SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VOPAZZI 400 mg Film Coated Tablets
Cytotoxic

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Active substance:
Pazopanib hydrochloride 433.4 mg (equivalent to 400 mg pazopanib)

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
White, oval film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Pazopanib is indicated for use as a single agent until progression in patients with non-resectable local relapse or metastatic renal cell cancer who have not previously used any VEGF-TKI (Vascular endothelial growth factor-Tyrosine kinase inhibitor).

- VOPAZZI is indicated for the following subtypes of metastatic sarcoma that have undergone at least one series of chemotherapy/at most two series of chemotherapy for metastatic disease or have subsequently progressed:

Fibroblastic sarcomas (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumor), fibrohistiocytic sarcomas (pleomorphic malignant fibrous histiocytoma, inflammatory malignant fibrous histiocytoma, giant cell malignant fibrous histiocytoma (also known as undifferentiated pleomorphic sarcoma [UPS]), leiomyosarcoma pleomorphic or alveolar rhabdomyosarcoma, epithelioid hemangioendothelioma, angiosarcomas, epithelioid sarcomas, synovial sarcoma, alveolar soft part sarcoma, malignant glomus tumor, clear cell sarcoma, desmoplastic small round cell sarcoma, malignant mesenchymoma, PEComa, intimal sarcoma, malignant peripheral nerve sheath tumors.

4.2 Posology and method of administration

Posology/Frequency and duration of administration
VOPAZZI treatment should only be initiated by a physician experienced in the administration of anti-cancer medicinal products.

The recommended dose of pazopanib for the treatment of renal cell carcinoma (RCC) or soft tissue sarcoma (STS) is 800 mg taken orally once daily.

Dose modifications
Dose modification should be in 200 mg decrements or increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of pazopanib should not exceed 800 mg.

Method of administration
Pazopanib should be taken without food, at least one hour before or two hours after a meal (see section 5.2). The film-coated tablets should be taken whole with plenty of water and not broken, crushed or chewed.

If a dose is missed and it is less than 12 hours before the next dose, the missed dose should not be taken.

Additional information on special populations

Renal impairment
Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites (see section 5.2). Therefore, no dose adjustment is required in patients with creatinine clearance above 30 mL/min. However, if pazopanib is to be used in patients with creatinine clearance below 30 mL/min, caution is advised.

Hepatic impairment
Dosing recommendations in hepatically impaired patients are based on pharmacokinetic studies of pazopanib in patients with varying degrees of hepatic dysfunction (see section 5.2). All patients should have liver function tests to determine whether they have hepatic impairment before starting and during pazopanib therapy (see section 4.4). Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring due to the potential for increased drug exposure. In patients with mild abnormalities in liver function tests [defined either as normal bilirubin and any degree of alanine aminotransferase (ALT) elevation or as an elevation of bilirubin (>35% direct) up to 1.5 x upper limit of normal (ULN) regardless of the ALT value], it is recommended to initiate treatment with a dose of 800 mg pazopanib once daily. A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (defined as an elevation of bilirubin>1.5 to 3 x ULN regardless of the ALT value) (see section 5.2).

Pazopanib is contraindicated in patients with severe hepatic impairment (defined as total bilirubin>3 x ULN regardless of the ALT value) (see section 4.3).

See section 4.4 for liver monitoring and dose modification for patients with drug-induced hepatotoxicity.

Pediatric population
Pazopanib should not be used in children younger than 2 years of age because of safety concerns with regard to organ growth and maturation (see sections 4.4 and 5.3).

The safety and efficacy of pazopanib in children aged 2 to 18 years of age have not yet been established (see section 5.1).

Geriatric population
There are limited data on the use of pazopanib in patients aged 65 years and older. In the clinical studies of pazopanib, overall no clinically significant differences in safety of pazopanib were observed between subjects aged at least 65 years and younger subjects. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some elderly patients cannot be ruled out.

4.3 Contraindications
VOPAZZI should not be used in patients with hypersensitivity to the active substance or any of the excipients and in patients with severe hepatic impairment.

It should not be used during pregnancy (see section 4.6).

It also should not be used in children under 2 years old.

4.4 Special warnings and precautions for use
Hepatic effects
Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities in serum liver tests (either normal bilirubin and any degree of ALT elevation or elevation of bilirubin up to 1.5 x ULN regardless of the ALT value). A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (elevation of bilirubin >1.5 to 3 x ULN regardless of the ALT value) (see sections 4.2 and 5.2). Pazopanib is not recommended in patients with severe hepatic impairment (total bilirubin >3 x ULN regardless of the ALT value) (see sections 4.2 and 5.2).Exposure at a 200 mg dose is markedly reduced, though highly variable, in these patients, with values considered insufficient to obtain a clinically relevant effect.

In clinical studies with pazopanib, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed (see section 4.8). In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. Patients over 60 years of age may be at greater risk for mild (>3 x ULN) to severe (>8 x ULN) elevation of ALT. Patients who carry the HLA-B*57:01 allele have an increased risk of pazopanib-associated ALT elevations. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype or age (see section 5.1).

Serum liver tests should be performed before initiation of treatment with pazopanib, at weeks 3, 5, 7 and 9, then at months 3 and 4, with additional tests as clinically indicated. Periodic testing should then continue after month 4.

The following dose modification guidance is for patients with baseline values of total bilirubin ≤1.5 x ULN and AST and ALT ≤2 x ULN:

- In patients with isolated elevations in serum transaminase levels between 3 and 8 x ULN, pazopanib therapy can be continued with weekly monitoring of liver function until serum transaminase levels return to Grade 1 (NCI CTCAE) or baseline.

- In patients with serum transaminase elevation of >8 x ULN, pazopanib therapy should be

discontinued until serum transaminase levels return to Grade 1 (NCI CTCAE) or baseline. If the potential benefit of reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg daily and perform serum liver tests weekly for 8 weeks (see section 4.2). Following reintroduction of pazopanib, if ALT levels >3 x ULN recur, then pazopanib should be permanently discontinued.

- In patients with serum transaminase elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN, pazopanib therapy should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. Pazopanib is a uridine glucuronosyl transferase (UGT1A1) inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in ALT >3 x ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations (see section 4.5) and should be undertaken with caution and close monitoring.

Hypertension
In clinical studies with pazopanib, events of hypertension including newly diagnosed symptomatic episodes of elevated blood pressure (hypertensive crisis) have occurred. Blood pressure should be well controlled prior to initiating pazopanib. Patients should be monitored for hypertension early after starting treatment (no longer than one week after starting pazopanib) and frequently thereafter to ensure blood pressure control. Elevated blood pressure levels (systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥100 mm Hg) occurred early in the course of treatment (approximately 40% of cases occurred by day 9 and approximately 90% of cases occurred in the first 18 weeks). Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of pazopanib (interruption and re-initiation at a reduced dose based on clinical judgement) (see sections 4.2 and 4.8). Pazopanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction.

Posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS)
PRES/RPLS has been reported in association with pazopanib. PRES/RPLS can present with headache, hypertension, seizure, lethargy, confusion, blindness and other visual and neurological disturbances, and can be fatal. Patients developing PRES/RPLS should permanently discontinue treatment with pazopanib.

Interstitial lung disease (ILD)/Pneumonitis
ILD, which can be fatal, has been reported in association with pazopanib (see section 4.8). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and pazopanib should be discontinued in patients developing ILD or pneumonitis.

Cardiac dysfunction/Heart failure
The risks and benefits of pazopanib should be considered before beginning therapy in patients who have pre-existing cardiac dysfunction. The safety and pharmacokinetics of pazopanib in patients with moderate to severe heart failure or those with a below normal left ventricular ejection fraction (LVEF) have not been studied.

In clinical studies with pazopanib, events of cardiac dysfunction such as congestive heart failure and decreased LVEF have occurred (see section 4.8). In a randomized study comparing pazopanib and sunitinib in RCC (VEG108844), subjects had baseline and follow up LVEF measurements. Myocardial dysfunction occurred in 13% (47/362) of subjects in the pazopanib arm compared to 11% (42/369) of subjects in the sunitinib arm. Congestive heart failure was observed in 0.5% of subjects in each treatment arm. Congestive heart failure was reported in 3 out of 240 subjects (1%) in the Phase III VEG110727 STS study. Decreases in LVEF in subjects who had post-baseline and follow-up LVEF measurement were detected in 11% (15/140) in the pazopanib arm, compared with 3% (1/39) in the placebo arm.

Risk factors
Thirteen of the 15 subjects in the pazopanib arm of the STS Phase III study had concurrent hypertension which may have exacerbated cardiac dysfunction in patients at risk by increasing cardiac after-load. Ninety-nine percent (99%) of patients (243/246) enrolled in the STS Phase III study, including the 15 subjects, received anthracycline. Prior anthracycline therapy may be a risk factor for cardiac dysfunction.

Outcome
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). One subject did not recover and follow-up data were not available for the other 5 subjects.

Management
Interruption of pazopanib and/or dose reduction should be combined with treatment of hypertension (if present, refer to hypertension warning section above) in patients with significant reductions in LVEF, as clinically indicated.

Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction.

<u>QT prolongation and Torsade de Pointes</u>
In clinical studies with pazopanib, events of QT prolongation and torsade de pointes have occurred (see section 4.8). Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medicinal products that may prolong QT interval and in patients with relevant pre-existing cardiac disease. When using pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within normal range is recommended.

<u>Arterial thrombotic events</u>
In clinical studies with pazopanib, myocardial infarction, myocardial ischemia, ischemic stroke and transient ischemic attack were observed (see section 4.8). Fatal events have been observed. Pazopanib should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. Pazopanib has not been studied in patients who have had an event within the previous 6 months. A treatment decision should be made based on the assessment of individual patient's benefit/risk.

<u>Venous thromboembolic events</u>
In clinical studies with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. While observed in both RCC and STS studies, the incidence

was higher in the STS population (5%) than in the RCC population (2%).

Thrombotic microangiopathy (TMA)
TMA has been reported in clinical studies of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan (see section 4.8). Patients developing TMA should permanently discontinue treatment with pazopanib. Reversal of effects of TMA has been observed after treatment was discontinued. Pazopanib is not indicated for use in combination with other agents.

Hemorrhagic events
In clinical studies with pazopanib hemorrhagic events have been reported (see section 4.8). Fatal hemorrhagic events have occurred. Pazopanib should not be used in patients who had a history of hemoptysis, cerebral hemorrhage or clinically significant gastrointestinal (GI) hemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of hemorrhage.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating pazopanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysms.

Gastrointestinal (GI) perforations and fistula
In clinical studies with pazopanib, events of GI perforation or fistula have occurred (see section 4.8). Fatal perforation events have occurred. Pazopanib should be used with caution in patients at risk for GI perforation or fistula.

Wound healing
No formal studies of the effect of pazopanib on wound healing have been conducted. Since vascular endothelial growth factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgement of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

Hypothyroidism
In clinical studies with pazopanib, events of hypothyroidism have occurred (see section 4.8). Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of pazopanib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on pazopanib treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice.

Proteinuria
In clinical studies with pazopanib, proteinuria has been reported. Baseline and periodic urinanalysis during treatment is recommended and patients should be monitored for worsening proteinuria. Pazopanib should be discontinued if the patient develops nephrotic syndrome.

Tumor lysis syndrome (TLS)
The occurrence of TLS, including fatal TLS, has been associated with the use of pazopanib (see section 4.8). Patients at increased risk of TLS are those with rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Preventative measures, such as treatment of high uric acid levels and intravenous hydration, should be considered prior to initiation of VOPAZZI. Patients at

risk should be closely monitored and treated as clinically indicated.

Pneumothorax
In clinical studies with pazopanib in advanced soft tissue sarcoma, events of pneumothorax have occurred (see section 4.8). Patients on pazopanib treatment should be observed closely for signs and symptoms of pneumothorax.

Infections
Cases of serious infections (with or without neutropenia), in some cases with fatal outcome, have been reported.

Combination with other systemic anti-cancer therapies
Clinical studies of pazopanib in combination with pemetrexed (non-small cell lung cancer [NSCLC]) and lapatinib (cervical cancer) were terminated early due to concerns over increased toxicity and/or mortality, and a safe and effective combination dose has not been established with these regimens.

Pediatric population
Because the mechanism of action of pazopanib can severely affect organ growth and maturation during early post-natal development (see section 5.3), pazopanib should not be given to pediatric patients younger than 2 years of age.

Pregnancy
Pre-clinical studies in animals have shown reproductive toxicity (see section 5.3). If pazopanib is used during pregnancy, or if the patient becomes pregnant whilst receiving pazopanib, the potential hazard to the fetus should be explained to the patient. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with pazopanib (see section 4.6).

Interactions
Concomitant treatment with strong inhibitors such as cytochrome P450(CYP)3A4, breast cancer resistance protein (BCRP) or P-glycoprotein (P-gp) should be avoided due to risk of increased exposure to pazopanib (see section 4.5). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BCRP should be considered.

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to pazopanib (see section 4.5).

Cases of hyperglycemia have been observed during concomitant treatment with ketoconazole.

Concomitant administration of pazopanib with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan) should be undertaken with caution since pazopanib is an inhibitor of UGT1A1 (see section 4.5).

Grapefruit juice should be avoided during treatment with pazopanib (see section 4.5).

4.5 Interactions with other medicinal products and other forms of interaction
Effects of other medicinal products on pazopanib
In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4, P-gp, BCRP inhibitors
Pazopanib is a substrate for CYP3A4, P-gp and BCRP.
Concurrent administration of pazopanib (400 mg once daily) with the strong CYP3A4 and P-gp inhibitor ketoconazole (400 mg once daily) for 5 consecutive days resulted in a 66% and 45% increase in mean pazopanib $AUC_{(0-24)}$ and C_{max}, respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days). Pharmacokinetic parameter comparisons of pazopanib C_{max} (range of means 27.5 to 58.1 microgram/mL) and $AUC_{(0-24)}$ (range of means 48.7 to 1040 microgram*hour/mL) after administration of pazopanib 800 mg alone and after administration of pazopanib 400 mg plus ketoconazole 400 mg (mean C_{max} 59.2 microgram/mL, mean $AUC_{(0-24)}$ 1300 microgram*hour/mL) indicated that, in the presence of a strong CYP3A4 and P-gp inhibitor a dose reduction to pazopanib 400 mg once daily will, in the majority of patients, result in systemic exposure similar to that observed after administration of 800 mg pazopanib once daily alone. Some patients however may have systemic pazopanib exposure greater than what has been observed after administration of 800 mg pazopanib alone.

Co-administration of pazopanib with other strong inhibitors of the CYP3A4 family (e.g. itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice contains an inhibitor of CYP3A4 and may also increase plasma concentrations of pazopanib.

Administration of 1500 mg lapatinib (a substrate for and weak inhibitor of CYP3A4 and P-gp and a potent inhibitor of BCRP) with 800 mg pazopanib resulted in an approximately 50% to 60% increase in mean pazopanib $AUC_{(0-24)}$ and C_{max} compared to administration of 800 mg pazopanib alone. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increased exposure to pazopanib.

Co-administration of pazopanib with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations. Co-administration with potent P-gp or BCRP inhibitors may also alter the exposure and distribution of pazopanib, including distribution into the central nervous systems (CNS).

Concomitant use of pazopanib with a strong CYP3A4 inhibitor should be avoided (see section 4.4). If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration. In such cases there should be close attention to adverse drug reaction, and further dose reduction may be considered if possible drug-related adverse events are observed.

Combination with strong P-gp or BCRP inhibitors should be avoided, or selection of an alternate concomitant medicinal product with no or minimal potential to inhibit P-gp or BCRP is recommended.

CYP3A4, P-gp, BCRP inducers
CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Co-administration of pazopanib with potent P-gp or BCRP inducers may alter the exposure and distribution of pazopanib, including distribution into the CNS. Selection of an alternative concomitant medication with no or minimal enzyme or transporter induction potential is recommended.

<u>Effects of pazopanib on other medicinal products</u>

In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human Pregnane X Receptor (PXR) assay. Clinical pharmacology studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30% in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextrometrophan to dextrophan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively.

Based on *in vitro* IC_{50} and *in vivo* plasma C_{max} values, pazopanib metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of pazopanib towards BCRP. Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Care should be taken when pazopanib is co-administered with other oral BCRP and P-gp substrates.

In vitro, pazopanib inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g. statins, see "Effect of concomitant use of pazopanib and simvastatin" below).

Pazopanib is an inhibitor of the uridine diphosphoglucuronosyl-transferase 1A1 (UGT1A1) enzyme *in vitro*. The active metabolite of irinotecan, SN-38, is a substrate for OATP1B1 and UGT1A1. Co-administration of pazopanib 400 mg once daily with cetuximab 250 mg/m^2 and irinotecan 150 mg/m^2 resulted in an approximately 20% increase in systemic exposure to SN-38. Pazopanib may have a greater impact on SN-38 disposition in subjects with the UGT1A1*28 polymorphism relative to subjects with the wild-type allele. However, the UGT1A1 genotype was not always predictive of the effect of pazopanib on SN-38 disposition. Care should be taken when pazopanib is co-administered with substrates of UGT1A1.

It cannot be excluded that pazopanib will affect the pharmacokinetics of OATP1B1 substrates (e.g. rosuvastatin).

<u>Effect of concomitant use of pazopanib and simvastatin</u>
Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. Results from a meta-analysis using pooled data from clinical studies with pazopanib show that ALT >3x ULN was reported in 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin (p =0.038). If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib posology and discontinue simvastatin (see section 4.4). In addition, concomitant use of pazopanib and other statins should be undertaken with caution as there are insufficient data available to assess their impact on ALT levels. It cannot be excluded that pazopanib will affect the pharmacokinetics of other statins (e.g. atorvastatin, fluvastatin, pravastatin, rosuvastatin).

<u>Effect of food on pazopanib</u>
Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal.

Medicinal products that raise gastric pH
Concomitant administration of pazopanib with esomeprazole decreases the bioavailability of pazopanib by approximately 40% (AUC and C_{max}), and co-administration of pazopanib with medicines that increase gastric pH should be avoided. If the concomitant use of a proton-pump inhibitor (PPI) is medically necessary, it is recommended that the dose of pazopanib be taken without food once daily in the evening concomitantly with the PPI. If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids. The recommendations for how PPIs and H2-receptor antagonists are co-administered are based on physiological considerations.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is D.

Women of child-bearing potential/Contraception
Women of childbearing potential should be advised to use adequate contraception during treatment and for at least 2weeks after the last dose of pazopanib and to avoid becoming pregnant while receiving treatment with pazopanib.

Male patients (including those who have had vasectomies) should use condoms during sexual intercourse while taking pazopanib and for at least 2 weeks after the last dose of pazopanib to avoid potential exposure to the medicinal product for pregnant partners and female partners of reproductive potential.

Pregnancy
There are no adequate data from the use of pazopanib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

If pazopanib is used during pregnancy, or if the patient becomes pregnant while receiving pazopanib, the potential hazard to the fetus should be explained to the patient. Pazopanib should not be used during pregnancy unless the clinical condition of the woman requires treatment with pazopanib.

Lactation
The safe use of pazopanib during breast-feeding has not been established. It is not known whether pazopanib or its metabolites are excreted in human milk. There are no animal data on the excretion of pazopanib in animal milk. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with pazopanib.

Fertility
Animal studies indicate that male and female fertility may be affected by treatment with pazopanib (see section 5.3).

4.7 Effects on ability to drive and use machinery
VOPAZZI has no or negligible influence on the ability to drive and use machines. A detrimental effect on such activities cannot be predicted from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of pazopanib should be borne in mind when considering

the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired or weak.

4.8 Undesirable effects

Summary of the safety profile

Pooled data from the pivotal RCC study (VEG105192, n=290), the extension study (VEG107769, n=71), the supportive Phase II study (VEG102616, n=225) and the randomized, open-label, parallel group Phase III non-inferiority study (VEG108844, n=557) were evaluated in the overall evaluation of safety and tolerability of pazopanib (total n=1149) in subjects with RCC (see section 5.1).

Pooled data from the pivotal STS study (VEG110727, n=369) and the supportive Phase II study (VEG20002, n=142) was evaluated in the overall evaluation of safety and tolerability of pazopanib (total safety population n=382) in subjects with STS (see section 5.1).

The most important serious adverse reactions associated with pazopanib therapy identified in the RCC or STS studies were transient ischemic attack, ischemic stroke, myocardial ischemia, myocardial and cerebral infarction, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation, Torsade de Pointes and pulmonary, gastrointestinal and cerebral hemorrhage, all adverse reactions being reported in <1% of treated patients. Other important serious adverse reactions identified in STS studies included venous thromboembolic events, left ventricular dysfunction and pneumothorax.

Fatal events that were considered possibly related to pazopanib included gastrointestinal hemorrhage, pulmonary hemorrhage/hemoptysis, abnormal hepatic function, intestinal perforation and ischemic stroke.

The most common adverse reactions (experienced by at least 10% of the patients) of any grade in the RCC and STS trials included: diarrhea, hair color change, skin hypopigmentation, exfoliative rash, hypertension, nausea, headache, fatigue, anorexia, vomiting, dysgeusia, stomatitis, weight decreased, pain, elevated alanine aminotransferase and elevated aspartate aminotransferase.

Adverse drug reactions, all grades, which were reported in RCC and STS subjects or during the post-marketing period are listed below by MedDRA body system organ class. The following convention has been utilized for the classification of frequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Categories have been assigned based on absolute frequencies in the clinical trial data. Post-marketing data on safety and tolerability across all pazopanib clinical studies and from spontaneous reports have also been evaluated. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Treatment-related adverse reactions reported in RCC studies (n = 1149) or during post-marketing period:

Infections and Infestations

Common: Infections (with or without neutropenia)[†]
Uncommon: Gingival infection, infectious peritonitis

Neoplasms benign and malignant (incl. cysts and polyps)
Uncommon: Tumor pain

Blood and lymphatic system disorders
Common: Thrombocytopenia, neutropenia, leukopenia
Uncommon: Polycythemia
Rare: Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome)[†]

Endocrine disorders
Common: Hypothyroidism

Metabolism and nutrition disorders
Very common: Decreased appetite[e]
Common: Dehydration, hypophosphatemia
Uncommon: Hypomagnesaemia
Not known: Tumor lysis syndrome*

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Very common: Dysgeusia[c], headache
Common: Dizziness, lethargy, paresthesia, peripheral sensory neuropathy
Uncommon: Hypoesthesia, transient ischemic attack, somnolence, cerebrovascular accident, ischemic stroke
Rare: Posterior reversible encephalopathy / reversible posterior leukoencephalopathy syndrome[†]

Eye disorders
Common: Vision blurred
Uncommon: Retinal detachment[†], retinal tear[†], eyelash discoloration

Cardiac disorders
Uncommon: Bradycardia, cardiac dysfunction[f], myocardial infarction, myocardial ischemia

Vascular disorders
Very common: Hypertension
Common: Hot flush, venous thromboembolic event[g], flushing
Uncommon: Hemorrhage, hypertensive crisis
Not known: Aneurysms and artery dissections

Respiratory, thoracic and mediastinal disorders
Common: Epistaxis, dysphonia, dyspnea, hemoptysis
Uncommon: Pulmonary hemorrhage, rhinorrhea, pneumothorax
Rare: Interstitial lung disease/pneumonitis[†]

Gastrointestinal disorders
Very common: Diarrhea, nausea, vomiting, abdominal pain[a]
Common: Dyspepsia, stomatitis, flatulence, abdominal distension, dry mouth, mouth ulceration

Uncommon: Pancreatitis, rectal hemorrhage, hematochezia, gastrointestinal hemorrhage, melena, frequent bowel movements, anal hemorrhage, large intestine perforation, mouth hemorrhage, upper gastrointestinal hemorrhage, enterocutaneous fistula, hematemesis, hemorrhoidal hemorrhage, ileal perforation, esophageal hemorrhage, retroperitoneal hemorrhage

Hepatobiliary disorders
Common: Hepatic function abnormal, hyperbilirubinemia, hepatotoxicity
Uncommon: Jaundice, hepatic failure, drug induced liver injury

Skin and subcutaneous disorders
Very common: Hair color change, palmar-plantar erythrodysesthesia syndrome, alopecia, rash
Common: Skin hypopigmentation, erythema, pruritus, skin depigmentation, dry skin, hyperhidrosis
Uncommon: Nail disorders, photosensitivity reaction, skin exfoliation, rash vesicular, pruritus generalized, rash papular, plantar erythema, rash erythematous, rash generalized, rash macular, rash pruritic, skin disorder

Musculoskeletal and connective tissue disorders
Common: Myalgia, muscle spasms, arthralgia
Uncommon: Musculoskeletal pain

Renal and urinary disorders
Very common: Proteinuria
Uncommon: Hemorrhage urinary tract

Reproductive system and breast disorders
Uncommon: Menorrhagia, metrorrhagia, vaginal hemorrhage

General disorders and administration site conditions
Very common: Fatigue
Common: Asthenia, mucosal inflammation, edema[b], chest pain
Uncommon: Mucous membrane disorder, chills

Investigations
Very common: Alanine aminotransferase increased, aspartate aminotransferase increased
Common: Weight decreased, blood creatinine increased, blood bilirubin increased, White blood cell count decreased[d], lipase increased, blood pressure increased, blood thyroid stimulating hormone increased, gamma-glutamyltransferase increased, amylase increased, liver function test abnormal, blood urea increased
Uncommon: Electrocardiogram QT prolonged, blood glucose decreased, transaminase increased, blood pressure diastolic increased, thyroid function test abnormal, blood pressure systolic increased, hepatic enzyme increased, †Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).

Tabulated list of adverse reactions:

Table 1. Treatment-related adverse reactions reported in RCC studies (n = 1149) or during post-marketing period

System Organ Class	Frequency (all grades)	Adverse reactions	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and Infestations	Common	Infections (with or without neutropenia)†	not known	not known	not known
	Uncommon	Gingival infection	1 (<1%)	0	0
		Infectious peritonitis	1 (<1%)	0	0
Neoplasms benign and malignant (incl. cysts and polyps)	Uncommon	Tumor pain	1 (<1%)	1 (<1%)	0
Blood and lymphatic system disorders	Common	Thrombocytopenia	80 (7%)	10 (<1%)	5 (<1%)
		Neutropenia	79 (7%)	20 (2%)	4 (<1%)
		Leukopenia	63 (5%)	5 (<1%)	0
	Uncommon	Polycythemia	6 (0.03%)	1	0
	Rare	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome)†	not known	not known	not known
Endocrine disorders	Common	Hypothyroidism	83 (7%)	1 (<1%)	0
Metabolism and nutrition disorders	Very common	Decreased appetite[e]	317 (28%)	14 (1%)	0
	Common	Hypophosphatemia	21 (2%)	7 (<1%)	0
		Dehydration	16 (1%)	5 (<1%)	0
	Uncommon	Hypomagnesaemia	10 (<1%)	0	0
	Not known	Tumor lysis syndrome*	not known	not known	not known
Psychiatric disorders	Common	Insomnia	30 (3%)	0	0
Nervous system disorders	Very common	Dysgeusia[c]	254 (22%)	1 (<1%)	0
		Headache	122 (11%)	11 (<1%)	0
	Common	Dizziness	55 (5%)	3 (<1%)	1 (<1%)
		Lethargy	30 (3%)	3 (<1%)	0
		Paresthesia	20 (2%)	2 (<1%)	0
		Peripheral sensory neuropathy	17 (1%)	0	0

	Uncommon	Hypoesthesia	8 (<1%)	0	0
		Transient ischemic attack	7 (<1%)	4 (<1%)	0
		Somnolence	3 (<1%)	1 (<1%)	0
		Cerebrovascular accident	2 (<1%)	1 (<1%)	1 (<1%)
		Ischemic stroke	2 (<1%)	0	1 (<1%)
	Rare	Posterior reversible encephalopathy / reversible posterior leukoencephalopathy syndrome†	not known	not known	not known
Eye disorders	Common	Vision blurred	19 (2%)	1 (<1%)	0
	Uncommon	Retinal detachment†	1 (<1%)	1 (<1%)	0
		Retinal tear†	1 (<1%)	1 (<1%)	0
		Eyelash discoloration	4 (<1%)	0	0
Cardiac disorders	Uncommon	Bradycardia	6 (<1%)	0	0
		Myocardial infarction	5 (<1%)	1 (<1%)	4 (<1%)
		Cardiac dysfunction[f]	4 (<1%)	1 (<1%)	0
		Myocardial ischemia	3 (<1%)	1 (<1%)	0
Vascular disorders	Very common	Hypertension	473 (41%)	115 (10%)	1 (<1%)
	Common	Hot flush	16 (1%)	0	0
		Venous thromboembolic event[g]	13 (1%)	6 (<1%)	7 (<1%)
		Flushing	12 (1%)	0	0
	Uncommon	Hypertensive crisis	6 (<1%)	0	2 (<1%)
		Hemorrhage	1 (<1%)	0	0
	Not known	Aneurysms and artery dissections	not known	not known	not known
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	50 (4%)	1 (<1%)	0
		Dysphonia	48 (4%)	0	0
		Dyspnea	42 (4%)	8 (<1%)	1 (<1%)
		Hemoptysis	15 (1%)	1 (<1%)	0
	Uncommon	Rhinorrhea	8 (<1%)	0	0
		Pulmonary hemorrhage	2 (<1%)	0	0
		Pneumothorax	1 (<1%)	0	0
	Rare	Interstitial lung disease/pneumonitis†	not known	not known	not known

Gastrointestinal disorders	Very common	Diarrhea	614 (53%)	65 (6%)	2 (<1%)
		Nausea	386 (34%)	14 (1%)	0
		Vomiting	225 (20%)	18 (2%)	1 (<1%)
		Abdominal pain[a]	139 (12%)	15 (1%)	0
	Common	Stomatitis	96 (8%)	4 (<1%)	0
		Dyspepsia	83 (7%)	2 (<1%)	0
		Flatulence	43 (4%)	0	0
		Abdominal distension	36 (3%)	2 (<1%)	0
		Mouth ulceration	28 (2%)	3 (<1%)	0
		Dry mouth	27 (2%)	0	0
	Uncommon	Pancreatitis	8 (<1%)	4 (<1%)	0
		Rectal hemorrhage	8 (<1%)	2 (<1%)	0
		Hematochezia	6 (<1%)	0	0
		Gastrointestinal hemorrhage	4 (<1%)	2 (<1%)	0
		Melaena	4 (<1%)	1(<1%)	0
		Frequent bowel movements	3 (<1%)	0	0
		Anal hemorrhage	2 (<1%)	0	0
		Large intestine perforation	2 (<1%)	1 (<1%)	0
		Mouth hemorrhage	2 (<1%)	0	0
		Upper gastrointestinal hemorrhage	2 (<1%)	1 (<1%)	0
		Enterocutaneous fistula	1 (<1%)	0	0
		Haematemesis	1 (<1%)	0	0
		Hemorrhoidal hemorrhage	1 (<1%)	0	0
		Ileal perforation	1 (<1%)	0	1 (<1%)
		Esophageal hemorrhage	1 (<1%)	0	0
		Retroperitoneal hemorrhage	1 (<1%)	0	0
Hepatobiliary disorders	Common	Hyperbilirubinemia	38 (3%)	2 (<1%)	1 (<1%)
		Hepatic function abnormal	29 (3%)	13 (1%)	2 (<1%)
		Hepatotoxicity	18 (2%)	11(<1%)	2 (<1%)
	Uncommon	Jaundice	3 (<1%)	1 (<1%)	0

		Hepatic failure	1 (<1%)	0	1 (<1%)
		Drug induced liver injury	2 (<1%)	2 (<1%)	0
Skin and subcutaneous disorders	Very common	Hair color change	404 (35%)	1 (<1%)	0
		Palmar-plantar erythrodysesthesia syndrome	206 (18%)	39 (3%)	0
		Alopecia	130 (11%)	0	0
		Rash	129 (11%)	7 (<1%)	0
	Common	Skin hypopigmentation	52 (5%)	0	0
		Dry skin	50 (4%)	0	0
		Pruritus	29 (3%)	0	0
		Erythema	25 (2%)	0	0
		Skin depigmentation	20 (2%)	0	0
		Hyperhidrosis	17 (1%)	0	0
	Uncommon	Nail disorders	11 (<1%)	0	0
		Skin exfoliation	10 (<1%)	0	0
		Photosensitivity reaction	7 (<1%)	0	0
		Rash erythematous	6 (<1%)	0	0
		Skin disorder	5 (<1%)	0	0
		Rash macular	4 (<1%)	0	0
		Rash pruritic	3 (<1%)	0	0
		Rash vesicular	3 (<1%)	0	0
		Pruritus generalized	2 (<1%)	1 (<1%)	0
		Rash generalized	2 (<1%)	0	0
		Rash papular	2 (<1%)	0	0
		Plantar erythema	1 (<1%)	0	0
Musculoskeletal and connective tissue disorders	Common	Arthralgia	48 (4%)	8 (<1%)	0
		Myalgia	35 (3%)	2 (<1%)	0
		Muscle spasms	25 (2%)	0	0
	Uncommon	Musculoskeletal pain	9 (<1%)	1 (<1%)	0
Renal and urinary disorders	Very Common	Proteinuria	135 (12%)	32 (3%)	0
	Uncommon	Hemorrhage urinary tract	1 (<1%)	0	0
Reproductive system and breast	Uncommon	Menorrhagia	3 (<1%)	0	0
		Vaginal hemorrhage	3 (<1%)	0	0

disorders		Metrorrhagia	1 (<1%)	0	0
General disorders and administration site conditions	Very common	Fatigue	415 (36%)	65 (6%)	1 (<1%)
	Common	Mucosal inflammation	86 (7%)	5 (<1%)	0
		Asthenia	82 (7%)	20 (2%)	1 (<1%)
		Edema[b]	72 (6%)	1 (<1%)	0
		Chest pain	18 (2%)	2 (<1%)	0
	Uncommon	Chills	4 (<1%)	0	0
		Mucous membrane disorder	1 (<1%)	0	0
Investigations	Very common	Alanine aminotransferase increased	246 (21%)	84 (7%)	14 (1%)
		Aspartate aminotransferase increased	211 (18%)	51 (4%)	10 (<1%)
	Common	Weight decreased	96 (8%)	7 (<1%)	0
		Blood bilirubin increased	61 (5%)	6 (<1%)	1 (<1%)
		Blood creatinine increased	55 (5%)	3 (<1%)	0
		Lipase increased	51 (4%)	21 (2%)	7 (<1%)
		White blood cell count decreased[d]	51 (4%)	3 (<1%)	0
		Blood thyroid stimulating hormone increased	36 (3%)	0	0
		Amylase increased	35 (3%)	7 (<1%)	0
		Gamma-glutamyltransferase increased	31 (3%)	9 (<1%)	4 (<1%)
		Blood pressure increased	15 (1%)	2 (<1%)	0
		Blood urea increased	12 (1%)	1 (<1%)	0
		Liver function test abnormal	12 (1%)	6 (<1%)	1 (<1%)
	Uncommon	Hepatic enzyme increased	11 (<1%)	4 (<1%)	3 (<1%)
		Blood glucose decreased	7 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolonged	7 (<1%)	2 (<1%)	0

		Transaminase increased	7 (<1%)	1 (<1%)	0
		Thyroid function test abnormal	3 (<1%)	0	0
		Blood pressure diastolic increased	2 (<1%)	0	0
		Blood pressure systolic increased	1 (<1%)	0	0

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).
*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.
The following terms have been combined:
[a] Abdominal pain, abdominal pain upper and abdominal pain lower
[b] Edema, edema peripheral, eye edema, localized edema and face edema
[c] Dysgeusia, ageusia and hypogeusia
[d] White cell count decreased, neutrophil count decreased and leukocyte count decreased
[e] Decreased appetite and anorexia
[f] Cardiac dysfunction, left ventricular dysfunction, cardiac failure and restrictive cardiomyopathy
[g] Venous thromboembolic event, deep vein thrombosis, pulmonary embolism and thrombosis

Neutropenia, thrombocytopenia and palmar-plantar erythrodysesthesia syndrome were observed more frequently in patients of East Asian descent.

Treatment-related adverse reactions reported in STS studies (n=382) or during post-marketing period

Infections and infestations
Common: Gingival infection

Neoplasms benign and malignant (incl. cysts and polyps)
Very common: Tumor pain

Blood and lymphatic system disorders[f]
Very common: Leukopenia, thrombocytopenia, neutropenia
Uncommon: Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome)

Endocrine disorders
Common: Hypothyroidism

Metabolism and nutrition disorders
Very common: Hypoalbuminemia, decreased appetite
Common: Dehydration
Uncommon: Hypomagnesaemia
Not known: Tumor lysis syndrome*

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Very common: Dysgeusia[c], headache
Common: Peripheral sensory neuropathy, dizziness
Uncommon: Somnolence, cerebral infarction, paresthesia

Eye disorders
Common: Vision blurred

Cardiac disorders
Common: Cardiac dysfunction[g], left ventricular dysfunction, bradycardia
Uncommon: Myocardial infarction

Vascular disorders
Very common: Hypertension,
Common: Venous thromboembolic event, hot flush, flushing
Uncommon: Hemorrhage
Not known: Aneurysms and artery dissections

Respiratory, thoracic and mediastinal disorders
Common: Epistaxis, dysphonia, dyspnea, cough, pneumothorax, hiccups, pulmonary hemorrhage
Uncommon: Oropharyngeal pain, bronchial hemorrhage, rhinorrhea, hemoptysis
Rare: Interstitial lung disease/pneumonitis††

Gastrointestinal disorders
Very common: Diarrhea, nausea, vomiting, abdominal pain[a], stomatitis
Common: Abdominal distension, dry mouth, dyspepsia, mouth hemorrhage, flatulence, anal hemorrhage
Uncommon: Gastrointestinal hemorrhage, rectal hemorrhage, enterocutaneous fistula, gastric hemorrhage, melena, esophageal hemorrhage, peritonitis, retroperitoneal hemorrhage, upper gastrointestinal hemorrhage, ileal perforation

Hepatobiliary disorders
Uncommon: Hepatic function abnormal
Not known: Hepatic failure*

Skin and subcutaneous disorders
Very common: Hair color change, skin hypopigmentation, exfoliative rash
Common: Alopecia, skin disorder[c], dry skin, nail disorder, pruritus, erythema, hyperhidrosis
Uncommon: Skin ulcer, blister, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, rash papular, rash

Musculoskeletal and connective tissue disorders
Common: Musculoskeletal pain, myalgia, muscle spasms
Uncommon: Arthralgia

Renal and urinary disorders
Uncommon: Proteinuria

Reproductive system and breast disorder
Uncommon: Vaginal hemorrhage, menorrhagia

General disorders and administration site conditions
Very common: Fatigue
Common: Edema[b], chest pain, chills
Uncommon: Mucosal inflammation[e], asthenia

Investigations[h]
Very common: Weight decreased
Common: Ear, nose and throat examination abnormal[e], alanine aminotransferase increased, blood cholesterol abnormal, aspartate aminotransferase increased, gamma glutamyltransferase increased
Uncommon: Blood bilirubin increased, aspartate aminotransferase, alanine aminotransferase, platelet count decreased, electrocardiogram QT prolonged

Tabulated list of adverse reactions:

Table 2. Treatment-related adverse reactions reported in STS studies (n=382) or during post-marketing period

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 and malignant (incl. cysts and polyps)	Very common	Tumor pain	121 (32%)	32 (8%)	0
Blood and lymphatic system disorders[f]	Very common	Leukopenia	106 (44%)	3 (1%)	0
		Thrombocytopenia	86 (36%)	7 (3%)	2 (<1%)
		Neutropenia	79 (33%)	10 (4%)	0
	Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome)	1 (<1%)	1 (<1%)	0
Endocrine disorders	Common	Hypothyroidism	18 (5%)	0	0
Metabolism and nutrition disorders	Very common	Decreased appetite	108 (28%)	12 (3%)	0
		Hypoalbuminemia[f]	81 (34%)	2 (<1%)	0
	Common	Dehydration	4 (1%)	2 (1%)	0
	Uncommon	Hypomagnesaemia	1 (<1%)	0	0
	Not known	Tumor lysis syndrome*	not known	not known	not known
Psychiatric	Common	Insomnia	5 (1%)	1 (<1%)	0

disorders					
Nervous system disorders	Very common	Dysgeusia[c]	79 (21%)	0	0
		Headache	54 (14%)	2 (<1%)	0
	Common	Peripheral sensory neuropathy	30 (8%)	1 (<1%)	0
		Dizziness	15 (4%)	0	0
	Uncommon	Somnolence	3 (<1%)	0	0
		Paresthesia	1 (<1%)	0	0
		Cerebral infarction	1 (<1%)	0	1 (<1%)
Eye disorders	Common	Vision blurred	15 (4%)	0	0
Cardiac disorders	Common	Cardiac dysfunction[g]	21 (5%)	3 (<1%)	1 (<1%)
		Left ventricular dysfunction	13 (3%)	3 (<1%)	0
		Bradycardia	4 (1%)	0	0
	Uncommon	Myocardial infarction	1 (<1%)	0	0
Vascular disorders	Very common	Hypertension	152 (40%)	26 (7%)	0
	Common	Venous thromboembolic event[d]	13 (3%)	4 (1%)	5 (1%)
		Hot flush	12 (3%)	0	0
		Flushing	4 (1%)	0	0
	Uncommon	Hemorrhage	2 (<1%)	1 (<1%)	0
	Rare	Aneurysms and artery dissections	not known	not known	not known
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	22 (6%)	0	0
		Dysphonia	20 (5%)	0	0
		Dyspnea	14 (4%)	3 (<1%)	0
		Cough	12 (3%)	0	0
		Pneumothorax	7 (2%)	2 (<1%)	1 (<1%)
		Hiccups	4 (1%)	0	0
		Pulmonary hemorrhage	4 (1%)	1 (<1%)	0
	Uncommon	Oropharyngeal pain	3 (<1%)	0	0
		Bronchial hemorrhage	2 (<1%)	0	0
		Rhinorrhea	1 (<1%)	0	0
		Hemoptysis	1 (<1%)	0	0
	Rare	Interstitial lung disease/pneumonitis†	not known	not known	not known
Gastrointestinal disorders	Very common	Diarrhea	174 (46%)	17 (4%)	0
		Nausea	167 (44%)	8 (2%)	0

		Vomiting	96 (25%)	7 (2%)	0
		Abdominal pain[a]	55 (14%)	4 (1%)	0
		Stomatitis	41 (11%)	1 (<1%)	0
	Common	Abdominal distension	16 (4%)	2 (1%)	0
		Dry mouth	14 (4%)	0	0
		Dyspepsia	12 (3%)	0	0
		Mouth hemorrhage	5 (1%)	0	0
		Flatulence	5 (1%)	0	0
		Anal hemorrhage	4 (1%)	0	0
	Uncommon	Gastrointestinal hemorrhage	2 (<1%)	0	0
		Rectal hemorrhage	2 (<1%)	0	0
		Enterocutaneous fistula	1 (<1%)	1 (<1%)	0
		Gastric hemorrhage	1 (<1%)	0	0
		Melaena	2 (<1%)	0	0
		Esophageal hemorrhage	1 (<1%)	0	1 (<1%)
		Peritonitis	1 (<1%)	0	0
		Retroperitoneal hemorrhage	1 (<1%)	0	0
		Upper gastrointestinal hemorrhage	1 (<1%)	1 (<1%)	0
		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 color change	93 (24%)	0	0
		Skin hypopigmentation	80 (21%)	0	0
		Exfoliative rash	52 (14%)	2 (<1%)	0
	Common	Alopecia	30 (8%)	0	0
		Skin disorder[c]	26 (7%)	4 (1%)	0
		Dry skin	21 (5%)	0	0
		Hyperhidrosis	18 (5%)	0	0
		Nail disorder	13 (3%)	0	0
		Pruritus	11 (3%)	0	0
		Erythema	4 (1%)	0	0
	Uncommon	Skin ulcer	3 (<1%)	1 (<1%)	0
		Rash	1 (<1%)	0	0
		Rash papular	1 (<1%)	0	0
		Photosensitivity	1 (<1%)	0	0

		reaction			
		Palmar-plantar erythrodysesthesia syndrome	2 (<1%)	0	0
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain	35 (9%)	2 (<1%)	0
		Myalgia	28 (7%)	2 (<1%)	0
		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 hemorrhage	3 (<1%)	0	0
		Menorrhagia	1 (<1%)	0	0
General disorders and administration site conditions	Very common	Fatigue	178 (47%)	34 (9%)	1 (<1%)
	Common	Edema[b]	18 (5%)	1 (<1%)	0
		Chest pain	12 (3%)	4 (1%)	0
		Chills	10 (3%)	0	0
	Uncommon	Mucosal inflammation[e]	1 (<1%)	0	0
		Asthenia	1 (<1%	0	0
Investigations[h]	Very common	Weight decreased	86 (23%)	5 (1%)	0
	Common	Ear, nose and throat examination abnormal[e]	29 (8%)	4 (1%)	0
		Alanine aminotransferase increased	8 (2%)	4 (1%)	2 (<1%)
		Blood cholesterol abnormal	6 (2%)	0	0
		Aspartate aminotransferase increased	5 (1%)	2 (<1%)	2 (<1%)
		Gamma glutamyltransferase increased	4 (1%)	0	3 (<1%)
	Uncommon	Blood bilirubin increased	2 (<1%)	0	0
		Aspartate aminotransferase	2 (<1%)	0	2 (<1%)
		Alanine aminotransferase	1 (<1%)	0	1 (<1%)
		Platelet count decreased	1 (<1%)	0	1 (<1%)
		Electrocardiogram QT	2 (<1%)	1 (<1%)	0

		prolonged			

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).
*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.
The following terms have been combined:
[a] Abdominal pain, abdominal pain upper and gastrointestinal pain
[b] Edema, edema peripheral and eyelid edema
[c] The majority of these cases were Palmar-plantar erythrodysesthesia syndrome
[d] Venous thromboembolic events – includes Deep vein thrombosis, Pulmonary embolism and Thrombosis terms
[e] The majority of these cases describe mucositis
[f] Frequency is based on laboratory value tables from VEG110727 (N=240). These were reported as adverse events less frequently by investigators than as indicated by laboratory value tables.
[g] Cardiac dysfunction events – includes Left ventricular dysfunction, Cardiac failure and Restrictive cardiomyopathy
[h] Frequency is based on adverse events reported by investigators. Laboratory abnormalities were reported as adverse events less frequently by investigators than as indicated by laboratory value tables.

Neutropenia, thrombocytopenia and palmar-plantar erythrodysesthesia syndrome were observed more frequently in patients of East Asian descent.

Pediatric population
The safety profile in pediatric patients was similar to that reported with pazopanib in adults in the approved indications based on data from 44 pediatric patients from Phase I study ADVL0815 and 57 pediatric patients from Phase II study PZP034X2203 (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99)

4.9 Overdose
Pazopanib doses up to 2000 mg have been evaluated in clinical studies. Grade 3 fatigue (dose-limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2000 mg and 1000 mg daily, respectively.

Treatment
There is no specific antidote for overdose with pazopanib and treatment of overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic and immunomodulatory agents, protein-kinase inhibitors; other protein kinase inhibitors.
ATC code: L01EX03

Mechanism of action
Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR) -α and –β, and stem cell factor receptor (c-KIT), with IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose-dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR-β receptors in cells. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in various animal models, and the growth of multiple human tumor xenografts in mice.

Pharmacogenomics
In a pharmacogenetic meta-analysis of data from 31 clinical studies of pazopanib administered either as monotherapy or in combination with other agents, ALT >5 x ULN (NCI CTC Grade 3) occurred in 19% of HLA-B*57:01 allele carriers and in 10% of non-carriers. In this dataset, 133/2235 (6%) of the patients carried the HLA-B*57:01 allele (see section 4.4).

Clinical studies
Renal cell carcinoma (RCC)
The safety and efficacy of pazopanib in renal carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multicenter study. Patients (N = 435) with locally advanced and/or metastatic RCC were randomized to receive pazopanib 800 mg once daily or placebo. The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS) and the principle secondary endpoint was overall survival (OS). The other objectives were to evaluate the overall response rate and duration of response.

From the total of 435 patients in this study, 233 patients were treatment-naive and 202 were second-line patients who had received one prior IL-2 or INFα-based therapy. The performance status (ECOG) was similar between the pazopanib and placebo groups (ECOG 0: 42% vs. 41%, ECOG 1: 58% vs. 59%). The majority of patients had either favorable (39%) or intermediate (54%), MSKCC (Memorial Sloan Kettering Cancer Centre) / Motzer prognostic factors. All patients had clear cell histology or predominantly clear cell histology. Approximately half of all patients had 3 or more organs involved in their disease and most patients had the lung (74%), and/or lymph nodes (54%) as a metastatic location for disease at baseline.

A similar proportion of patients in each arm were treatment-naive and cytokine pre-treated (53% and 47% in pazopanib arm, 54% and 46% in placebo arm). In the cytokine pre-treated subgroup, the majority (75%) had received interferon-based treatment.

Similar proportions of patients in each arm had prior nephrectomy (89% and 88% in the pazopanib and placebo arms, respectively) and/or prior radiotherapy (22% and 15% in the pazopanib and placebo arms, respectively).

The primary analysis of the primary endpoint PFS is based on disease assessment by independent radiological review in the entire study population (treatment-naive and cytokine pre-treated).

Table 3. Overall efficacy results in RCC by independent assessment (VEG105192)

Endpoints/Study population	Pazopanib	Placebo	HR (95% CI)	P value (one-sided)
PFS				
Overall* ITT	N = 290	N = 145		
Median (months)	9.2	4.2	0.46 (0.34, 0.62)	<0.0000001
Response rate % (95% CI)	N = 290 30 (25.1,35.6)	N = 145 3 (0.5, 6.4)	–	<0.001
HR = hazard ratio; ITT = intent to treat; PFS = progression-free survival. * - treatment-naive and cytokine pre-treated populations, CI = Confidence Interval				

Figure 1. Kaplan-Meier curve for progression-free survival by independent assessment for the overall population (treatment-naive and cytokine pre-treated populations) (VEG105192)

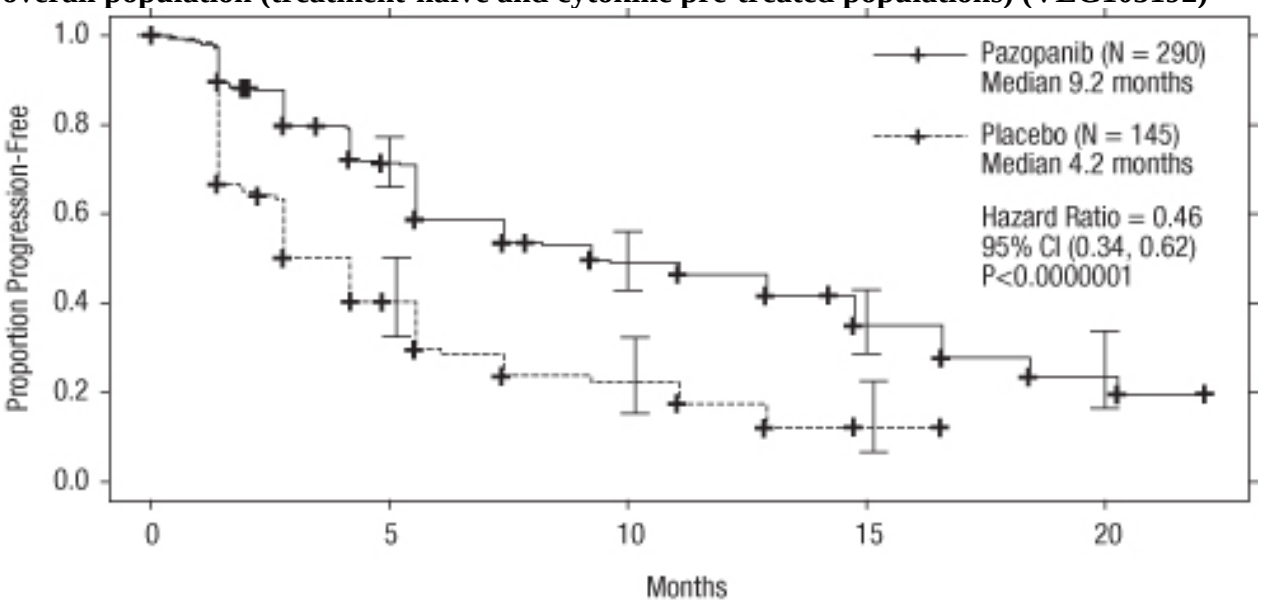


Figure 2. Kaplan-Meier curve for progression-free survival by independent assessment for the treatment-naive population (VEG105192)

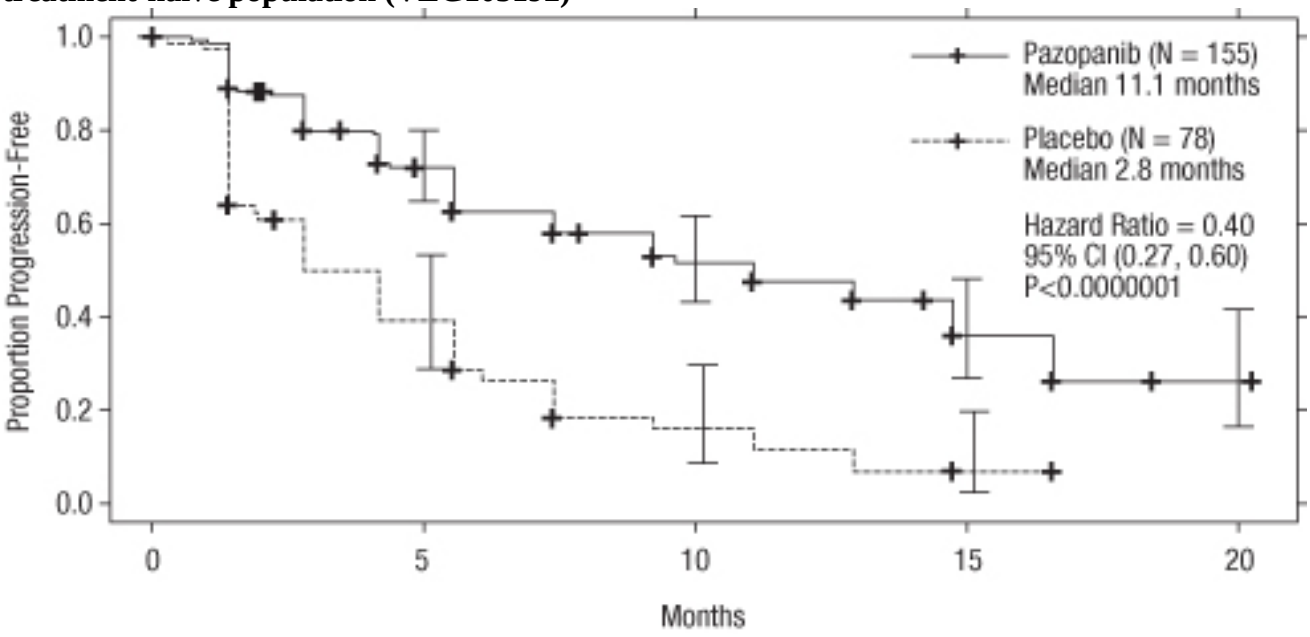
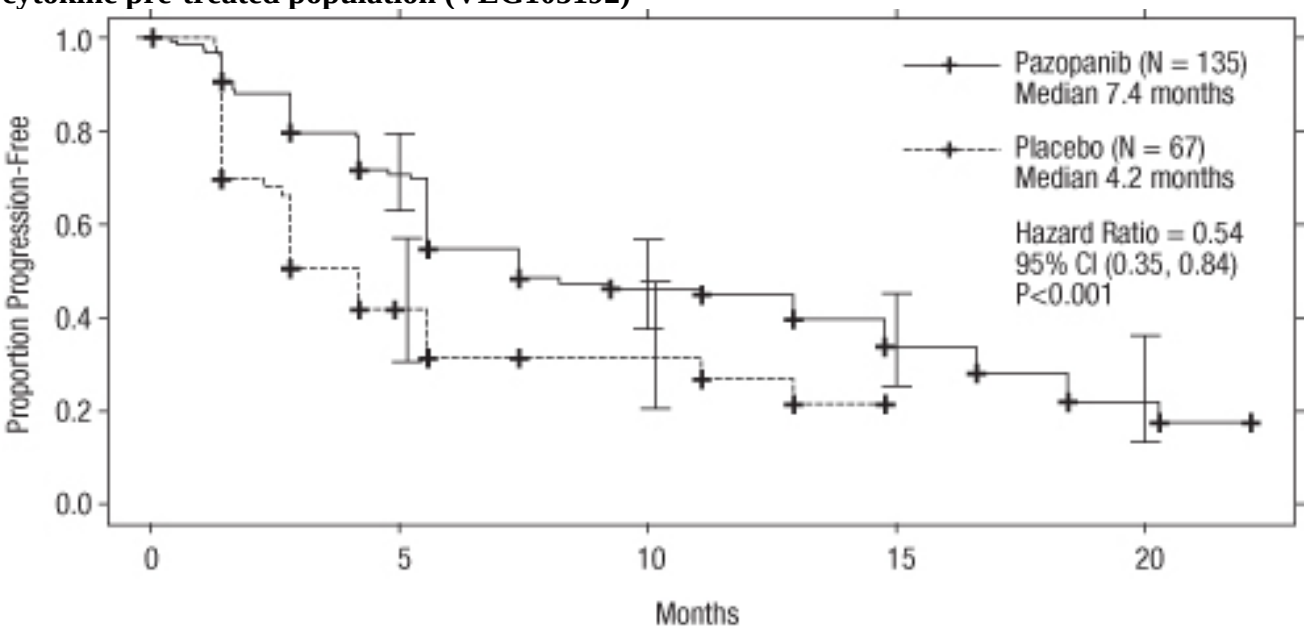


Figure 3. Kaplan-Meier Curve for progression-free survival by independent assessment for the cytokine pre-treated population (VEG105192)



For patients who responded to treatment, the median time to response was 11.9 weeks and the median duration of response was 58.7 weeks as per independent review (VEG105192).

The median overall survival (OS) data at the protocol-specified final survival analysis were 22.9 months and 20.5 months [HR = 0.91 (95% CI: 0.71, 1.16; p = 0.224)] for patients randomized to the pazopanib and placebo arms, respectively. The OS results are subject to potential bias as 54% of patients in the placebo arm also received pazopanib in the extension part of this study following

disease progression. Sixty-six (66%) percent of placebo patients received post-study therapy compared to 30% of pazopanib patients.

No statistical differences were observed between treatment groups for Global Quality of Life using EORTC QLQ-C30 and EuroQoL EQ-5D.

In a Phase II study of 225 patients with locally recurrent or metastatic clear cell renal cell carcinoma, objective response rate was 35% and median duration of response was 68 weeks, as per independent review. Median PFS was 11.9 months.

The safety, efficacy and quality of life of pazopanib versus sunitinib was evaluated in a randomized, open-label, parallel group Phase III non-inferiority study (VEG108844).

In VEG108844, patients (N = 1110) with locally advanced and/or metastatic RCC who had not received prior systemic therapy, were randomized to receive either pazopanib 800 mg once daily continuously or sunitinib 50 mg once daily in 6-week cycles of dosing with 4 weeks on treatment followed by 2 weeks without treatment.

The primary objective of this study was to evaluate and compare PFS in patients treated with pazopanib to those treated with sunitinib. Demographic characteristics were similar between the treatment arms. Disease characteristics at initial diagnosis and at screening were balanced between the treatment arms with the majority of patients having clear cell histology and Stage IV disease.

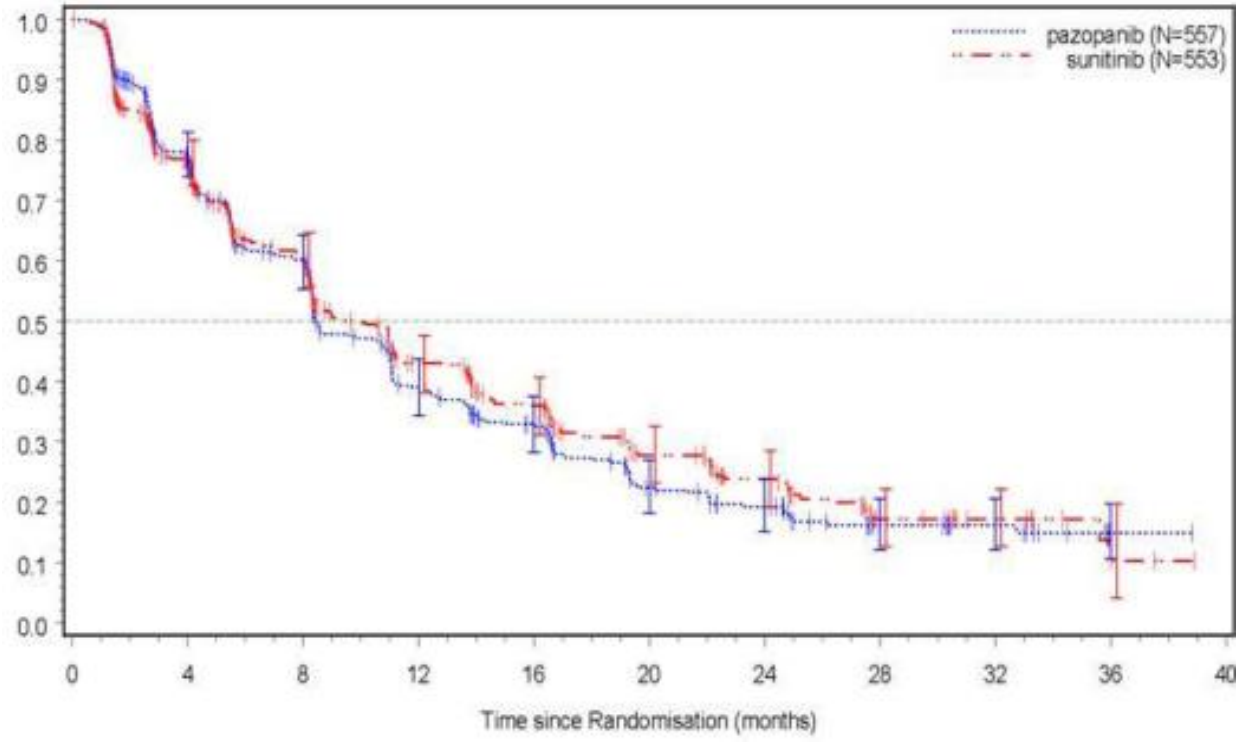
VEG108844 achieved its primary endpoint of PFS and demonstrated that pazopanib was non-inferior to sunitinib, as the upper bound of the 95% CI for the hazard ratio was less than the protocol-specified non-inferiority margin of 1.25. Overall efficacy results are summarized in Table 4.

Table 4. Overall efficacy results (VEG108844)

Endpoint	Pazopanib N = 557	Sunitinib N = 553	HR (95% CI)
PFS			
Overall			
Median (months) (95% CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.0)	1.047 (0.898, 1.220)
Overall Survival Median (months) (95% CI)	 28.3 (26.0, 35.5)	 29.1 (25.4, 33.1)	 0.915[a] (0.786, 1.065)

HR = hazard ratio; PFS = progression-free survival based on independent review committee (IRC) evaluation; CI = Confidence Interval; [a] *P* value = 0.245 (2-sided)

Figure 4. Kaplan-Meier curve for progression-free survival by independent assessment for the overall population (VEG108844)



Subgroup analyses of PFS were performed for 20 demographic and prognostic factors. The 95% confidence intervals for all subgroups include a hazard ratio of 1. In the three smallest of these 20 subgroups, the point estimate of the hazard ratio exceeded 1.25; i.e. in subjects with no prior nephrectomy (n=186, HR=1.403, 95% CI [0.955, 2.061]), baseline LDH>1.5 x ULN (n=68, HR=1.72, 95% CI [0.943, 3.139]), and MSKCC: poor risk (n=119, HR=1.472, 95% CI [0.937, 2.313]).

Soft-tissue sarcoma (STS)

The efficacy and safety of pazopanib in STS were evaluated in a pivotal Phase III randomized, double-blind, placebo-controlled multicenter study (VEG110727). A total of 369 patients with advanced STS were randomized to receive pazopanib 800 mg once daily or placebo. Importantly, only patients with selective histological subtypes of STS were allowed to participate to the study, therefore efficacy and safety of pazopanib can only be considered established for those subgroups of STS and treatment with pazopanib should be restricted to such STS subtypes.

The following tumor types were eligible:

Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumors), so-called fibrohistiocytic (pleomorphic malignant fibrous histiocytoma [MFH], giant cell MFH also known as undifferentiated pleomorphic sarcoma [UPS], inflammatory MFH), leiomyosarcoma, malignant glomus tumors, skeletal muscles (pleomorphic and alveolar rhabdomyosarcoma), vascular (epithelioid hemangioendothelioma, angiosarcoma), uncertain differentiation (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma), malignant peripheral

nerve sheath tumors, undifferentiated soft tissue sarcomas not otherwise specified (NOS) and other types of sarcoma (not listed as ineligible).

The following tumor types were not eligible:
Adipocytic sarcoma (all subtypes), all rhabdomyosarcoma that were not alveolar or pleomorphic, chondrosarcoma, osteosarcoma, Ewing tumors/primitive neuroectodermal tumors (PNET), GIST, dermofibromatosis sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumors of the uterus.

Of note, patients with adipocytic sarcoma were excluded from the pivotal Phase III study as in a preliminary Phase II study (VEG20002) activity (PFS at week 12) observed with pazopanib in adipocytic did not meet the prerequisite rate to allow further clinical testing.

Other key eligibility criteria of the VEG110727 study were: histological evidence of high or intermediate grade malignant STS and disease progression within 6 months of therapy for metastatic disease, or recurrence within 12 months of (neo)-/adjuvant therapy.

Ninety-eight percent (98%) of subjects received prior doxorubicin, 70% prior ifosfamide, and 65% of subjects had received at least three or more chemotherapeutic agents prior to study enrolment.

Patients were stratified by the factors of WHO performance status (WHO PS) (0 or 1) at baseline and the number of lines of prior systemic therapy for advanced disease (0 or 1 vs. 2+). In each treatment group, there was a slightly greater percentage of subjects in the 2+ lines of prior systemic therapy for advanced disease (58% and 55%, respectively, for placebo and pazopanib treatment arms) compared with 0 or 1 lines of prior systemic therapy (42% and 45%, respectively, for placebo and pazopanib treatment arms). The median duration of follow-up of subjects (defined as date of randomization to date of last contact or death) was similar for both treatment arms (9.36 months for placebo [range 0.69 to 23.0 months] and 10.04 months for pazopanib [range 0.2 to 24.3 months]).

The primary objective of the study was progression-free survival (PFS assessed by independent radiological review); the secondary endpoints included overall survival (OS), overall response rate and duration of response.

Table 5. Overall efficacy results in STS by independent assessment (VEG110727)

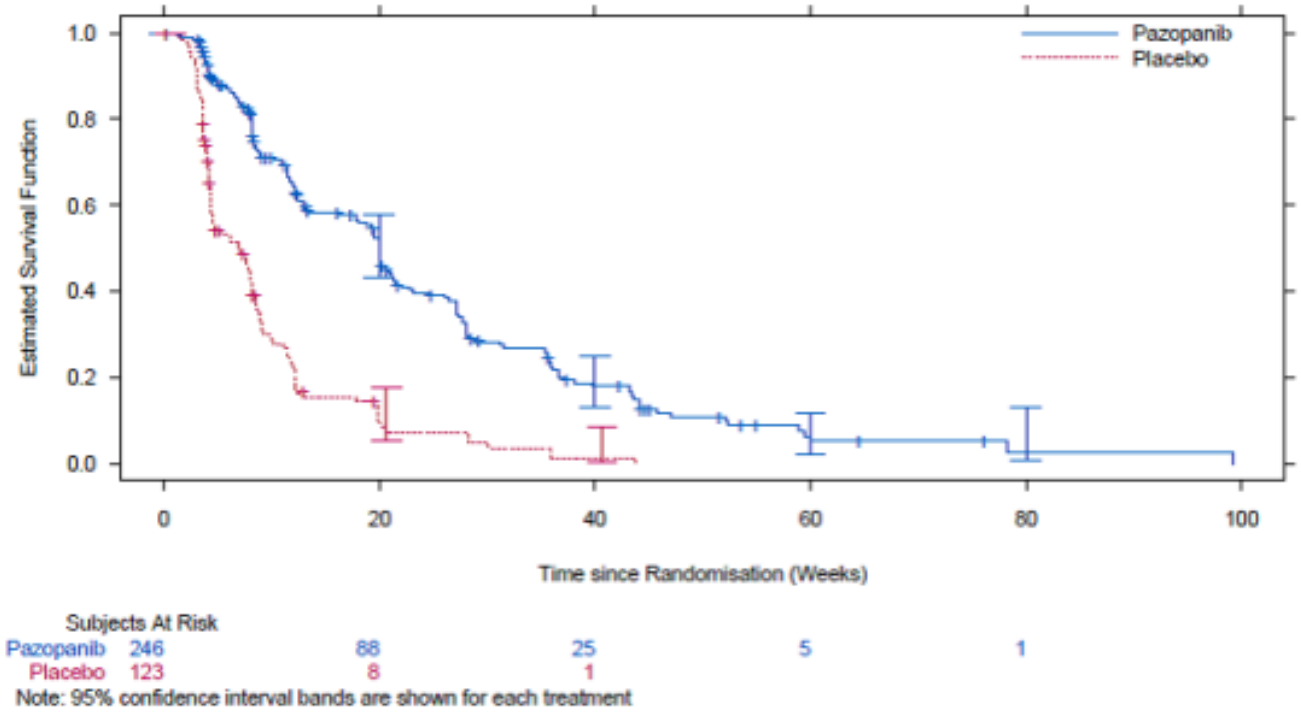
Endpoints / study population	Pazopanib	Placebo	HR (95% CI)	P value (two-sided)
PFS				
Overall ITT	N = 246	N = 123		
Median (weeks)	20.0	7.0	0.35 (0.26, 0.48)	<0.001
Leiomyosarcoma	N = 109	N = 49		
Median (weeks)	20.1	8.1	0.37 (0.23, 0.60)	<0.001
Synovial sarcoma subgroups	N = 25	N = 13		
Median (weeks)	17.9	4.1	0.43 (0.19, 0.98)	0.005
'Other STS' subgroups	N = 112	N = 61		
Median (weeks)	20.1	4.3	0.39 (0.25, 0.60)	<0.001
OS				

Overall ITT	N = 246	N = 123		
Median (months)	12.6	10.7	0.87 (0.67, 1.12)	0.256
Leiomyosarcoma*	N = 109	N = 49		
Median (months)	16.7	14.1	0.84 (0.56, 1.26)	0.363
Synovial sarcoma subgroups*	N = 25	N = 13		
Median (months)	8.7	21.6	1.62 (0.79, 3.33)	0.115
"Other STS" subgroups*	N = 112	N = 61		
Median (months)	10.3	9.5	0.84 (0.59, 1.21)	0.325
Response rate (CR+PR)				
% (95% CI)	4 (2.3, 7.9)	0 (0.0, 3.0)		
Duration of response				
Median (weeks) (95% CI)	38.9 (16.7, 40.0)			

HR = hazard ratio; ITT = intent to treat; PFS = progression-free survival; CR = complete response; PR = partial response.
CI = confidence interval; OS = overall survival
* Overall survival for the respective STS histological subgroups (leiomyosarcoma, synovial sarcoma and "Other" STS) should be interpreted with caution due to the small number of subjects and wide confidence intervals

A similar improvement in PFS based on investigator assessments was observed in the pazopanib arm compared with the placebo arm (in the overall ITT population HR: 0.39; 95% CI, 0.30 to 0.52, p <0.001).

Figure 5. Kaplan-Meier Curve for Progression-Free Survival in STS by Independent Assessment for the Overall Population (VEG110727)



No significant difference in OS was observed between the two treatment arms at the final OS analysis performed after 76% (280/369) of the events had occurred (HR 0.87, 95% CI 0.67, 1.12 p=0.256).

Pediatric population
A Phase I study (ADVL0815) of pazopanib was conducted in 44 pediatric patients with various recurrent or refractory solid tumors. The primary objective was to investigate the maximum tolerated dose (MTD), the safety profile and the pharmacokinetic properties of pazopanib in children. The median duration of exposure in this study was 3 months (1-23 months).

A Phase II study (PZP034X2203) of pazopanib was conducted in 57 pediatric patients with refractory solid tumors including rhabdomyosarcoma (N=12), non-rhabdomyosarcoma soft tissue sarcoma (N=11), Ewing sarcoma/pPNET (N=10), osteosarcoma (N=10), neuroblastoma (N=8) and hepatoblastoma (N=6). The study was a single-agent, non-controlled, open-label study to determine the therapeutic activity of pazopanib in children and adolescents aged 1 to <18years of age. Pazopanib was administered daily as a tablet at a dose of 450 mg/m^2/dose or as an oral suspension at 225 mg/m^2/dose. The maximum daily dose permitted was 800 mg for the tablet and 400 mg for the oral suspension. The median duration of exposure was 1.8 months (1 day-29 months).

Results of this study did not show any meaningful anti-tumor activity in the respective pediatric population. Pazopanib is therefore not recommended for treatment of these tumors in the pediatric population (see section 4.2 for information on pediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with pazopanib in all subsets of the pediatric population in treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumor of the kidney) (see section 4.2 for information on pediatric use).

5.2 Pharmacokinetic properties

General properties
Absorption:
Upon oral administration of a single pazopanib 800 mg dose to patients with solid tumors, maximum plasma concentration (C_{max}) of approximately 19 ± 13 microgram/mL was obtained after median 3.5 hours (range 1.0-11.9 hours) and an $AUC_{0-\infty}$ of approximately 650 ± 500 microgram.hour/mL was obtained. Daily dosing results in 1.23- to 4-fold increase in AUC_{0-T}.

There was no consistent increase in AUC or C_{max} at pazopanib doses above 800 mg.

Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least two hours after food or at least one hour before food (see section 4.2).

Administration of a pazopanib 400 mg crushed tablet increased $AUC_{(0-72)}$ by 46% and C_{max} by approximately 2-fold and decreased t_{max} by approximately 2 hours compared to administration of the

whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet (see section 4.2).

Distribution
Binding of pazopanib to human plasma protein *in vivo* was greater than 99% with no concentration dependence over the range of 10-100 microgram/mL. *In vitro* studies suggest that pazopanib is a substrate for P-gp and BCRP.

Biotransformation
Results from *in vitro* studies demonstrated that metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. The four principle pazopanib metabolites account for only 6% of the exposure in plasma. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a similar potency to that of pazopanib, the others are 10- to 20-fold less active. Therefore, activity of pazopanib is mainly dependent on parent pazopanib exposure.

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

Characteristics in patients
Renal impairment
Results indicate that less than 4% of an orally administered pazopanib dose is excreted in the urine as pazopanib and metabolites. Results from population pharmacokinetic modelling (data from subjects with baseline CLCR values ranging from 30.8 mL/min to 150 mL/min) indicated that renal impairment is unlikely to have clinically relevant effect on pazopanib pharmacokinetics. No dose adjustment is required in patients with creatinine clearance above 30 mL/min. Caution is advised in patients with creatinine clearance below 30 mL/min as there is no experience of pazopanib in this patient population (see section 4.2).

Hepatic impairment
Mild: The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild abnormalities in hepatic parameters (defined as either normal bilirubin and any degree of ALT elevation or as an elevation of bilirubin up to 1.5 x ULN regardless of the ALT value) after administration of 800 mg once daily are similar to the median in patients with normal hepatic function (see Table 4). 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities of serum liver tests (see section 4.2).

Moderate: The maximally tolerated pazopanib dose (MTD) in patients with moderate hepatic impairment (defined as an elevation of bilirubin >1.5 x to 3 x ULN regardless of the ALT values) was 200 mg once daily. The median steady-state C_{max} and $AUC_{(0-24)}$ values after administration of 200 mg pazopanib once daily in patients with moderate hepatic impairment were approximately 44% and 39%, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function, respectively (see Table 7).

Based on safety and tolerability data, the dose of pazopanib should be reduced to 200 mg once daily in subjects with moderate hepatic impairment (see section 4.2).

Severe: The median steady-state C_{max} and $AUC_{(0-24)}$ values after administration of 200 mg pazopanib once daily in patients with severe hepatic impairment were approximately 18% and 15%, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function. Based on the diminished exposure and limited hepatic reserve pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin >3 X ULN regardless of any level of ALT) (see section 4.2).

Table 6. Median steady-state pazopanib pharmacokinetics measured in subjects with hepatic impairment.

Group	Investigated dose	C_{max} (microgram/mL)	$AUC_{(0-24)}$ (microgram x hour/mL)	Recommended dose
Normal Hepatic Function	800 mg OD	52.0 (17.1-85.7)	888.2 (345.5-1482)	800 mg OD
Mild Hepatic Impairment	800 mg OD	33.5 (11.3-104.2)	774.2 (214.7-2034.4)	800 mg OD
Moderate Hepatic Impairment	200 mg OD	22.2 (4.2-32.9)	256.8 (65.7-487.7)	200 mg OD
Severe Hepatic Impairment	200 mg OD	9.4 (2.4-24.3)	130.6 (46.9-473.2)	Not recommended
OD – once daily				

Pediatric population
Upon administration of pazopanib 225 mg/m^2 (as oral suspension) in pediatric patients, the pharmacokinetic parameters (C_{max}, T_{max} and AUC) were similar to those previously reported in adult patients treated with 800 mg pazopanib. Results indicated no marked difference in the clearance of pazopanib, normalized by body surface area, between children and adults.

5.3. Preclinical safety data

The preclinical safety profile of pazopanib was assessed in mice, rats, rabbits and monkeys. In repeat dose studies in rodents, effects in a variety of tissues (bone, teeth, nail beds, reproductive organs, hematological tissues, kidney and pancreas) appear related to the pharmacology of VEGFR inhibition and/or disruption of VEGF signaling pathways, with most effects occurring at plasma exposure levels below those observed in the clinic. Other observed effects include bodyweight loss, diarrhea and/or morbidity that were either secondary to local gastrointestinal effects caused by high local mucosal medicinal product exposure (monkeys) or pharmacological effects (rodents). Proliferative hepatic lesions (eosinophilic foci and adenoma) were seen in female mice at exposures 2.5 times human exposure based on AUC.

In juvenile toxicity studies, when pre-weaning rats were dosed from day 9 post-partum through to day 14 post-partum, 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 post-weaning rats were dosed from day 21 post-partum to day 62 post-partum, toxicological findings were similar to adult rats at comparable exposures. Human pediatric 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 remodeling 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) (see section 4.4).

Reproductive, fertility and teratogenic effects
Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures more than 300-fold lower than the human exposure (based on AUC). Effects included reduced female fertility, increased pre-and post-implantation loss, early resorptions, embryolethality, decreased fetal body weight and cardiovascular malformation. Decreased corpora lutea, increased cysts and ovarian atrophy have also been noted in rodents. In a rat male fertility study, there was no effect on mating or fertility, but decreased testicular and epididymal weights were noted with reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at exposures 0.3 times human exposure based on AUC.

Genotoxicity
Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat *in vivo* micronucleus). A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance in low amounts, was not mutagenic in the Ames assay but genotoxic in the mouse lymphoma assay and *in vivo* mouse micronucleus assay.

Carcinogenicity
In two-year carcinogenicity studies with pazopanib, there were increased numbers of liver adenomas noted in mice and duodenal adenocarcinomas noted in rats. Based on the rodent-specific pathogenesis and mechanism for these findings, they are not considered to represent an increased carcinogenic risk for patients taking pazopanib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet Core
Microcrystalline cellulose, Type 102
Sodium starch glycolate, Type A
Povidone, K30
Magnesium stearate

Film-coating material: Opadry White® YS-1-7706-G
Titanium Dioxide
Hypromellose 2910 (6 cps)
Hypromellose 2910 (3 cps)
Polyethylene glycol/Macrogol
Polysorbate 80

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at room temperature below 30°C.

6.5 Nature and contents of container
PVC/Aclar and Aluminum foil blister as primary packaging materials
In blister packs containing 60 film-coated tablets, with the patient leaflet, all in cardboard boxes.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.: 1
34303 Küçükçekmece /Istanbul -TURKEY

8. MARKETING AUTHORIZATION NUMBER

2021/501

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 09.12.2021
Date of renewal :

10. DATE OF REVISION OF THE TEXT