycline. Only 3 cases were symptomatic and the recommended dose adjustment was not performed for 2 of these cases. Eight of the 15 patients either continued on study drug without interruption or resumed study drug following interruption. Six of the 8 patients who continued study drug did so at a reduced dose of 600 mg (one of these had a second dose reduction to 400 mg). One patient, who resumed drug following an interruption, experienced recurrence of LVEF decline following resumption of pazopanib; each episode of LVEF decline preceded by hypertension. Four of the 15 subjects had full recovery (within 5 % of baseline) and 5 had partial recovery (within the normal range, but > 5 % below baseline). Five patients had insufficient follow-up data; whereas one patient did not recover; this patient had several cardiac risk factors, and died in hospice with terminal care. Hypertension and/or requirement of new anti-hypertensive medication and/or dose modifications were observed in 13 of the 15 patients treated with pazopanib with LVEF decline.

In study VEG20002, where LVEF by imaging assessment was only performed at baseline, there were no reports of AE of myocardial dysfunction.

b) Arrhythmia

In study VEG110727 the incidence of cardiac arrhythmias was 6% in the pazopanib arm and 9% in the placebo arm. Of these, 5 (2%) of pazopanib treated patients experienced QT prolongation of any grade, with 2 patients with grade≥ 3 events (QTc> 500 msec) without associated arrhythmias. There were no reports of QT prolongation in the placebo group.

The percentage of STS patients developing cardiac arrhythmia AEs from the integrated pazopanib dataset was 6% which is identical to the incidence observed in the pivotal study performed with pazopanib in RCC. The incidence of AE of QT prolongation was 1% in the STS population, and Grade 3 QT prolongation occurred in both the STS and RCC populations at <1%. There were no reports of AE of torsades de pointes (TdP), or sudden death in the STS patients. However, in study VEG110727 one fatal event in the pazopanib arm could have been associated with arrhythmia as he died at home and cause was unknown, although the investigator considered the event as related to disease progression.

The exposure adjusted rate per/100 patient years (PY) for arrhythmia was 11.57 for pazopanib-treated patients in pivotal STS study and 6.85 in the pazopanib arm of the pivotal RCC study. In the placebo arm of STS study the rate was 29.21 compared with 6.39 in the placebo arm of RCC study.

c) Venous Embolic and Thrombotic Events (VTE)

In study VEG110727, 13 patients (5%) in the pazopanib arm and 3 patients (2%) in the placebo arm experienced on-therapy or post therapy VTEs. More specifically, 10 of these 13 patients on pazopanib

developed deep venous thrombosis (DVT) (including inferior vena cava (IVC) thrombosis and vascular graft thrombosis) without reports of associated pulmonary embolism (PE). Three patients treated with pazopanib experienced PEs, with a fatal outcome in two of them, which have not been considered related to study treatment but to disease progression. The PE event experienced by the third patient was an incidental asymptomatic finding at a tumour assessment showing progressive disease. In the placebo arm, 2 of the 3 patients developed DVTs (including renal vein thrombosis) without reports of associated PE, and 1 patient experienced a PE.

In study VEG20002, 8 (6%) patients reported on-therapy VTEs. All events were non-fatal; 5 events of PE, 1 IVC thrombosis and 3 DVTs were reported. One patient had 2 events of IVC thrombosis and a PE. Of the 5 events of PE, two of these were diagnosed in association with progressive disease; three of the events were asymptomatic events diagnosed either at scheduled tumour assessments or by chest CT scan upon diagnosis of a DVT.

The exposure adjusted rate of VTEs in VEG110727 study was 10.03 events per 100 PY for patients treated with pazopanib and 7.97 events per 100 PY for patients treated with placebo. The exposure adjusted rate of VTE was 9.84 events per 100 PY for the integrated STS population. The exposure adjusted rate of PE was similar in the placebo and pazopanib arm of study VEG110727. 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. The incidence of VTEs in pazopanib-treated patients was higher in the STS population (5%) than in the RCC population (2%).

d) Arterial Embolic and Thrombotic Events

In study VEG110727, 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 1 patient experienced a Grade 4 cerebrovascular accident 85 days following the last dose of pazopanib that resolved 4 days later.

In study VEG20002, there were 2 on-therapy arterial thromboembolic events: 1 patient had Grade 3 coronary artery disease, and 1 patient had a Grade 4 thrombosis of a mechanical aortic valve.

The exposure adjusted rates for arterial thrombo-embolic events for the STS integrated dataset was 3.28/100 PY versus 3.85/100 PY to the RCC dataset.

Arterial thrombo-embolic events were more frequently reported with pazopanib than with placebo in both STS and RCC studies.

d) Haemorrhagic events

In study VEG110727 the incidence of haemorrhagic events (all grades) was 22% in the pazopanib arm and 8% in the placebo arm; the incidence rates of Grade 3 or Grade 4 haemorrhagic events were 1% or <1% and similar between the treatment arms. No patients reported Grade 5 events. Epistaxis (2%), mouth (3%) and anal (2%) haemorrhage were the most common categories of haemorrhage observed with pazopanib. Two patients in the pazopanib arm experienced Grade 4 haemorrhagic events: 1 patient had abdominal bleeding (assessed as potentially related to study drug as well as to abdominal metastasis) 4 days after stop of study drug, whereas the second patient experienced intracranial haemorrhage during treatment with pazopanib in presence of cerebral metastasis.

In the integrated STS database haemorrhagic events (all grades) were reported by 75 (20%) patients, of which 4 (1%) patients had Grade 3, and 3 (<1%) Grade 4 events. No fatal events based on the pre-specified MedDRA term list were reported.

Based on the RCC database, 16% of patients reported haemorrhagic events all grades, and 2% Grades 3 to 5 events.

Pneumothorax

In VEG110727 study 8 (3%) of pazopanib-treated patients versus none in the placebo arm reported on-therapy AEs of pneumothorax.

Overall, in both STS studies, 15 (4%) of the 382 pazopanib-treated STS patients experienced pneumothorax: 10 patients were Grade 1 or 2 events, whereas 5 patients reported Grade 3 or 4 events. At the time of clinical cut-off, 9/15 (60%) patients had recovered from the pneumothorax AE, additional 2 recovered with sequelae, and 4 patients had the event reported as ongoing. Of the 5 cases of Grade 3 or Grade 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.

In the pivotal RCC study 1 of 290 (<1%) patients treated with pazopanib developed a pneumothorax.

Thyroid Function Abnormalities

In study VEG110727, the incidence of thyroid function abnormalities (and/or aggravation of previously altered thyroid function tests) was 34% in the pazopanib arm and 2% in the placebo arm. Across the STS studies, 15 pazopanib-treated patients experienced concomitant elevations in TSH and decreases in T4 (5 <TSH ≤10 MU/L or >10 MU/L and T4 <LLN) that were consistent with hypothyroidism. Laboratory evidence of hyperthyroidism (TSH <0.3 MU/L and T4 >ULN) was confirmed in 5 patients in the pazopanib arm, all from study VEG110727. Twenty (5%) patients in the STS studies reported on-therapy AEs of hypothyroidism. Based on RCC studies a rate of 4% reported in the current prescribing information for pazopanib. Two STS patients (<1%) reported AEs of hyperthyroidism. All thyroid-related AEs were Grade 1 or 2 in severity, and no SAEs were reported.

Bowel Perforations and Enteral Fistulae

Across VEG110727 and VEG20002 studies, 4/382 (1%) patients experienced bowel perforations or fistulae. All these patients were known to have abdominal metastases at study entry; for the 2 patients with perforations, these developed at the site of metastatic lesions. One of the two patients died due to associated fatal peritonitis. Of the 2 patients with fistulas, one had a fistula at baseline and then developed another during study; events in both patients resolved. In the integrated RCC study data, gastrointestinal perforation or fistula has been reported in 5/586 patients (0.9%), and fatal perforation events have occurred in 2/586 (0.3%).

Proteinuria

In the STS studies, proteinuria was reported as an AE for 2 patients (<1%), one Grade 1 and one Grade 2. An additional patient enrolled in study VEG110727 reported Grade 4 nephrotic syndrome with a concurrent SAE of increased urine protein/creatinine ratio (UPC) and was permanently discontinued from study treatment as a result.

In addition to AE incidence, regular urinalysis was performed in both STS studies, but an integrated analysis of urine protein/creatinine ratio data was not performed because this data was not available for VEG20002 trial. In study VEG110727, the protocol pre-specified that a ratio ≥3 prompted a 24-hour urine protein collection and, if the urine protein was ≥3 g, treatment was interrupted until UPC returned to <3 and then restarted at a lower dose. In study VEG20002 patients with a 24 hr urine protein ≥2 g/24 hr had study drug interrupted and eventually resumed when reduced to <2 g/24 hr.

In study VEG110727 3 patients (1%) in the pazopanib arm and 3 patients (3%) in the placebo arm experienced a UPC ratio ≥3. These 3 pazopanib-treated patients had also proteinuria ≥3 gr at 24 hours urine analysis. All 3 patients had dose interruptions per the protocol followed by re-challenge at a lower dose. All three had repeat UPC ≥3 following re-challenge and were permanently discontinued from study.

In study VEG20002, 7 patients had Grade 2 proteinuria (1 - 2 gm/24 hr) and 1 patient had Grade 3 proteinuria (5.05 gm/24 hr). For this last patient no subsequent urine protein determinations were available, as the patient discontinued study on the same day due to disease progression.

In studies conducted with advanced RCC, proteinuria AEs were reported in 44/586 (8%) patients (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]).

Serious adverse event/deaths/other significant events

Deaths

As of the clinical cut-off date (24 October 2011) 95 patients had died in the placebo arm (77%) vs. 181 patients in the pazopanib arm (75%). The most common cause of death was progressive disease (165/181 deaths (91%) in the pazopanib arm vs. 86/95 (90%) in the placebo arm).

The summary of deaths for the pivotal study is presented in Table 23.

Table 23. Summary of Death (Safety Population) for study VEG110727

	Number (%) of Subjects	
	Placebo (N=123)	**Pazopanib (N=240)**
Subject 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)
Haematologic toxicity	0	0
Non-haematologic toxicity	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)

Serious Adverse events

In the pivotal study seven Grade 5 (fatal) events were reported in 6 placebo-treated patients (5%) and nine fatal events were reported in 8 pazopanib-treated patients (3%) (Table 24). In the pazopanib arm, only one event (multi-organ failure) was reported as treatment-related. However, the primary cause of death is not clear in all the cases. In comparison, the incidence of fatal SAEs was 4% in the pazopanib arm vs. 3% in the placebo arm in the pivotal study in the RCC indication. In the supportive study VEG20002, 10 patients had reports of fatal AEs. Three of these events were considered possibly treatment-related (disseminated intravascular coagulation (DIC), depression, peritonitis/peritoneal infection/small intestine perforation).

Table 24. Summary of fatal Serious Adverse Events (Safety Population) for Study VEG110727.

Preferred term	Number (%) of Subjects	
	Placebo (N=123)	Pazopanib (N=240)
Subjects with any event	**6 (5)**	**8 (3)**
Pulmonary embolism	0	2 (<1)
Disease progression	1 (<1)	1 (<1)
Cardio-respiratory arrest	0	1 (<1)
Death	0	1 (<1)
Lung disorder	0	1 (<1)
Multi-organ failure	0	1 (<1)
Pericardial effusion	0	1 (<1)
Pneumonia	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

The incidence of patients reporting SAEs was 41% in the pazopanib arm compared to 24% the placebo arm in the pivotal study. Treatment-related SAEs were reported in 24% of pazopanib-treated patients and in 5% of placebo-treated patients. The most common SAEs associated with pazopanib were increased liver transaminases, pneumothorax, embolism, fatigue and left ventricular dysfunction.

In comparison, the observed incidence of SAEs was 24% in the pazopanib arm in the pivotal RCC study. The summary of SAEs occurred in at least 2 patients in either treatment group in the pivotal study are displayed in Table 25.

Table 25. Summary of Serious Adverse Events in at Least 2 Subjects in Either Treatment Group (Safety Population) for Study VEG110727

Preferred term	Number (%) of Subjects			
	Placebo (N=123)		Pazopanib (N=240)	
	All Events	Related[a]	All Events	Related[a]
Subjects with any event	**29 (24)**	**6 (5)**	**99 (41)**	**57 (24)**
Dyspnoea	3 (2)	0	10 (4)	2 (<1)
Alanine aminotransferase increased	1 (<1)	1 (<1)	9 (4)	8 (3)
Haemoglobin decreased	2 (2)	0	8 (3)	3 (1)
Aspartate aminotransferase increased	0	0	6 (3)	5 (2)
Gamma-glutamyltransferase increased	0	0	6 (3)	4 (2)
Pneumothorax	0	0	6 (3)	5 (2)
Embolism	2 (2)	1 (<1)	6 (3)	4 (2)
Fatigue	1 (<1)	1 (<1)	5 (2)	4 (2)
Left ventricular dysfunction	0	0	5 (2)	4 (2)
Pleural effusion	1 (<1)	0	4 (2)	0
Gastrointestinal pain	2 (2)	1 (<1)	4 (2)	3 (1)
Vomiting	1 (<1)	1 (<1)	4 (2)	3 (1)
Chest pain	0	0	4 (2)	1 (<1)
Tumour pain	3 (2)	0	4 (2)	0
Platelet count decreased	1 (<1)	0	3 (1)	0
Pneumonia	0	0	3 (1)	1 (<1)
Performance status decreased	0	0	3 (1)	0
Blood bilirubin increased	1 (<1)	0	2 (<1)	2 (<1)
Neutrophil percentage	1 (<1)	0	2 (<1)	0
Aspartate aminotransferase	0	0	2 (<1)	1 (<1)
Neutrophil count decreased	0	0	2 (<1)	0
Weight decreased	0	0	2 (<1)	1 (<1)
Lung disorder	0	0	2 (<1)	0

Preferred term	Number (%) of Subjects			
	Placebo (N=123)		Pazopanib (N=240)	
	All Events	Related[a]	All Events	Related[a]
Small intestinal obstruction	0	0	2 (<1)	0
Malignant pleural effusion	1 (<1)	0	2 (<1)	0
Decreased appetite	0	0	2 (<1)	1 (<1)
Dehydration	0	0	2 (<1)	1 (<1)
Myalgia	1 (<1)	1 (<1)	2 (<1)	0
Renal failure	0	0	2 (<1)	0
Febrile neutropenia	0	0	2 (<1)	0
Pyrexia	3 (2)	1 (<1)	1 (<1)	1 (<1)
Lymphocyte percentage	2 (2)	0	0	0
Respiratory failure	2 (2)	0	0	0

Related SAE are also included in the All Events columns
Note – SAEs are sorted from highest to lowest incidence in the pazopanib treatment arm.

Laboratory findings

Haematology: Shifts in haematology parameters were consistent with observations in RCC patients. A higher incidence of neutropenia, leucopenia, and thrombocytopenia occurred in pazopanib-treated patients but most cases were mild/moderate in severity. Grade 4 anaemia occurred in 2% of pazopanib-treated patients.

Clinical Chemistry: The most important findings are liver enzyme elevations, thyroid function abnormalities and proteinuria that are mentioned under events of special interest. Most other shifts in chemistry parameters were mild in severity.

ECGs: Patients enrolled in the pivotal STS study had no clinically significant ECG findings at baseline. Post-baseline recordings revealed clinically significant ECG changes in 3% of patients (6 patients) in the pazopanib arm vs. 2% of patients in the placebo arm. Two pazopanib-treated patients had grade 3 QTc prolongations without associated ventricular arrhythmias. Two patients had tachycardia. The last 2 patients presented with cardiac ischemia and T wave/QRS abnormalities.

Safety in special populations

WHO PS status

During the on-therapy portion of the study, 54% of patients treated with pazopanib vs. 35% of patients on placebo reported deterioration in performance status, which is worse than what was observed in the RCC population (46% of pazopanib-treated patients vs. 35% of placebo-treated patients). As expected, a poorer PS was also associated with a higher incidence of Grade 3/4/5 events (65% in patients with PS 1 or 2 compared to 51% in patients with PS 0).

Further to the CHMP request, two analyses (ITT population) to assess the dynamics of WHO performance status (PS) have been conducted by using the following 2 definitions in a 'time to deterioration' analysis : a) If the subject shows a 1 point increase in their WHO PS score from baseline which is then confirmed by remaining higher at the next visit or if a subject dies before this occurs, the subject is considered as experiencing an event at either the time of the 1 point increase or the date of death (the first occurring event) and b) If a subject shows a 2 point increase in their WHO PS score from baseline or if a subject dies before this occurs, the subject is considered as experiencing an event at either the time of the 2 point increase or the date of death (the first occurring event). For both analyses, if the subject didn't experience either, the subject is censored in the analysis at the time of the last WHO performance status score.

The results from the analyses are displayed in the tables 26 and 27 and the corresponding Kaplan Meier curves in figures 4 and 5.

Table 26. Summary of Statistical analysis of Time to Performance Status Deterioration Death or Confirmed 1 Point Increase in WHO PS

	Placebo (N=123)	Pazopanib (N=246)
Number of Subjects		
Deteriorated or Died (event)	92(75%)	193 (78%)
Censored	31(25%)	53 (22%)
Adjusted Hazard Ratio [2]		
Estimate (95% CI)	1.05 (0.82,1.35)	
Stratified Log-Rank P-value [1]	0.685	
Estimate for performance status deterioration (months) [3]		
1st Quartile (95% CI)	1.87 (1.08, 2.79)	1.77 (1.08,1.87)
Median (95% CI)	5.78 (3.71,7.79)	4.86 (3.91, 6.08)
3rd Quartile (95% CI)	12.8 (8.57,14.68)	12.0 (9.30,16.13)

[1] Hazard ratios are estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo.
[2] 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.
[3] Confidence intervals for quartiles are estimated using the Brookmeyer-Crowley method.

Table 27. Summary of Statistical analysis of Time to Performance Status Deterioration Death or Confirmed 2 Point Increase in WHO PS

	Placebo (N=123)	Pazopanib (N=246)
Number of Subjects		
Deteriorated (event)	39 (32%)	76 (31%)
Died (event)	47 (38%)	96 (39%)
Censored	37 (30%)	74 (30%)
Adjusted Hazard Ratio [2]		
Estimate (95% CI)	0.91 (0.70,1.18)	
Stratified Log-Rank P-value [1]	0.461	
Estimate for performance status deterioration (months) [3]		
1st Quartile (95% CI)	3.71 (2.30, 5.49)	4.34 (3.22, 5.26)
Median (95% CI)	8.08 (6.83, 11.56)	10.02 (7.89,11.33)
3rd Quartile (95% CI)	17.91 (13.21, 26.25)	21.33 (18.04, 25.99)

[1] Hazard ratios are estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo.
[2] 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.
[3] Confidence intervals for quartiles are estimated using the Brookmeyer-Crowley method.

Figure 4. Graph of Kaplan Meier curve Time to Performance Status Deterioration Death or Confirmed 1 Point Increase in WHO PS

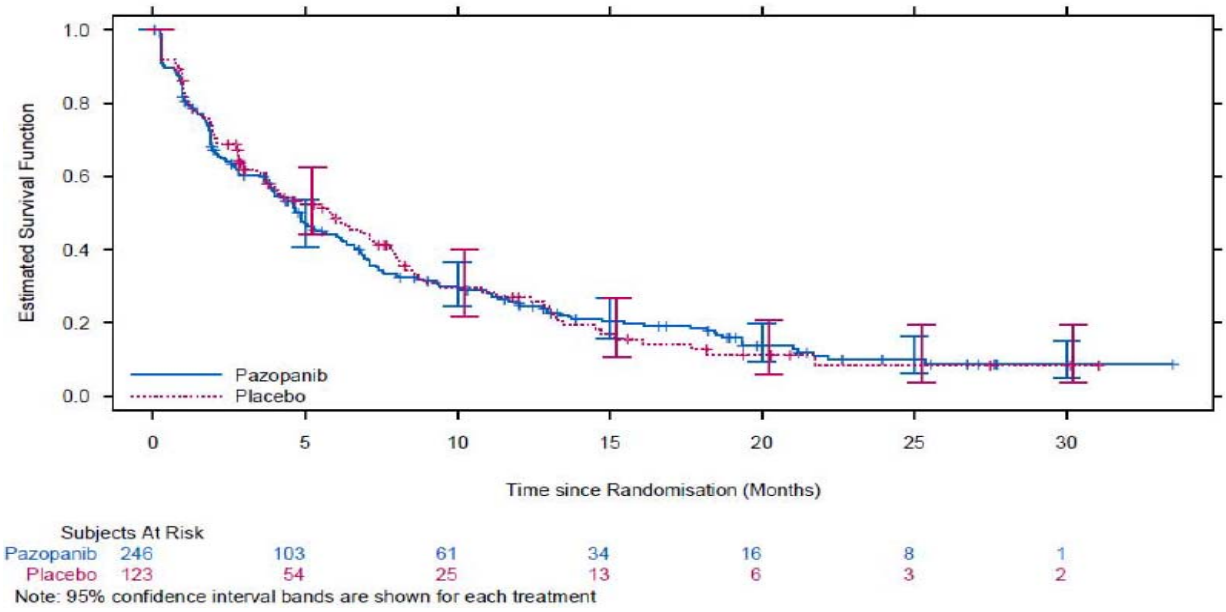
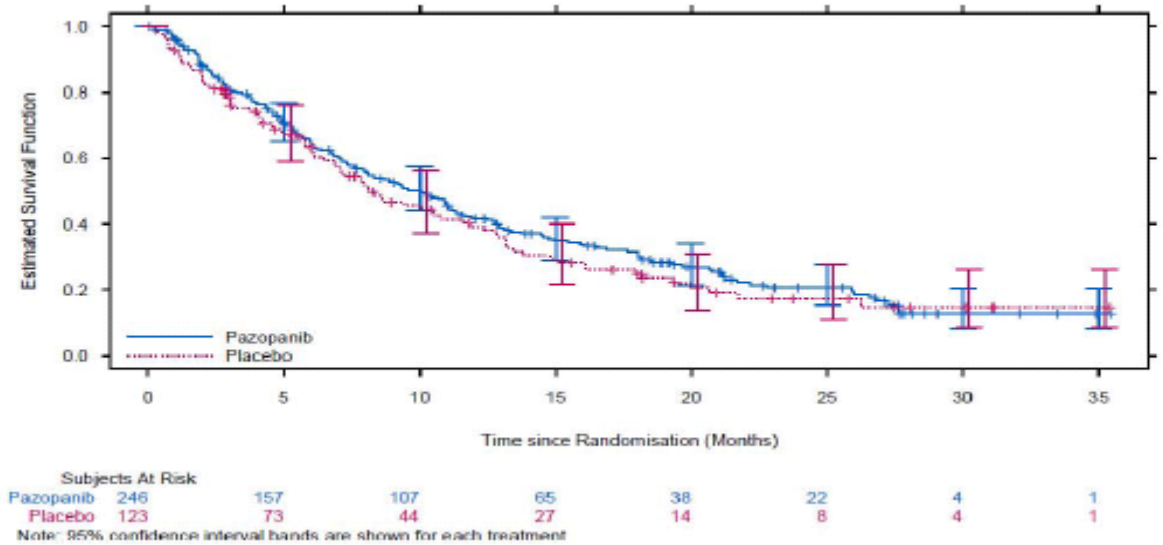


Figure 5. Graph of Kaplan Meier curve Time to Performance Status Deterioration Death or Confirmed 2 Point Increase in WHO PS



Age

The overall incidence of AEs was similar between patients aged < 65 years (n=289) and ≥65 years (n=93) across STS studies. Similarly, the overall incidence of severe events was comparable between these subsets (58% in younger patients vs. 57% in the elderly). There were 1% of fatal events in the elderly vs. 4% in the younger so there is no indication that elderly patients were more susceptible to severe toxicities. On the individual AE level, AEs like fatigue, hypertension, decreased appetite and liver enzyme elevations occurred more frequently in the elderly whereas the younger reported a higher incidence of diarrhoea, vomiting, infections and tumour pain. Overall, 38% of the younger age group

reported SAEs compared to 33% in the elderly. There was no specific accumulation of specific events in one or the other of the age groups.

Gender

Overall, no marked differences in AEs were noted between male and female patients.

Race

In the pivotal study pazopanib-associated AEs involving the skin and hair colour changes were more common in Asians than in White patients. On the other hand AEs of high grades of toxicity occurred at a slightly higher frequency in White patients.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

No new information relevant to the proposed indication is available.

Discontinuation due to adverse events

In the pivotal study 20% of pazopanib-treated patients permanently discontinued therapy due to AEs compared to 5% in the placebo arm. The most common AEs that led to discontinuation in the pazopanib arm were ALT increased, dyspnoea, left ventricular dysfunction, fatigue, hypertension and vomiting. In pazopanib arm, 32% of patients had AEs that lead to dose reductions compared to < 1% in the placebo arm. Similarly, 50% of patients treated with pazopanib had AEs leading to dose interruptions compared to 10% in the control arm. The AEs most frequently leading to dose reductions and dose interruptions were fatigue, hypertension, nausea and diarrhoea.

2.6.1 Discussion on clinical safety

The safety profile of pazopanib has already been well characterized in patients with RCC and many of the former safety findings have been confirmed in patients with STS but important differences have also been noted, including development of pneumothorax and myocardial dysfunction. Although the overall tolerability of the treatment expressed in terms of mean daily dose (approximately 700 mg) was acceptable and similar between RCC and STS studies, the mean treatment duration (exposure) was markedly lower in STS patients (4.5 months) compared to RCC patients (7.4 months). In the pivotal STS trial almost all patients in the pazopanib arm reported AEs (99%). A very high number of patients in the placebo arm also reported AEs (89%). This is indicative of the poorer general condition and the many physical symptoms that can be related to the underlying, advanced disease stage in the STS patient population.

Common AEs associated with pazopanib in the STS population were fatigue (65%), diarrhoea (59%), nausea (56%), weight decreased (48%), hypertension (42%), decreased appetite (40%) and hair colour changes (39%). These events were often severe; 49% and 10% of patients reported an AE of grade 3 or grade 4 severity, respectively. The most common grade 3 events were fatigue (13%), tumour pain (8%), hypertension (7%), decreased appetite (6%), dyspnoea (5%) and diarrhoea (5%).

The incidence of patients reporting SAEs was also relatively high in the pivotal study, particularly in the pazopanib arm (41%) compared to the placebo arm (24%). Treatment-related SAEs were reported in 24% of pazopanib-treated patients compared to 5% of placebo-treated patients. The most common

SAEs associated with pazopanib were increased liver transaminases, pneumothorax, embolism, fatigue and left ventricular systolic dysfunction (LVSD). In comparison, the observed incidence of SAEs was 24% in the pazopanib arm in the pivotal RCC study. Eight (3%) of patients in the pazopanib arm had fatal grade 5 events vs. 5% in the placebo arm. This is in line with what was observed in the RCC population. The most common cause of death was progressive disease (91%) in both treatment arms.

Pneumothorax and venous embolisms are newly identified risks in the STS population. Left ventricular systolic dysfunction (demonstrated as decreased LVEF) was also reported in the RCC population but it seems to be a larger issue in the advanced STS population as these patients have often been pre-treated with anthracyclines that are cardiotoxic. It appears that a higher percentage of subjects with decreased LVEF had current or a prior history of hypertension. The development of hypertension and the resulting increased cardiac after load may lead to exacerbation of a subclinical decreased LVEF due to previous treatment with anthracyclines. The sections 4.4 and 4.8 SmPC have been adequately updated in order to inform about potential risk factors (prior anthracycline therapy, concurrent hypertension). Interruption of pazopanib and/or dose reduction should be combined with treatment of hypertension in patients with significant reductions in LVEF. This information is reflected in section 4.4 of the SmPC. Furthermore, a more detailed warning on cardiac dysfunction has been implemented in section 4.4 of the SmPC in order to reflect that the risks and benefits of pazopanib should be considered before beginning therapy in patients who have pre-existing cardiac dysfunction, especially those with STS. As additional pharmacovigilance activities the MAH will send targeted follow-up questionnaires to healthcare professionals who report LVEF decreases during treatment with pazopanib in order to increase the collection of background details. Furthermore, LVSD will be included in the future PSURs. These measures are considered appropriate. Finally based on data from the pivotal RCC study (VEG105192), the rate of LVSD was very low in the RCC population (and similar across treatment arms) despite hypertension being a common AE in the pazopanib arm. However, LVEF assessments were not obtained regularly in that study as it has been done in the ongoing study VEG108844 study comparing pazopanib and sunitinib in RCC. Therefore the CHMP recommended the MAH to comment on this particular issue when submitting the CSR from study VEG108844 in June 2013.

Slightly more patients in the STS pivotal trial (20%) discontinued pazopanib due to AEs than in the RCC pivotal trial (15%).

The MAH has performed an exploratory "time to deterioration of PS" analysis. Patients who experienced a confirmed 1 or 2 point increase in their WHO score from baseline or death were regarded as events whereas other subjects were censored. Although these results should be interpreted with caution since patients in the pazopanib arm stayed longer on treatment and had slightly more PS scores than patients in the placebo arm, the Kaplan-Meier curves displayed a very similar pattern in terms of deterioration in PS across treatment arms over time.

2.6.2 Conclusions on clinical safety

Many of the safety findings from the trials in RCC patients have been confirmed in the STS population but it appears that the burden of the treatment is heavier in patients with advanced STS who are heavily pre-treated, constitutively more symptomatic, in a poorer general condition and consequently more vulnerable when it comes to treatment-related toxicities. Relevant warnings and advice to the treating physician have been added to the SmPC on myocardial dysfunction and pneumothorax, the two new safety signals that have been observed.

Overall, the safety profile of pazopanib is still considered manageable and acceptable in the proposed indication.

2.7 Pharmacovigilance

Risk Management plan

The MAH submitted an updated risk management plan within this variation procedure.

Table 28. Summary of the EU risk management plan (including the changes related to the application presented underlined)

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important identified risks		
Hepatic dysfunction	Routine proactive pharmacovigilance activities Utilising oncology-specific electronic medical record epidemiological databases, to monitor the rates of liver chemistry abnormalities in pazopanib users with RCC.	ALT increased, AST increased, blood bilirubin increased, hyperbilirubinaemia, and hepatic function abnormal are included as adverse events in SmPC Section 4.8 (Undesirable Effects). SmPC Section 4.4 (Special Warnings and Precautions for Use) includes guidance on the frequency of periodic monitoring of LFTs when isolated transaminase elevations occur, and when transaminase and bilirubin elevations are observed concurrently. Increase in enzymes produced by the liver is included as adverse event in the package leaflet.
Pulmonary haemorrhage	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) cautions that pazopanib is not recommended in patients who had a history of haemoptysis in the past six months, and recommends that pazopanib be used with caution in patients with a significant risk of haemorrhage.
GI bleeding	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) cautions that pazopanib is not recommended in patients who had a history of clinically significant GI haemorrhage in the past six months, and recommends that pazopanib be used with caution in patients with a significant risk of haemorrhage.
Cerebral haemorrhage	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) cautions that pazopanib is not recommended in patients who had a

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		history of cerebral haemorrhage in the past six months, and recommends that pazopanib be used with caution in patients with a significant risk of haemorrhage, such as in patients with a history of brain metastasis.
GI perforation and fistula	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) recommends that pazopanib should be used with caution in patients at risk for GI perforation or fistula.
Cardiac arrhythmias	Routine pharmacovigilance Utilising epidemiological healthcare insurance claims databases to monitor events of torsade de pointes in pazopanib users with RCC. Study VEG111485 has established that pazopanib has an effect on cardiac conduction.	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) recommends that pazopanib should be used with caution in patients who have a history of QT interval prolongation, are taking antiarrhythmics or other medications that may prolong QT interval, or have a relevant pre-existing cardiac disease. Additionally, there is a recommendation that baseline and periodic monitoring of ECGs and electrolytes should be performed when using pazopanib.
Cardiac ischaemia	Routine pharmacovigilance Utilising epidemiological healthcare insurance claims databases to monitor cardiac ischaemic events (MI, angina) in pazopanib users with RCC.	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) recommends that pazopanib should be used with caution in patients at risk for cardiac ischaemic events such as MI.
Cerebrovascular ischaemic events	Routine pharmacovigilance Utilising epidemiological healthcare insurance claims databases to monitor cerebrovascular ischaemic events (CVA, TIA) in pazopanib users with RCC.	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) recommends that pazopanib should be used with caution in patients at risk for cerebrovascular ischaemic events such as ischaemic stroke and TIA.

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Hypertension	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) cautions that BP should be well controlled prior to initiating pazopanib, and provides guidance on pazopanib treatment when hypertension is present despite anti-hypertensive therapy. Hypertensive crisis has been added to SmPC Section 4.4 following a Type II variation approval by CHMP.
Hypothyroidism	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) recommends monitoring of thyroid function tests at baseline and periodically.
Diarrhoea	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Fatigue/Asthenia	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Hypoglycaemia	Routine pharmacovigilance	Blood glucose decreased is included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Impaired Healing	Routine pharmacovigilance	SmPC Section 4.4 (Special Warnings and Precautions for Use) recommends treatment with pazopanib be stopped 7 days prior to scheduled surgery, and that resumption of treatment should be based on clinical judgement of adequate wound healing. This SmPC section additionally states pazopanib should be discontinued in patients with wound dehiscence. No additional risk minimisation activities are proposed.
Proteinuria	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Precautions for Use) recommends baseline and periodic urinalyses during pazopanib treatment, and treatment discontinuation if Grade 4 proteinuria develops. No additional risk minimisation activities are proposed.
Thrombocytopenia	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Leucopenia and Neutropenia	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. Following the CHMP assessor's report on the 19 April 2010 to 18 October 2010 VOTRIENT PSUR, the CHMP adopted a positive opinion to a Type II variation to the SmPC on 23 September 2011 to add infections to the Special Warnings and Precautions for Use and the Undesirable Effects sections. No additional risk minimisation activities are proposed.
Cardiac dysfunction	Routine pharmacovigilance Utilising a targeted follow-up questionnaire which will contain a series of queries aimed at collecting pertinent past medical history (e.g. prior chest radiation or anthracycline use) and event details that will aide in the evaluation and interpretation of events of myocardial dysfunction that occur in patients treated with pazopanib.	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) recommends baseline and periodic LVEF monitoring in patients who are at risk for developing cardiac dysfunction (eg, those who have received prior anthracyclines), monitoring patients for signs and symptoms of CHF, and interruption of pazopanib and/or dose reduction combined with treatment of hypertension (if present). No additional risk minimisation activities are proposed.
Venous thromboembolic events	Routine pharmacovigilance	Included in Section 4.8 (Undesirable Effects) of the SmPC and package leaflet, due to the occurrence of these events more frequently in the STS population than in the RCC population. Section 4.4 (Special Warnings and Precautions for Use) of the SmPC also indicates VTEs have occurred in RCC and STS studies, but have occurred more frequently in the STS population than in the RCC population. Section 4.4 also indicates that VTEs such as venous thrombosis and fatal pulmonary embolus have occurred.

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		No additional risk minimisation activities are proposed.
Pneumothorax	Routine pharmacovigilance	Included as adverse event in SmPC Section 4.8 (Undesirable Effects) and package leaflet. No additional risk minimisation activities are proposed.
Inhibition of P-gp and BCRP by co-administered drugs	Routine pharmacovigilance	The effects attributed to inhibition of p-gp and BCRP when lapatinib was co-administered with pazopanib are included in SmPC Section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) and package leaflet.
Concomitant use of pazopanib with UGT1A1 substrates	Routine pharmacovigilance	A warning about co-administration of pazopanib with UGT1A1 substrates such as irinotecan, as pazopanib is an inhibitor of UGT1A1, is included in SmPC Section 4.4 (Special Warnings and Precautions for Use) and package leaflet.
Concomitant use of pazopanib and simvastatin (Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A)	Routine pharmacovigilance	A Type II variation was submitted in May 2011 to add to SmPC Section 4.5 (Interaction with Medicinal Products and Other Forms of Interaction) a statement that concomitant administration of pazopanib with simvastatin has been associated with ALT elevations,
Important potential risks		
Drug interactions with substrates of cytochrome P450	Routine pharmacovigilance	The effects of pazopanib on cytochrome P450 substrates are included in SmPC Section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) and package leaflet.
Drug interactions with inhibitors of CYP3A4	Routine pharmacovigilance	The effects of CYP3A4 inhibitors on pazopanib, and a recommendation to either avoid the use of strong CYP3A4 inhibitors or use a concomitant medication with no or minimal potential to inhibit CYP3A4, are included in SmPC Section 4.2 (Posology and Method of Administration) and Section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) and package leaflet. SmPC Section 4.4 (Special Warnings and Precautions for Use) includes the recommendation to avoid the use of strong CYP3A4 inhibitors, and cross-references SmPC Section 4.2 and Section 4.5.
Food effect	Routine pharmacovigilance	The effect of either a high fat or low fat meal on pazopanib is described in SmPC Section 4.5 (Interaction with Medicinal

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Products and Other Forms of Interaction). The recommendation to take pazopanib without food, at least one hour before or two hours after a meal, is included in SmPC Section 4.2 (Posology and Method of Administration) and package leaflet.
Concomitant treatment with inducers of CYP3A4	Routine pharmacovigilance	The recommendation to avoid concomitant treatment with inducers of CYP3A4 due to risk of decreased exposure to pazopanib is included in SmPC Section 4.4. (Special Warnings and Precautions for Use). A statement that CYP3A4 inducers may decrease pazopanib plasma concentrations, and a recommendation to use a concomitant medication with no or minimal enzyme induction potential, is included in SmPC Section 4.5 (Interactions with Medicinal Products and Other Forms of Interaction).
Drug interactions with substrates of P-gp and BCRP	Routine pharmacovigilance	A statement that *in vitro* studies suggested pazopanib is a substrate for p-gp and BCRP is included in SmPC Section 5.2 (Pharmacokinetic Properties).
Drug interactions related to inhibition of OATP1B1 by pazopanib	Routine pharmacovigilance	Statements that *in vitro* studies showed pazopanib inhibits OATP1B1, and that it cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g. rosuvastatin) are included in SmPC Section 4.5 (Interactions with Medicinal Products and Other Forms of Interaction).
Reproductive effects	Routine pharmacovigilance	SmPC Section 4.4 (Special Warnings and Precautions for Use) cautions that if pazopanib is used during pregnancy, or if the patient becomes pregnant whilst using pazopanib, the potential harm to the foetus should be explained to the patient. Similarly, the package leaflet recommends that a patient who is pregnant or considering pregnancy should talk with her doctor about the risks and potential benefits of taking pazopanib during pregnancy. SmPC Section 4.6 (Pregnancy and Lactation) and the package leaflet indicate that women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant whilst taking pazopanib. Additionally, SmPC Section 4.6 and the package leaflet indicate that as the safe use of pazopanib during lactation has not been established, and as it is not known if pazopanib is excreted in human milk, breast feeding should be discontinued during pazopanib treatment.

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		SmPC Section 5.3 (Preclinical Safety Data) includes foetal teratogenic effects observed during preclinical studies with pazopanib.
Potential for carcinogenicity	Routine pharmacovigilance Two-year carcinogenicity studies in rats and mice will be conducted in the future to determine a potential for carcinogenicity.	SmPC Section 5.3 (Preclinical Safety Data) indicates that although definitive carcinogenicity studies with pazopanib have not been performed, proliferative lesions in the liver (eosinophilic foci and adenoma) were observed during preclinical studies in mice.
Adult Off-Label Use	Routine pharmacovigilance	SmPC Section 4.1 (Therapeutic Indications) indicates that pazopanib is indicated for the treatment of advanced RCC. Additionally, SmPC Section 4.2 (Posology and Method of Administration) states that treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.
Paediatric Off-Label Use	Routine pharmacovigilance	SmPC Section 4.2 (Posology and Method of Administration), under *Paediatrics*, indicates that pazopanib is not recommended for use in children and adolescents under 18 years of age due to insufficient data on safety and efficacy. A cross-reference to Section 5.3 (Preclinical Safety Data) has been added due to the incorporation of results from the juvenile rat toxicity studies in Section 5.3.
Important missing information		
Use in patients with severe hepatic dysfunction	Routine pharmacovigilance Ongoing NCI study 8063 will establish recommendations for use in patients with severe hepatic dysfunction.	SmPC Section 4.2 (Posology and Method of Administration) includes a statement that the safety and pharmacokinetics of pazopanib in patients with hepatic impairment have not been fully established, and cross-references SmPC Section 4.4 (Special Warnings and Precautions for Use). It also includes the recommended dose of 200 mg pazopanib daily for patients with moderate hepatic impairment. Following the recommendation of an initial dose of 800 mg once daily for patients with mild hepatic impairment, a proposed update to SmPC Section 4.2 has been submitted to the CHMP as a Type II variation, and received a positive CHMP opinion in March 2011. SmPC Section 4.3. (Contraindications) indicates that pazopanib is not recommended for patients with severe hepatic impairment. SmPC Section 4.4 (Special Warnings and Precautions for Use) cautions about the use of pazopanib in patients with pre-existing hepatic impairment.

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Use in patients with severe renal impairment	Routine pharmacovigilance	Section 4.2 (Posology and Method of Administration) of the SmPC includes statements that no dose adjustment is required for patients with creatinine clearance above 30 ml/min, and that caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience with pazopanib in this patient population. Section 5.2 (Pharmacokinetic Properties) of the SmPC includes a statement that <4% of an orally administered pazopanib dose is excreted in the urine as pazopanib and metabolites.

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The MAH should continue to collect information regarding potential risk factors development of left ventricular systolic dysfunction (LVSD) and discuss this issue in upcoming PSURS.	PSUR submissions
Based on data from the pivotal RCC study (VEG105192), the rate of LVSD was very low in the RCC population (and similar across treatment arms) despite hypertension being a common AE in the pazopanib arm. However, LVEF assessments were not obtained regularly in that study as it has been done in the ongoing study VEG108844 study comparing pazopanib and sunitinib in RCC. The MAH is requested to comment on this particular issue when submitting the CSR from study VEG108844.	June 2013

2.8 Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC in order extend the indication of Votrient for the treatment of patients with advanced Soft Tissue Sarcoma (STS).

During the procedure, the CHMP requested further amendments to the PI as discussed in detail above (see discussion on clinical efficacy):

Update of section 4.4 of the SmPC to include a warning about increased risk of pneumothorax in STS patients treated with pazopanib.

The Package Leaflet is updated in accordance.

2.9. Benefit-risk balance

Benefits

Beneficial effects

In the pivotal trial patients treated with pazopanib demonstrated a median PFS of 20.0 weeks vs. 7.0 weeks in patients treated with placebo by independent review. This results in a gain in median PFS of 13 weeks. The HR for PFS was 0.35 (95% CI: 0.26, 0.48, p< 0.001) which corresponds to a 65% reduction in the risk of progression or death in patients treated with pazopanib. This PFS benefit is considered clinically relevant. Several sensitivity and subgroups analyses consistently support the results of the primary PFS analysis.

Response rates were low (11% in the pazopanib arm vs. 0% in the placebo arm per independent review), but more patients in the pazopanib arm obtained stable disease (54%) compared with the control arm (27%).

The supportive study VEG20002 showed activity for pazopanib and the endpoint as set for this study (progression-free rate ≥ 40%) was met in three out of the four histological subgroups of STS enrolled.

Uncertainty in the knowledge about the beneficial effects

According to eligibility criteria of study VEG110727 not only adipocytic sarcoma and GIST but also other histological subtypes of STS where excluded. The benefit of pazopanib in all these subgroups excluded from the study population is not proven, and therefore the benefit/risk is uncertain. Reference to these criteria under section 5.1 of the SmPC was considered appropriate to identify the target population.

Response rates were low (11% in the pazopanib arm vs. 0% in the placebo arm), however more patients in the pazopanib arm obtained stable disease (54%) compared with the control arm (27%).

The final OS analysis from trial VEG110727 showed no statistically significant difference between pazopanib and placebo. However, it is acknowledged that the trial was not adequately powered to show differences in OS of less than four months.

In terms of QoL, a numerical trend favouring placebo has been observed, potentially related to the negative impact of pazopanib-related toxicity (in particular fatigue, nausea, vomiting, and diarrhoea) on the QoL of patients treated. However, an exploratory analysis of "time to deterioration of performance status" including both on- and post-therapy assessments of PS reassuringly demonstrated a very similar pattern in terms of deterioration in PS across treatment arms over time.

Risks

Unfavourable effects

Practically all patients treated with pazopanib reported AEs (99%). Common AEs were well-known and included fatigue (65%), diarrhoea (59%), nausea (56%), weight decreased (48%), hypertension (42%), decreased appetite (40%) and hair colour changes (39%). Severe events were also seen relatively frequently; 49% and 10% of patients reported an AE of grade 3 or grade 4 severity, respectively. The most common grade 3 events were fatigue (13%), tumour pain (8%), hypertension (7%), decreased appetite (6%), dyspnoea (5%) and diarrhoea (5%). The incidence of SAEs was also high in the pazopanib arm (41%) compared to the placebo arm (24%). Treatment-related SAEs were

reported in 24% of pazopanib-treated patients and included increased liver transaminases, pneumothorax, embolism, fatigue and LVSD. The proportion of pazopanib-treated patients experienced fatal grade 5 events was 3%.

Newly identified risks to the STS population that have been associated with pazopanib are pneumothorax and myocardial dysfunction. Pneumothorax was reported in 15 (4%) of the 382 pazopanib-treated STS patients. Congestive heart failure was reported in 2 out of 382 patients (0.5 %) in the STS population. Decreases in LVEF in subjects who had post-baseline measurement were detected in 11 % (15/140) in the pazopanib arm compared with 3 % (1/39) in the placebo arm.

Both pneumothorax and cardiac dysfunction are considered as identified risks for pazopanib therapy.

Uncertainty in the knowledge about the unfavourable effects

The pathogenesis and the clinical relevance of the myocardial dysfunction AEs observed in STS patients treated with pazopanib are not completely clear. Routine and additional pharmacovigilance activities (see Table 28 above) are expected to provide further information on the these adverse events.

Benefit-risk balance

Importance of favourable and unfavourable effects

A reduction in the risk of disease progression or death of 65% and an improvement of 13 weeks in median PFS represents an important benefit to patients. In addition, the benefit of PFS in the pivotal study has proven to be very robust in sensitivity analyses and consistent in subgroup analyses.

The characteristic safety findings of pazopanib were overall similar to previous findings in RCC patients, but the tolerability was poorer in patients with advanced STS. It appears that the burden of the treatment is heavier in patients with advanced STS who are heavily pre-treated, constitutively more symptomatic, in a poorer general condition and consequently more vulnerable when it comes to treatment-related toxicities. Overall, the safety profile is considered acceptable and generally manageable.

Benefit-risk balance

A reduction in the risk of disease progression or death of 65% and an improvement of 13 weeks in median PFS represents an important benefit to patients. In addition, the benefit of PFS in the pivotal study has proven to be very robust in sensitivity analyses and consistent in subgroup analyses.

The safety findings of pazopanib were overall similar to previous findings in RCC patients. New safety concerns have been identified as well however these are generally manageable and relevant warnings with very detailed recommendations regarding monitoring and further lines to take have been adequate provided.

Discussion on the benefit risk balance

The benefit-risk balance for pazopanib for the treatment of patients with selective subtypes of advanced Soft Tissue Sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy is considered positive as the

demonstrated statistically significant improvement of PFS outweighs the added toxicity of pazopanib in this target population with a high unmet medical need.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change to therapeutic indication - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC in order extend the indication of Votrient for the treatment of patients with advanced Soft Tissue Sarcoma (STS). The Package Leaflet is updated accordingly.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Votrient is not similar to Yondelis within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

Additional data / Market exclusivity

Furthermore, the CHMP reviewed the data submitted by the applicant, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results are reflected in the Summary of Product Characteristics (SmPC) and as appropriate, the Package Leaflet.

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