SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VOPAZZI 200 mg Film Coated Tablets
Cytotoxic

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Active ingredient:

Pazopanib hydrochloride.....216.7 mg (equivalent to 200 mg of pazopanib)

Excipients:

Sodium starch glycolate, Type A.....21 mg
See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film coated tablet.
Pink-colored, round, biconvex, film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Pazopanib is indicated as a single agent until progression in patients with unresectable locally recurrent or metastatic renal cell carcinoma who have not previously received any VEGF-TKI (Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitor).

- VOPAZZI is indicated for the following subtypes of metastatic sarcoma in patients who have received at least one series of chemotherapy/up to two series of chemotherapy for metastatic disease and have subsequently progressed:

Fibroblastic sarcomas (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumor), fibrohistiocytic sarcomas (pleomorphic malignant fibrous histiocytoma, giant cell malignant fibrous histiocytoma (also known as undifferentiated pleomorphic sarcoma (UPS)), inflammatory malignant fibrous histiocytoma), 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

Dosage/administration frequency and duration:

VOPAZZI therapy should only be initiated by a physician experienced in the administration of anticancer drugs.

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

Dose Modification
Dose modification (reduction or increase) to manage adverse reactions should be gradual, in increments or decrements of 200 mg, based on individual tolerability. The daily dose of pazopanib should not exceed 800 mg.

Method of dministration:
Pazopanib is for oral use. Pazopanib should be taken on an empty stomach (at least one hour before or two hours after meals) (see Section 5.2). Film coated tablets should be swallowed whole with water and should not be broken or crushed (see Section 5.2).

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

Additional information for specific populations:
Renal impairment:
Given the low renal excretion of pazopanib and its metabolites, renal impairment is not expected to have a clinically significant effect on the pharmacokinetics of pazopanib (see Section 5.2). Therefore, no dose adjustment is necessary in patients with a creatinine clearance above 30 mL/min. As there is no experience with pazopanib in this patient population, caution is advised in patients with a creatinine clearance below 30 mL/min.

Hepatic impairment:
Dosage recommendations for patients with hepatic impairment are based on pharmacokinetic studies of pazopanib in patients with varying degrees of hepatic dysfunction (see Section 5.2). Liver function tests should be performed in all patients prior to initiation of pazopanib treatment and during treatment to determine the presence of liver dysfunction (see Section 4.4). Pazopanib should be administered with caution and tolerability should be closely monitored in patients with mild to moderate hepatic impairment. In patients with mild abnormalities in liver function tests (normal bilirubin and any level of alanine aminotransferase (ALT) increase or an increase in bilirubin exceeding 1.5 times the upper limit of normal ((ULN) 1.5 times the upper limit of normal (ULN) and a direct bilirubin increase of > 35%. In patients with moderate hepatic impairment (defined as an increase in bilirubin of >1.5 to 3 times ULN, independent of ALT values), it is recommended that the pazopanib dose be reduced to 200 mg once daily (see Section 5.2).

Pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin >3 x ULN, regardless of ALT levels).

Refer to Section 4.4 for monitoring liver function and dose adjustment in patients with drug-induced liver toxicity.

Pediatric population:
Due to safety concerns related to organ growth and maturation, pazopanib should not be used in children under 2 years of age (see Sections 4.4 and 5.3).

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

Currently available data are described in Sections 4.8, 5.1, and 5.2. However, no recommendations can be made regarding posology.

Geriatric population:
There is limited data on the use of pazopanib in patients aged 65 years and older. In clinical studies with pazopanib, no clinically meaningful differences in the safety of pazopanib were found between patients aged 65 years and older and younger patients. Clinical experience has not identified differences in response between elderly and younger patients, but the possibility of increased sensitivity in some elderly patients cannot be ruled out.

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

VOPAZZI should not be used during pregnancy (see Section 4.6).

It should not be used in children under 2 years of age.

4.4 Special warnings and precautions for use
Hepatic effects:
Cases of hepatic impairment (including fatal cases) have been reported during pazopanib use. Pazopanib should be administered with caution to patients with mild to moderate hepatic impairment, and these patients should be closely monitored.
In patients with mild abnormalities in serum liver tests (either normal bilirubin and any degree of ALT elevation or bilirubin elevation up to 1.5 x ULN regardless of ALT value), treatment should be initiated with a dose of 800 mg pazopanib once daily. A reduced dose of 200 mg pazopanib daily is recommended in patients with moderate hepatic impairment (elevated bilirubin > 1.5 to 3 x ULN, regardless of 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 ALT value) (see Sections 4.2 and 5.2). In these patients, exposure at a 200 mg dose is significantly reduced, although highly variable; it is considered that the values are insufficient to achieve a clinically meaningful effect.

Increases in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin levels have been observed in clinical studies with pazopanib (see Section 4.8). In most cases, isolated

increases in ALT and AST have been reported without accompanying increases in alkaline phosphatase or bilirubin. Patients over 60 years of age may be at higher risk for mild (>3xULN) to severe (>8xULN) ALT elevations. Patients carrying the HLA-B*57:01 allele are at higher risk for pazopanib-related ALT elevations. Liver function should be monitored in all patients receiving pazopanib, regardless of genotype or age (see Section 5.1).

Serum liver tests should be monitored before starting pazopanib treatment and at weeks 3, 5, 7, and 9 of treatment. Serum liver tests should then be performed at months 3 and 4, and other tests should be monitored as clinically indicated. Periodic monitoring should continue after month 4.

The guidelines in Table 1 are intended for patients with baseline total bilirubin values ≤1.5 x ULN and AST and ALT ≤2 x ULN.

Table 1: Dose modifications for drug-induced hepatotoxicity

Liver test values	Dose modification
Isolated increases in serum transaminase levels between 3 and 8 x ULN	Pazopanib treatment may be continued with weekly monitoring of liver function until serum transaminase levels return to stage 1 or baseline levels.
Serum transaminase levels > 8 x ULN	Pazopanib treatment should be discontinued until serum transaminase levels return to stage 1 or baseline levels. If the potential benefit of restarting pazopanib therapy is considered to outweigh the risk of hepatotoxicity, pazopanib therapy should be restarted at a lower dose of 400 mg daily, and serum liver tests should be performed weekly for 8 weeks. If ALT levels rise again to > 3 x ULN following the reinitiation of pazopanib, pazopanib treatment should be permanently discontinued.
If serum transaminase levels rise to > 3 x ULN and bilirubin levels rise to > 2 x ULN	Pazopanib treatment should be permanently discontinued. Patients should be monitored until they return to stage 1 or baseline. Pazopanib is an uridine glucuronosyl transferase (uridine glucuronosyl transferase; UGT1A1) inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert syndrome. Patients with known or suspected Gilbert syndrome who have only mild indirect hyperbilirubinemia and an increase in ALT levels > 3 x ULN should be monitored according to the recommendations for isolated ALT increases.

Concomitant use of pazopanib and simvastatin increases the risk of elevated ALT levels (see Section 4.5) and these drugs should be used with caution and under close supervision.

Hypertension:
Hypertensive events, including newly diagnosed symptomatic episodes of elevated blood pressure (hypertensive crises), have occurred in clinical studies with pazopanib. Blood pressure should be well controlled prior to pazopanib treatment. Patients should be evaluated for hypertension immediately after starting treatment (within one week of starting pazopanib

therapy) and monitored frequently thereafter to keep blood pressure under control. Blood pressure increases (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mmHg) occur in the early stages of pazopanib treatment (approximately 40% of cases occur before day 9, while approximately 90% occur within the first 18 weeks). Blood pressure should be monitored and immediately controlled using a combination of antihypertensive therapy and pazopanib dose modification (interrupting treatment and restarting at a lower dose based on clinical judgment) (see Sections 4.2 and 4.8). If there is an indication of a hypertensive crisis or if hypertension is severe and persists despite antihypertensive therapy and reduction of the pazopanib dose, pazopanib treatment should be discontinued.

Posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS)
PRES/RPLS has been reported in association with pazopanib. PRES/RPLS may present with headache, hypertension, seizures, lethargy, confusion, blindness, and other visual and neurological disturbances and may be fatal. Pazopanib should be permanently discontinued in patients who develop PRES/RPLS.

Interstitial lung disease (ILD)/Pneumonia
Fatal ILD associated with pazopanib has been reported (see Section 4.8). Patients should be monitored for pulmonary symptoms that may indicate ILD/pneumonia, and pazopanib treatment should be discontinued in patients who develop ILD or pneumonia.

Cardiac Dysfunction/Heart Failure
The risks and benefits of pazopanib should be considered before initiating treatment in patients with pre-existing cardiac dysfunction. The safety and pharmacokinetics of pazopanib have not been studied in patients with moderate to severe heart failure or with LVEF below normal.

Cardiovascular events such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have been reported in clinical studies with pazopanib (see Section 4.8). In a randomized clinical trial comparing pazopanib with sunitinib in RCC (VEG108844), LVEF measurements were performed at baseline and during the study. Myocardial dysfunction was observed in 13% of patients (47/362) in the pazopanib arm and 11% (42/369) in the sunitinib arm. Congestive heart failure was observed in 0.5% of patients in both treatment arms. In the Phase III VEG110727 STS study, congestive heart failure was reported in 3 of 240 patients (1%). LVEF decreases were observed in 11% of patients (15/140) in the pazopanib arm and 3% (1/39) in the placebo arm in patients with baseline and follow-up LVEF measurements.

Risk factors: Concomitant hypertension was present in 13 of the 15 patients in the pazopanib arm of the STS phase III study, which may have worsened cardiac dysfunction in at-risk patients by increasing cardiac afterload. Including these 15 patients, 99% (243/246) of patients enrolled in the STS phase III study had been treated with anthracyclines. Prior anthracycline therapy may be a risk factor for cardiac dysfunction.

Treatment outcome: Ultimately, 4 of the 15 patients recovered completely (within 5% of baseline) and 5 recovered partially (within the normal range, but below 5% of baseline). One patient did not recover, and follow-up data are not available for the other 5 patients.

Treatment: In patients with significant decreases in LVEF, discontinuation and/or dose reduction of pazopanib should be accompanied by treatment for hypertension (if present, see the hypertension warning section above), as clinically indicated. Patients should be closely monitored for clinical signs and symptoms indicative of congestive heart failure. LVEF assessment is recommended at baseline and periodically in patients at risk for cardiac dysfunction.

QT prolongation and Torsade de Pointes:
Cases of QT prolongation and Torsade de Pointes have been reported in clinical studies with pazopanib (see Section 4.8). Pazopanib should be used with caution in patients with a history of QT interval prolongation, those taking antiarrhythmics or other drugs that may cause QT interval prolongation, or those with pre-existing significant cardiac disease.

Monitoring of ECG parameters at baseline and periodically during pazopanib treatment, and maintaining electrolyte balance (e.g., calcium, magnesium, potassium) within normal ranges is recommended.

Arterial thrombotic events:
Myocardial infarction, myocardial ischemia, ischemic stroke, and transient ischemic attack have been observed in clinical studies with pazopanib (see Section 4.8). Fatal events have been observed. Pazopanib should be used with caution in patients at high risk of thrombotic events or with a history of thrombotic events. Pazopanib has not been studied in patients who have experienced an event within the past 6 months. A treatment decision should be made based on an assessment of the individual patient's benefit/risk situation.

Venous thromboembolic events:
Venous thromboembolic events, including venous thrombosis and fatal pulmonary embolism, have occurred in clinical studies with pazopanib. Although observed in both RCC and STS studies, the incidence was higher in the STS population (5%) compared to the RCC population (2%).

Thrombotic Microangiopathy (TMA):
Thrombotic microangiopathy (TMA) has been reported in clinical trials with pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan (see Section 4.8). Pazopanib should be permanently discontinued in patients who develop TMA. Improvement in TMA effects has been observed after discontinuation of treatment. Pazopanib is not indicated for use in combination with other agents.

Hemorrhagic events:

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

Aneurysms and Arterial Dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may facilitate the formation of aneurysms and/or arterial dissections. Before starting pazopanib, this risk should be carefully evaluated in patients with risk factors such as hypertension or a history of aneurysm.

Gastrointestinal (GI) perforation and fistula:
GI perforation or fistula events have occurred in clinical studies with pazopanib (see Section 4.8). Fatal perforation events have occurred. Pazopanib should be used with caution in patients at high risk for GI perforation or fistula.

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

Hypothyroidism:
Cases of hypothyroidism have been reported in clinical studies with pazopanib (see Section 4.8). Baseline laboratory measurements of thyroid function are recommended, and patients with hypothyroidism should be treated according to standard medical practice before starting pazopanib therapy. All patients should be closely monitored for signs of thyroid dysfunction during pazopanib treatment. Thyroid function tests should be monitored periodically and treated according to standard medical practice.

Proteinuria:
Proteinuria has been reported in clinical studies with pazopanib. Urinalysis is recommended at baseline and periodically during treatment, and patients should be monitored for worsening proteinuria. If nephrotic syndrome develops, pazopanib should be discontinued.

Tumor lysis syndrome (TLS):
The use of pazopanib has been associated with the development of TLS, including fatal TLS (see Section 4.8). Patients at increased risk of TLS include those with rapidly growing tumors, high tumor burden, renal dysfunction, or dehydration. Before initiating VOPAZZI, preventive measures such as treatment of elevated uric acid levels and intravenous hydration should be

considered. At-risk patients should be closely monitored and treated when clinically indicated.

Pneumothorax:
Cases of pneumothorax have been reported in clinical studies with pazopanib in advanced soft tissue sarcoma (see Section 4.8). Patients receiving pazopanib therapy should be closely monitored for signs and symptoms of pneumothorax.

Pediatric population:
Due to the mechanism of action of pazopanib, which can significantly affect organ growth and maturation during the early postnatal development period in rodents (see Section 5.3), pazopanib therapy should not be administered to pediatric patients under 2 years of age.

Infections:
Serious infection cases, some resulting in death (with or without neutropenia), have been reported.

Combination with other systemic anticancer therapies:
Clinical studies combining pazopanib with a range of other anticancer therapies (including pemetrexed, lapatinib, or pembrolizumab) were terminated early due to concerns about increased toxicity and/or mortality, and a safe and effective combination dose with these regimens has not been established.

Pregnancy:
Preclinical studies in animals have shown reproductive toxicity (see Section 5.3). If pazopanib is used during pregnancy or if the patient becomes pregnant while taking pazopanib, the potential risk to the fetus should be explained to the patient. Women with the potential to become pregnant should be advised to avoid pregnancy while taking pazopanib (see Section 4.6).

Interactions:
Concomitant use with strong cytochrome P450 (CYP)3A4, breast cancer resistance protein (BCRP), or P-glycoprotein (P-gp) inhibitors should be avoided as it increases the risk of exposure to pazopanib (see Section 4.5). The selection of alternative combinations of medicinal products with no or minimal CYP3A4, BCRP, or P-gp inhibition potential should be considered.

Avoid concomitant use with CYP3A4 inducers due to the risk of reduced pazopanib exposure (see Section 4.5).

Cases of hyperglycemia have been observed with concomitant use of ketoconazole.

Since pazopanib is an uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) inhibitor, caution should be exercised when pazopanib is used concomitantly with UGT1A1 substrates (e.g., irinotecan) (see Section 4.5).

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

Excipients:
This medicinal product contains less than 1 mmol (23 mg) of sodium per film coated tablet, i.e., it is essentially "sodium-free."

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other drugs on pazopanib

In vitro studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is primarily mediated by the CYP3A4 enzyme, with minor contributions from the CYP1A2 and CYP2C8 enzymes. Therefore, CYP3A4 inhibitors and inducers may alter pazopanib metabolism.

CYP3A4, P-gp, BCRP inhibitors

Pazopanib is a substrate for CYP3A4, P-gp, and BCRP.
Concomitant administration of pazopanib (400 mg once daily) with the potent CYP3A4 and P-gp inhibitor ketoconazole (400 mg once daily) for 5 consecutive days resulted in a 66% and 45% increase in the mean pazopanib Area Under the Curve (AUC) $_{0\text{-}24}$and $_{Cmax}$values increased by 66% and 45%, respectively, compared to pazopanib alone (400 mg once daily for 7 days). Comparisons of pharmacokinetic parameters (C_{max} (range of means 27.5 to 58.1 micrograms/mL) and $AUC_{(0\text{-}24)}$ (range of means 48.7 to 1040 micrograms*h/mL) pharmacokinetic parameters were compared (mean C_{max} 59.2 micrograms/mL, mean $AUC_{(0\text{-}24)}$1300 micrograms*h/mL), reducing the dose to 400 mg pazopanib once daily in the presence of a strong CYP3A4 and P-gp inhibitor results in similar systemic exposure in most patients as observed after administration of 800 mg pazopanib once daily alone, as shown in . However, some patients may exhibit greater systemic exposure than that observed after administration of 800 mg of pazopanib once daily alone.

Concomitant use of pazopanib with other potent CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice contains a CYP3A4 inhibitor and may also increase plasma pazopanib concentrations.

Administration of 1500 mg lapatinib (a 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 $AUC_{0\text{-}24}$ and C_{max} values by approximately 50% to 60% compared to 800 mg pazopanib alone. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increase in pazopanib exposure.

Co-administration of pazopanib with CYP3A4, P-gp, and BCRP inhibitors such as lapatinib will result in increased plasma pazopanib concentrations. Co-administration with strong P-gp or BCRP inhibitors may also alter pazopanib exposure and distribution, including distribution to the central nervous system (CNS). Concomitant use of pazopanib with a strong CYP3A4 inhibitor should be avoided (see Section 4.4). If a medically appropriate alternative to a strong CYP3A4 inhibitor is not available, the dose of pazopanib should be reduced to 400 mg daily during concomitant use. In this case, close monitoring for adverse reactions is required, and further dose reductions may be considered if appropriate upon observation of drug-related side effects.

Combination with strong P-gp or BCRP inhibitors should be avoided, or an alternative concomitant drug with minimal or no inhibition potential for 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 pazopanib exposure and distribution, including distribution to the CNS. It is recommended to select alternative concomitant medications with the lowest potential for enzyme or transporter induction or none at all.

Effects of pazopanib on other drugs

In vitro studies using human liver microsomes have shown that pazopanib inhibits CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 enzymes has been demonstrated in an *in vitro* human Pregnane X Receptor (PXR) assay. Clinical pharmacology studies with 800 mg pazopanib once daily showed that pazopanib had no clinically significant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib caused an approximately 30% increase in mean midazolam AUC and C_{max} (CYP3A4 probe substrate) , and a 33% to 64% increase in the ratio of dextromethorphan to dextrorphan concentration in urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of 800 mg pazopanib once daily and 80 mg/m² paclitaxel (CYP3A4 and CYP2C8 substrate) once weekly resulted in an average increase of 26% and 31% in paclitaxel AUC and C_{max} values, respectively.

Based on *in vitro* IC_{50} and *in vivo* C_{max} values, the GSK1268992 and GSK1268997 metabolites of pazopanib may contribute to the net inhibitory effect of pazopanib via BCRP. Furthermore, the potential inhibition of BCRP and P-gp in the gastrointestinal tract by pazopanib cannot be disregarded. Caution should be exercised when pazopanib is used in combination with other oral BCRP and P-gp substrates.

In *vitro*, pazopanib inhibited human organic anion transporter polypeptide 1B1 (OATP1B1). The possibility that pazopanib may alter the pharmacokinetic properties of OATP1B1

substrates (e.g., statins, see below "Effect on concomitant use of Pazopanib and Simvastatin") cannot be disregarded.

Pazopanib is an inhibitor of the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) enzyme in *vitro*. The active metabolite of irinotecan, SN-38, is a substrate of OATP1B1 and UGT1A1.
Co-administration of pazopanib 400 mg once daily with cetuximab 250 mg/m² and irinotecan 150 mg/m² resulted in an approximately 20% increase in systemic exposure to SN-38. Compared to individuals with the wild-type allele, individuals with the UGT1A1*28 polymorphism may have a greater effect on pazopanib and SN-38 disposition. However, the effect of the UGT1A1 genotype on SN-38 disposition has not always been predictive. Caution should be exercised when pazopanib is administered concomitantly with UGT1A1 substrates.

Effect of concomitant use of pazopanib and simvastatin
Concomitant use of pazopanib and simvastatin increases the incidence of elevated ALT levels. Results from a meta-analysis using data from clinical studies with pazopanib showed that ALT >3x ULN was reported in 126/895 (14%) patients who did not use statins compared to 11/41 (27%) patients who used concomitant simvastatin (p = 0.038). If ALT levels increase in a patient receiving concomitant simvastatin, pazopanib dosing guidelines should be followed and simvastatin should be discontinued (see Section 4.4). Caution should be exercised when pazopanib is administered concomitantly with other statins, as there is insufficient data to determine their effects on ALT levels. The possibility that pazopanib may affect the pharmacokinetics of other statins (e.g., atorvastatin, fluvastatin, pravastatin, rosuvastatin) cannot be excluded.

Use with food and drink
Administration of pazopanib with meals high or low in fat resulted in approximately a 2-fold increase in AUC and C_{max} values. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after meals.

Medications that increase gastric pH
The use of pazopanib with esomeprazole reduces the bioavailability of pazopanib by approximately 40% (AUC and C_{max}). Pazopanib should not be administered with drugs that increase gastric pH. If concomitant use with a proton pump inhibitor (PPI) is medically necessary, it is recommended that the pazopanib dose be taken once daily in the evening on an empty stomach with the PPI. If concomitant use with an H2-receptor antagonist is medically necessary, pazopanib should be taken on an empty stomach at least 2 hours before or at least 10 hours after the H2-receptor antagonist dose. Pazopanib should be taken 1 hour before or 2 hours after taking a short-acting antacid. Recommendations regarding the concomitant use of PPIs and H2-receptor antagonists are based on physiological considerations.

4.6 Pregnancy and lactation
General recommendation

Pregnancy category: D

Women of childbearing potential/Birth control (Contraception)
Women of childbearing potential should be advised to use adequate contraception and avoid pregnancy during pazopanib treatment and for at least 2 weeks after treatment.

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

Pregnancy
There are no adequate data on the use of pazopanib in pregnant women. Reproductive toxicity has been seen in animal studies (see Section 5.3). The potential risk to humans is unknown.

VOPAZZI should not be used during pregnancy unless the patient's clinical condition requires treatment with pazopanib. If pazopanib is used during pregnancy or if the patient becomes pregnant while taking pazopanib, the potential risk to the fetus should be explained to the patient.

Lactation
The safe use of pazopanib during lactation has not been established. It is unknown whether pazopanib or its metabolites are excreted in human milk. There is no information on the excretion of pazopanib in animal milk. The risk to the breastfed child cannot be ruled out. Breastfeeding should be discontinued during pazopanib treatment.

Reproductive ability/Fertility
Animal studies indicate that treatment with pazopanib may affect male and female fertility (see Section 5.3).

4.7 Effects on the ability to drive and use machines
VOPAZZI has no or negligible effects on the ability to drive and use machines. Given the pharmacology of pazopanib, it is not possible to predict whether it has any harmful effects on these activities. The patient's ability to perform tasks requiring judgment, motor, or cognitive skills should be evaluated based on the patient's clinical condition and the adverse effect profile of pazopanib. Patients should avoid driving or operating machinery if they experience dizziness, fatigue, or weakness.

4.8 Undesirable effects
The overall assessment of the safety and tolerability of pazopanib (total n=1149) in patients with RCC included the pivotal RCC study (VEG105192, n=290), an extension study (VEG107769, n=71), a supportive Phase II study (VEG102616, n=225), and a randomized,

open-label, parallel-group Phase III equivalence study (VEG108844, n=557) were evaluated (see Section 5.1).

Pooled data from the pivotal STS study (VEG110727, n=369) and the supportive Phase II study (VEG20002, n=142) were evaluated in the overall safety population of 382 patients with STS to assess the general safety and tolerability of pazopanib (see Section 5.1).

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

Fatal events potentially related to pazopanib include gastrointestinal hemorrhage, pulmonary hemorrhage/hemoptysis, abnormal hepatic function, intestinal perforation, and ischemic stroke.

The most common adverse effects associated with treatment at any stage in RCC and STS studies (occurring in at least 10% of patients) are as follows: Diarrhea, hair color change, skin hypopigmentation, exfoliative rash, hypertension, nausea, headache, fatigue, anorexia, vomiting, taste disturbance, stomatitis, weight loss, pain, increased alanine aminotransferase levels, and increased aspartate aminotransferase levels.

Treatment-related adverse events reported in RCC and STS patients across all phases are listed below according to the MedDRA body system organ class. The following frequency category scale has been used:
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), not known (cannot be estimated from the available data).

Categories are based on absolute frequencies from clinical trial data. Post-marketing safety and tolerability data from all pazopanib clinical trials and spontaneous reports were also evaluated. Within each system organ class, adverse reactions with the same frequency are presented in descending order of severity.

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

Infections and infestations

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

Benign and malignant neoplasms (including 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

Metabolic and nutritional disorders
Very common: Decreased appetite [e]
Common: Hypophosphatemia, dehydration
Uncommon: Hypomagnesemia
Unknown: Tumor lysis syndrome*

Psychiatric disorders
Common: Insomnia

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

Eye disorders
Common: Blurred vision
Uncommon: Retinal detachment †, retinal tear †, loss of color in the iris

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

Vascular diseases
Very common: Hypertension
Common: Hot flushes, venous thromboembolic events[g] , flushing
Uncommon: Hypertensive crisis, hemorrhage
Rare: Aneurysms and arterial dissections†

Respiratory, thoracic disorders, and mediastinal diseases
Common: Epistaxis, dysphonia, dyspnea, hemoptysis

Uncommon: Rhinorrhea, pulmonary hemorrhage, pneumothorax
Rare: Interstitial lung disease/pneumonia†

Gastrointestinal disorders
Very common: Diarrhea, nausea, vomiting, abdominal pain[a]
Common: Stomatitis, dyspepsia, flatulence (gas and bloating in the abdomen), abdominal distension, mouth ulcers, dry mouth
Uncommon: Pancreatitis, rectal hemorrhage, hematochezia, gastrointestinal hemorrhage, melena, frequent bowel movements, anal hemorrhage, colon perforation, oral hemorrhage, upper gastrointestinal hemorrhage, enterocutaneous fistula, hematemesis, hemorrhoidal hemorrhage, ileum perforation, esophageal hemorrhage, retroperitoneal hemorrhage

Hepatobiliary disorders
Common: Hyperbilirubinemia, abnormal hepatic function, hepatotoxicity
Uncommon: Jaundice, drug-induced liver injury, liver failure†

Skin and subcutaneous tissue disorders
Very common: Change in hair color, palmar-plantar erythrodysesthesia syndrome, alopecia, rash
Common: Hypopigmentation of the skin, dry skin, pruritus, erythema, depigmentation of the skin, hyperhidrosis
Uncommon: Nail disorders, skin exfoliation (peeling), photosensitivity reaction, erythematous rash, skin disorder, macular rash, pruritic rash, vesicular rash, generalized pruritus, generalized rash, papular rash, plantar erythema, skin ulcer†

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

Renal and urinary tract disorders
Very common: Proteinuria
Uncommon: Hemorrhage in the urinary system

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

General disorders and administration site conditions
Very common: Fatigue
Common: Mucosal inflammation, asthenia, edema[b], chest pain
Uncommon: Chills, mucosal membrane disorder

Investigations
Very common: Increased alanine aminotransferase, increased aspartate aminotransferase

Common: Weight loss, increased bilirubin in blood, increased creatinine in blood, increased lipase, decreased white blood cell count[d], increased thyroid-stimulating hormone in blood, increased amylase, increased gamma-glutamyltransferase, increased blood pressure, increased urea in blood, abnormal liver function test
Uncommon: Increased hepatic enzymes, decreased blood glucose, QT prolongation on electrocardiogram, increased transaminases, abnormal thyroid function test, increased diastolic blood pressure, increased systolic blood pressure

Table listing of adverse reactions

Table 2: Treatment-related adverse reactions reported in the RCC study (n=1149) or during the post-marketing period

System Organ Class	Frequency (all stages)	Adverse reaction	All stages Number (%)	Stage 3 Number (%)	Stage 4 Number (%)
Infections and infestations	Common	Infections (with or without neutropenia)†	Unknown	Unknown	Unknown
	Uncommon	Gum infection	1 (<1%)	0	0
		Infectious peritonitis	1 (<1%)	0	0
(Including cysts and polyps) Benign and malignant neoplasms	**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)†	Unknown	Unknown	Unknown
Endocrine diseases	Common	Hypothyroidism	83 (7%)	1 (<1%)	0
Metabolic and	Very	Decrease appetite	317 (28%)	14 (1%)	0

System Organ Class	Frequency (all stages)	Adverse reaction	All stages Number (%)	Stage 3 Number (%)	Stage 4 Number (%)
nutritional disorders	Common				
	Common	Hypophosphatemia	21 (2%)	7 (<1%)	0
		Dehydration	16 (1%)	5 (<1%)	0
	Uncommon	Hypomagnesemia	10 (<1%)	0	0
	Unknown	Tumor lysis syndrome*	Unknown	Unknown	Unknown
Psychiatric disorders	Common	Insomnia	30 (3%)	0	0
Nervous system diseases	Very common	Impaired sense of taste[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
		Drowsiness	3 (<1%)	1 (<1%)	0
		Cerebrovascular event	2 (<1%)	1 (<1%)	1 (<1%)
		Ischemic stroke	2 (<1%)	0	1 (<1%)
	Rare	Posterior reversible encephalopathy syndrome / Reversible posterior leukoencephalopathy syndrome †	Unknown	Unknown	Unknown
Eye disorders	Common	Blurred vision	19 (2%)	1 (<1%)	0
	Uncommon	Retinal detachment †	1 (<1%)	1 (<1%)	0
		Retinal tear †	1 (<1%)	1 (<1%)	0
		Eyelash loss of color	4 (<1%)	0	0
Cardiac diseases	Uncommon	Bradycardia	6 (<1%)	0	0
		Myocardial infarction	5 (<1%)	1 (<1%)	4 (<1%)

System Organ Class	Frequency (all stages)	Adverse reaction	All stages Number (%)	Stage 3 Number (%)	Stage 4 Number (%)
		Cardiac dysfunction f	4 (<1%)	1 (<1%)	0
		Myocardial ischemia	3 (<1%)	1 (<1%)	0
Vascular diseases	Very common	Hypertension	473 (41%)	115 (10%)	1 (<1%)
	Common	Hot flashes	16 (1%)	0	0
		Venous thromboembolic eventsg	13 (1%)	6 (<1%)	7 (<1%)
		Flushing	12 (1%)	0	0
	Uncommon	Hypertensive crisis	6 (<1%)	0	2 (<1%)
		Hemorrhage	1 (<1%)	0	0
	Rare	Aneurysms and arterial dissections†	Unknown	Unknown	Unknown
Respiratory, thoracic disorders, and mediastinal diseases	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/pneumonia†	Unknown	Unknown	Unknown
Gastrointestinal diseases	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 (gas and bloating in the abdomen)	43 (4%)	0	0
		Abdominal distension	36 (3%)	2 (<1%)	0
		Mouth ulcer	28 (2%)	3 (<1%)	0

System Organ Class	Frequency (all stages)	Adverse reaction	All stages Number (%)	Stage 3 Number (%)	Stage 4 Number (%)
		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
		Melena	4 (<1%)	1 (<1%)	0
		Frequent bowel movements	3 (<1%)	0	0
		Anal hemorrhage	2 (<1%)	0	0
		Colonic perforation	2 (<1%)	1 (<1%)	0
		Oral hemorrhage	2 (<1%)	0	0
		Upper gastrointestinal hemorrhage	2 (<1%)	1 (<1%)	0
		Enterocutaneous fistula	1 (<1%)	0	0
		Hematemesis	1 (<1%)	0	0
		Hemorrhoial 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 diseases	Common	Hyperbilirubinemia	38 (3%)	2 (<1%)	1 (<1%)
		Abnormal hepatic function	29 (3%)	13 (1%)	2 (<1%)
		Hepatotoxicity	18 (2%)	11 (<1%)	2 (<1%)
	Uncommon	Jaundice	3 (<1%)	1 (<1%)	0
		Drug-induced liver injury	2 (<1%)	2 (<1%)	0
		Liver failure†	1 (<1%)	0	1 (<1%)
Skin and subcutaneous tissue disorders	Very Common	Change in hair color	404 (35%)	1 (<1%)	0
		Palmar-plantar erythrodysesthesia syndrome	206 (18%)	39 (3%)	0

System Organ Class	Frequency (all stages)	Adverse reaction	All stages Number (%)	Stage 3 Number (%)	Stage 4 Number (%)
		Alopecia	130 (11%)	0	0
		Rash	129 (11%)	7 (<1%)	0
	Common	Hypopigmentation of the skin	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 (peeling)	10 (<1%)	0	0
		Photosensitivity reaction	7 (<1%)	0	0
		Erythematous rash	6 (<1%)	0	0
		Skin disorder	5 (<1%)	0	0
		Macular rash	4 (<1%)	0	0
		Pruritic rash	3 (<1%)	0	0
		Blistering rash	3 (<1%)	0	0
		Generalized pruritus	2 (<1%)	0	0
		Generalized rash	2 (<1%)	1 (<1%)	0
		Papular rash	2 (<1%)	0	0
		Plantar erythema	1 (<1%)	0	0
		Skin ulcer†	Unknown	Unknown	Unknown
Musculoskeletal disorders, connective tissue and bone diseases	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
Kidney and urinary tract disorders	Very Common	Proteinuria	135 (12%)	32 (3%)	0
	Uncommon	Urinary system hemorrhage	1 (<1%)	0	0
Reproductive system and breast	Uncommon	Menorrhagia	3 (<1%)	0	0

System Organ Class	Frequency (all stages)	Adverse reaction	All stages Number (%)	Stage 3 Number (%)	Stage 4 Number (%)
disorders					
		Vaginal hemorrhage	3 (<1%)	0	0
		Metrorrhagia	1 (<1%)	0	0
General disorders and diseases related to the application area	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
		Mucosal membrane disorder	1 (<1%)	0	0
Research	Very common	Increased alanine aminotransferase	246 (21%)	84 (7%)	14 (1%)
		Increased aspartate aminotransferase	211 (18%)	51 (4%)	10 (<1%)
	Common	Weight loss	96 (8%)	7 (<1%)	0
		Increased bilirubin in the blood	61 (5%)	6 (<1%)	1 (<1%)
		Increased creatinine in the blood	55 (5%)	3 (<1%)	0
		Increased lipase	51 (4%)	21 (2%)	7 (<1%)
		White blood cell decrease[d]	51 (4%)	3 (<1%)	0
		Increase in thyroid-stimulating hormone in the blood	36 (3%)	0	0
		Increased amylase	35 (3%)	7 (<1%)	0
		Increased gamma-glutamyltransferase	31 (3%)	9 (<1%)	4 (<1%)
		Increased blood pressure	15 (1%)	2 (<1%)	0
		Increase in blood urea	12 (1%)	1 (<1%)	0
		Abnormal liver function test	12 (1%)	6 (<1%)	1 (<1%)
	Uncommon	Increased liver enzymes	11 (<1%)	4 (<1%)	3 (<1%)

System Organ Class	Frequency (all stages)	Adverse reaction	All stages Number (%)	Stage 3 Number (%)	Stage 4 Number (%)
		Decreased blood glucose	7 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolongation	7 (<1%)	2 (<1%)	0
		Elevated transaminases	7 (<1%)	1 (<1%)	0
		Abnormal thyroid function test	3 (<1%)	0	0
		Increase in diastolic blood pressure	2 (<1%)	0	0
		Increase in systolic blood pressure	1 (<1%)	0	0

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

Neutropenia, thrombocytopenia, and palmar-plantar erythrodysesthesia syndrome have been observed more frequently in patients of East Asian origin.

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

Infections and infestations
Common: Gingival infection

Benign and malignant neoplasms (including 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

Metabolic and nutritional disorders
Very common: Decreased appetite, hypoalbuminemia[f]
Common: Dehydration
Uncommon: Hypomagnesemia
Unknown: Tumor lysis syndrome*

Psychiatric disorders
Common: Insomnia

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

Eye disorders
Common: Blurred vision

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

Vascular diseases
Very common: Hypertension
Common: Venous thromboembolic events[d], hot flushes, flushing
Uncommon: Hemorrhage
Rare: Aneurysms and arterial dissections

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

Gastrointestinal disorders
Very common: Diarrhea, nausea, vomiting, abdominal pain[a], stomatitis
Common: Abdominal distension, dry mouth, dyspepsia, oral 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: Abnormal hepatic function
Unknown: Liver failure*

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

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

Kidney and urinary tract disorders
Uncommon: Proteinuria

Reproductive system and breast disorders
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 loss
Common: Abnormal ear, nose, throat examination[e], increased alanine aminotransferase, abnormal blood cholesterol level, increased aspartate aminotransferase, increased gamma-glutamyltransferase
Uncommon: Increased blood bilirubin levels, aspartate aminotransferase, alanine aminotransferase,
decreased platelet count, QT prolongation on electrocardiogram

Table listing of adverse reactions

Table 3: Treatment-related adverse reactions reported in STS studies (n=382) or during the post-marketing period

System Organ Class	Frequency (all stages)	Adverse reaction	All stages	Stage 3 Number (%)	Stage 4 Number (%)
Infections and infestations	Common	Gingivitis	4 (1%)	0	0
(Including cysts and polyps) Benign and malignant neoplasms	Very Common	Tumor pain	121 (32%)	32 (8%)	0
Blood and lymphatic	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 diseases	Common	Hypothyroidism	18 (5%)	0	0
Metabolism and nutritional 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	Hypomagnesemia	1 (<1%)	0	0
	Not known	Tumor lysis syndrome*	Unknown	Unknown	Unknown
Psychiatric disorders	Common	Insomnia	5 (1%)	1 (<1%)	0
Nervous system disorders	Very Common	Impaired sense of taste[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
	Unknown	Drowsiness	3 (<1%)	0	0
		Paresthesia	1 (<1%)	0	0
		Cerebral infarction	1 (<1%)	0	1 (<1%)
Eye disorders	Common	Blurred vision	15 (4%)	0	0
Cardiac diseases	Common	Cardiac dysfunction [g]	21 (<5%)	3 (<1%)	1 (<1%)
		Left ventricular dysfunction	13 (3%)	3 (<1%)	0

System Organ Class	Frequency (all stages)	Adverse reaction	All stages	Stage 3 Number (%)	Stage 4 Number (%)
		Bradycardia	4 (1%)	0	0
	Uncommon	Myocardial infarction	1 (<1%)	0	0
Vascular diseases	Very common	Hypertension	152 (40%)	26 (7%)	0
	Common	Venous thromboembolic events [d]	13 (3%)	4 (1%)	5 (1%)
		Hot flashes	12 (3%)	0	0
		Flushing	4 (1%)	0	0
	Uncommon	Hemorrhage	2 (<1%)	1 (<1%)	0
	Rare	Aneurysms and arterial dissections	Unknown	Unknown	Unknown
Respiratory, chest disorders, and mediastinal diseases	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/ Pneumonia †	Unknown	Unknown	Unknown
Gastrointestinal diseases	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
		Oral hemorrhage	5 (1%)	0	0
		Flatulence	5 (1%)	0	0
		Anal hemorrhage	4 (1%)	0	0
	Uncommon	Gastrointestinal hemorrhage	2 (<1%)	0	0

System Organ Class	Frequency (all stages)	Adverse reaction	All stages	Stage 3 Number (%)	Stage 4 Number (%)
		Rectal hemorrhage	2 (<1%)	0	0
		Enterocutaneous fistula	1 (<1%)	1 (<1%)	0
		Gastric hemorrhage	1 (<1%)	0	0
		Melena	2 (<1%)	0	0
		Esophageal hemorrhage	1 (<1%)	0	1 (<1%)
		Peritonitis	1 (<1%)	0	0
		Retroperitoneal hemorrhage	1 (<1%)	0	0
		Upper gastrointestinal	1 (<1%)	1 (<1%)	0
		Ileal perforation	1 (<1%)	0	1 (<1%)
Hepatobiliary diseases	Uncommon	Abnormal hepatic function	2 (<1%)	0	1 (<1%)
	Not known	Liver failure*	Unknown	Unknown	Unknown
Skin and subcutaneous tissue disorders	Very Common	Change in hair color	93 (24%)	0	0
		Hypopigmentation of the	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
		Papular rash	1 (<1%)	0	0
		Light sensitivity reaction	1 (<1%)	0	0
		Palmar-plantar erythrodysesthesia	2 (<1%)	0	0
Musculoskeletal disorders, connective tissue and bone diseases	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
Kidney and urinary tract disorders	Uncommon	Proteinuria	2 (<1%)	0	0

System Organ Class	Frequency (all stages)	Adverse reaction	All stages	Stage 3 Number (%)	Stage 4 Number (%)
Reproductive and breast diseases	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	Swelling[b]	18 (5%)	1 (<1%)	0
		Chest pain	12 (3%)	4 (1%)	0
		Shivering	10 (3%)	0	0
	Uncommon	Mucosal inflammation	1 (<1%)	0	0
		Asthenia	1 (<1%)	0	0
Investigations	Very common	Weight loss	86 (23%)	5 (1%)	0
	Common	Abnormal ear, nose, throat examination [e]	29 (8%)	4 (1%)	0
		Increased alanine aminotransferase	8 (2%)	4 (1%)	0
		Abnormal blood cholesterol level	6 (2%)	0	0
		Increased aspartate aminotransferase	5 (1%)	2 (<1%)	2 (<1%)
		Increased gamma-glutamyltransferase	4 (1%)	0	3 (<1%)
	Uncommon	Increased blood bilirubin levels	2 (<1%)	0	0
		Aspartate aminotransferase	2 (<1%)	0	2 (<1%)
		Alanine aminotransferase	1 (<1%)	0	1 (<1%)
		Decrease in platelet count	1 (<1%)	0	0
		Electrocardiogram QT prolongation	2 (<1%)	1 (<1%)	0

[†]Adverse reactions related to treatment reported during the post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical trials).

*Adverse reactions related to treatment reported only in the post-marketing period. Frequency Cannot be estimated from the available data.

The following terms have been combined:

[a] Abdominal pain, upper abdominal pain, and gastrointestinal pain

[b] Edema, peripheral edema, eyelid edema

[c] The vast majority of these cases are Palmar-plantar erythrodysesthesia syndrome

[d] Venous thromboembolic events – Includes deep vein thrombosis, pulmonary embolism, and thrombosis
[e] The majority of these events describe mucositis
[f] Frequency is based on the laboratory values tables of the VEG110727 study (N=240). These have been reported by investigators as adverse events at a lower frequency than shown in the laboratory values tables.
[g] Cardiac dysfunction events include left ventricular dysfunction, heart failure, and restrictive cardiomyopathy.
[h] Frequency is based on adverse events reported by investigators. Laboratory abnormalities were reported by investigators as adverse events at a lower frequency than indicated by the laboratory values tables.

Neutropenia, thrombocytopenia, and palmar-plantar erythrodysesthesia syndrome have been observed more frequently in patients of East Asian origin.

Pediatric population
The safety profile in pediatric patients is similar to that reported in adults receiving pazopanib for approved indications, based on data from 44 pediatric patients in the ADVL0815 Phase I study and 57 pediatric patients in the PZP034X2203 Phase II study (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 via the national reporting system.

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 observed in 1 of 3 patients receiving 2000 mg and 1000 mg daily, respectively.

Treatment
There is no specific antidote for pazopanib overdose, and treatment should involve general supportive measures in cases of overdose.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors; other protein kinase inhibitors
ATC code: L01EX03

Mechanism of action
Pazopanib is administered orally and has IC_{50} values for 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). In preclinical studies, pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, c-Kit, and PDGFR-β receptors in cells in a dose-dependent manner. *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 pharmacogenomic meta-analysis of data from 31 clinical trials conducted with pazopanib as monotherapy or in combination with other agents, ALT values above 5 x ULN (NCI CTC Grade 3) ALT values were observed in 19% of HLA-B*57:01 allele carriers and 10% of non-carriers. In this data set, 133/2235 patients (6%) were HLA-B*57:01 allele carriers (see Section 4.4).

Clinical Studies
Renal Cell Carcinoma (RCC)
The safety and efficacy of pazopanib were evaluated in a randomized, double-blind, placebo-controlled, multicenter study in renal cell carcinoma (RCC). Patients with locally advanced and/or metastatic RCC (N=435) 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 in terms of progression-free survival (PFS), and the main secondary endpoint was overall survival (OS). Other objectives included evaluating the overall response rate and duration of response.

Of the total 435 patients in this study, 233 had not received prior treatment, while 202 had previously received IL-2 or INFα-based therapy. 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 Center)/Motzer prognostic factors. Clear cell histology or predominantly clear cell histology was identified in all patients. Approximately half of the patients had disease involvement in 3 or more organs, and most patients had lung (74%) and/or lymph node (54%) metastases at baseline.
Similar proportions of patients in both arms had not received prior treatment or had received prior cytokine therapy (53% and 47% in the pazopanib arm, 54% and 46% in the placebo arm). Among the subgroup receiving prior cytokine therapy, the vast majority of patients (75%) had received interferon-based therapy.

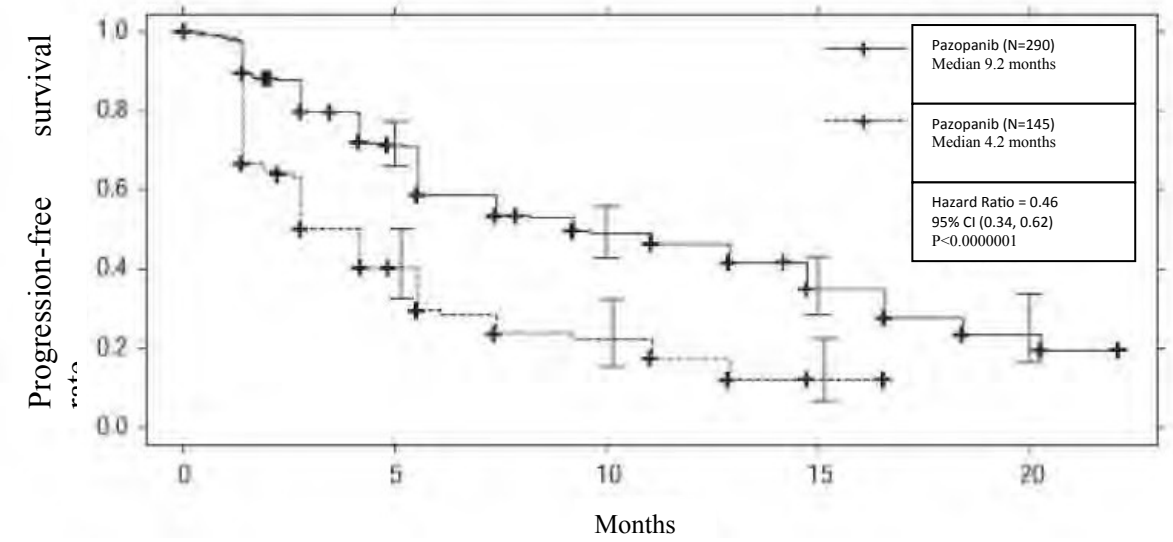
Similar proportions of patients in both arms had undergone prior nephrectomy (89% and 88% in the pazopanib and placebo arms, respectively) and/or prior radiotherapy (22% and 15% in the pazopanib and placebo arms, respectively).

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

Table 4. Overall efficacy findings in RCC based on independent assessment (VEG105192)

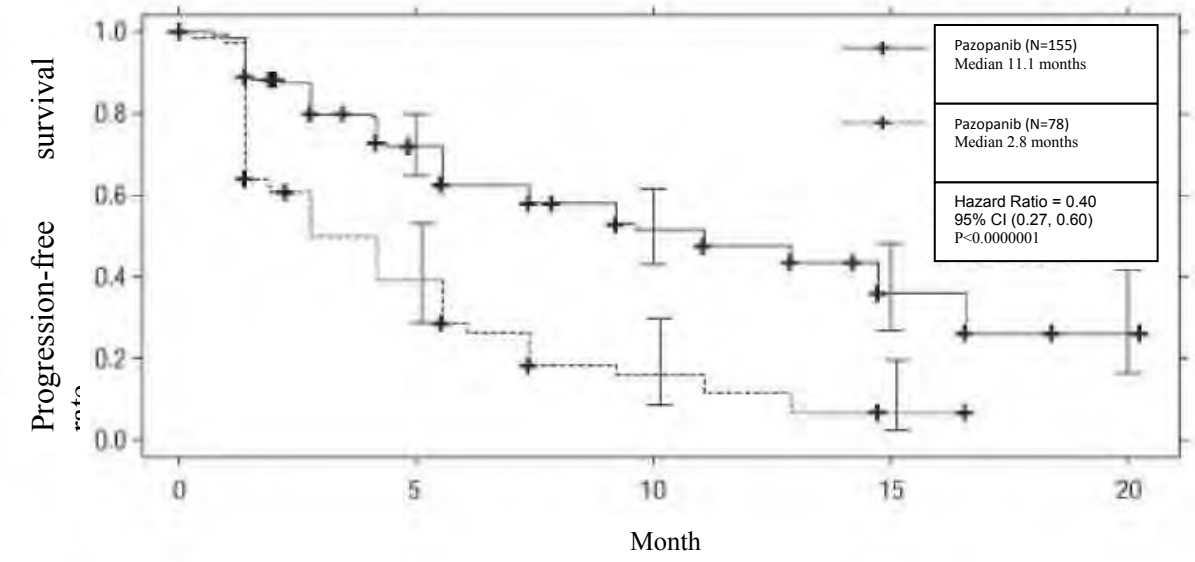
Endpoints/Study Population	Pazopanib	Placebo	HR (95% CI)	P value (one-sided)
PFS				
Overall * ITT	N = 290	N = 145		
Mean (months)	9.2	4.2	0.46 (0.34, 0.62)	<0.0000001
Response rate % (95% CI)	N = 290 30 (25.1, 35.6)	N = 145 3 (0.5, 6.4)	– 	<0.001
HR = Hazard ratio; ITT = Intention-to-treat; PFS = Progression-free survival. * - Untreated and cytokine pretreated populations, CI = Confidence interval				

Figure 1. Kaplan-Meier curve for progression-free survival in the general population (untreated and cytokine pretreated populations) with independent assessment (VEG105192)



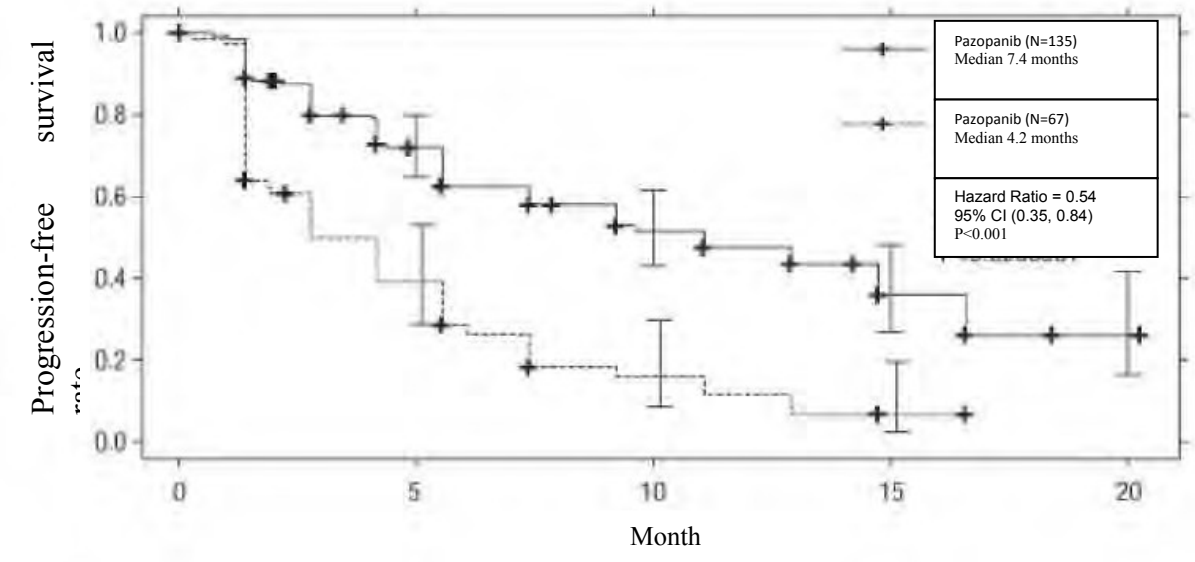
x-axis; Months, y-axis; Rate Progression-free, Pazopanib -------- (N = 290) Median 9.2 months; Placebo ------- (N = 145) Median 4.2 months; Hazard Ratio = 0.46, 95% CI (0.34; 0.62), P<0.0000001

Figure 2. Kaplan-Meier curve for progression-free survival in the untreated population with independent review (VEG105192)



x-axis; Months, y-axis; Rate of Progression-Free Survival, Pazopanib -------- (N = 155) Median 11.1 months; Placebo ------- (N = 78) Median 2.8 months; Hazard Ratio = 0.4, 95% CI (0.27; 0.6), P<0.0000001

Figure 3. Kaplan-Meier curve for progression-free survival in the cytokine-treated population with independent review



x-axis; Months, y-axis; Rate Progression-free, Pazopanib -------- (N = 135) Median 7.4 months; Placebo ------- (N = 67) Median 4.2 months; Hazard Ratio = 0.54, 95% CI (0.35; 0.84), P<0.001

The median time to response for responders was 11.9 weeks and the median duration of response was 58.7 weeks (VEG105192). The median overall survival (OS) data in the final

survival analysis specified in the protocol were 22.9 months and 20.5 months for patients randomized to the pazopanib and placebo arms, respectively [HR = 0.91 (95% CI: 0.71, 1.16; p = 0.224)]. OS results are subject to potential bias, as 54% of patients in the placebo arm received pazopanib in the extension part of this study due to disease progression. 66% of placebo patients received post-study treatment, compared to 30% of patients who received pazopanib.

No statistically significant differences in Global Quality of Life, measured using the EORTC QLQ-C30 and EuroQoL EQ-5D, were observed between treatment groups.

In a Phase 2 study involving 225 patients with locally recurrent or metastatic clear cell renal cell carcinoma, the objective response rate was 35% and the median response duration was 68 weeks, according to independent review. Median PFS was 11.9 months.

The safety, efficacy, and quality of pazopanib versus sunitinib were evaluated in a randomized, open-label, parallel-group Phase III "equivalence" study (VEG108844).

In VEG108844, patients with locally advanced and/or metastatic RCC who had not previously received systemic therapy (N = 1110) were randomized to receive either 50 mg of sunitinib once daily with continuous 800 mg of pazopanib once daily in 6-week cycles consisting of 4 weeks of treatment followed by a 2-week treatment-free period.

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

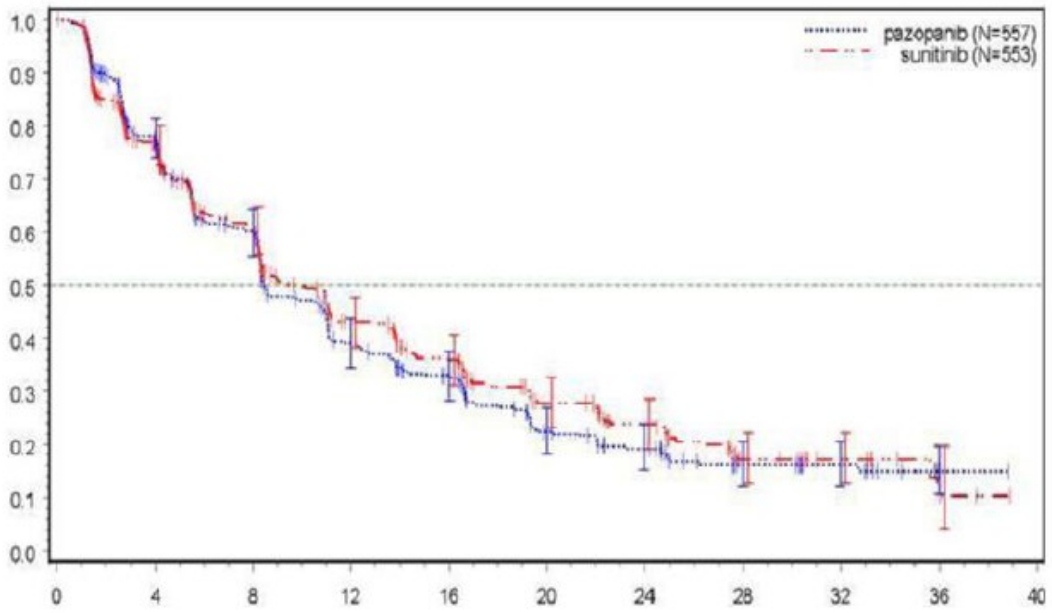
VEG108844 achieved its primary endpoint of PFS and demonstrated that pazopanib is equivalent to sunitinib, as the upper limit of the 95% CI for the hazard ratio was below the equivalence limit of 1.25 specified in the protocol. Overall efficacy findings are summarized in Table 5.

Table 5. Overall efficacy findings (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)	1.047 (0.898, 1.22)
Overall Survival			
Median (months) (95% CI)	28.3 (26, 35.5)	29.1 (25.4, 33.1)	0.915[a] (0.786, 1.065)

HR = Hazard Ratio; PFS = Independent Review Committee (IRC)
Based on the assessment, Progression-Free Survival, CI = Confidence Interval
[a]P-value = 0.245 (two-tailed)

Figure 4. Kaplan-Meier curve for progression-free survival in the general population based on independent assessment (VEG108844)



Time elapsed since randomization (months)

Subgroup analyses of PFS were performed for 20 demographic and prognostic factors. The 95% confidence intervals for all subgroups included a hazard ratio of 1. In the smallest three of these 20 subgroups, the point estimate for the hazard ratio exceeded 1.25; namely, no prior nephrectomy (n=186, HR=1.403, 95% CI (0.955, 2.061)), initial LDH value > 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 randomized, double-blind, placebo-controlled, multicenter pivotal phase III study (VEG110727). A total of 369 patients with advanced STS were randomized to receive either pazopanib 800 mg once daily or placebo. Importantly, only patients with selective histological subtypes of STS were allowed to participate in this study; therefore, the efficacy and safety of pazopanib can only be considered established for these STS subgroups, and treatment with pazopanib should be limited to these STS subtypes.

The following tumor types were considered eligible:

Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumors), fibrohistiocytic (pleomorphic malignant fibrous histiocytoma [MFH], giant cell MFH (also known as undifferentiated pleomorphic sarcoma (UPS)), inflammatory MFH), leiomyosarcoma, malignant glomus tumors, skeletal muscle (pleomorphic and alveolar rhabdomyosarcoma), vascular (epithelioid hemangioendothelioma, angiosarcoma), undifferentiated (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesothelioma, PEComa, intimal sarcoma), malignant peripheral nerve sheath tumors ( ), undifferentiated (indifferentiated) soft tissue sarcomas not otherwise specified (NOS), and other sarcoma types (not included in the inappropriate list).

The following tumor types have been deemed inappropriate:
Adipocytic sarcoma (all subtypes), all non-alveolar or non-pleomorphic rhabdomyosarcomas, chondrosarcoma, osteosarcoma, Ewing tumors/Primitive neuroectodermal tumors (PNET), GIST, dermofibromatous sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma, and mixed mesodermal uterine tumors.
Note: Patients with adipocytic sarcoma were excluded from the pivotal Phase III study, as they were from a preliminary Phase II study (VEG20002); the activity observed with pazopanib in adipocytic sarcoma (PFS at week 12) did not meet the required ratio for additional clinical testing.

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

Ninety-eight percent of volunteers had previously received doxorubicin, 70% had previously received ifosfamide, and 65% had used at least 3 or more chemotherapy agents prior to enrollment.
Patients were classified according to baseline WHO performance status (WHO PS) (0 or 1) and the number of prior systemic treatment lines for advanced disease (0 or 1 versus 2+). In each treatment group, the percentage of patients who had previously received 2+ lines of systemic therapy for advanced disease was slightly higher compared to patients who had previously received 0 or 1 line of systemic therapy (42% and 45% for the placebo and pazopanib treatment arms, respectively). (58% and 55% for the placebo and pazopanib treatment arms, respectively). The median follow-up duration for patients (defined as the time from randomization to the last contact or measurement) was similar between the two treatment arms (9.36 months [range: 0.69 to 23 months] for placebo and 10.04 months [range: 0.2 to 24.3 months] for pazopanib).

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

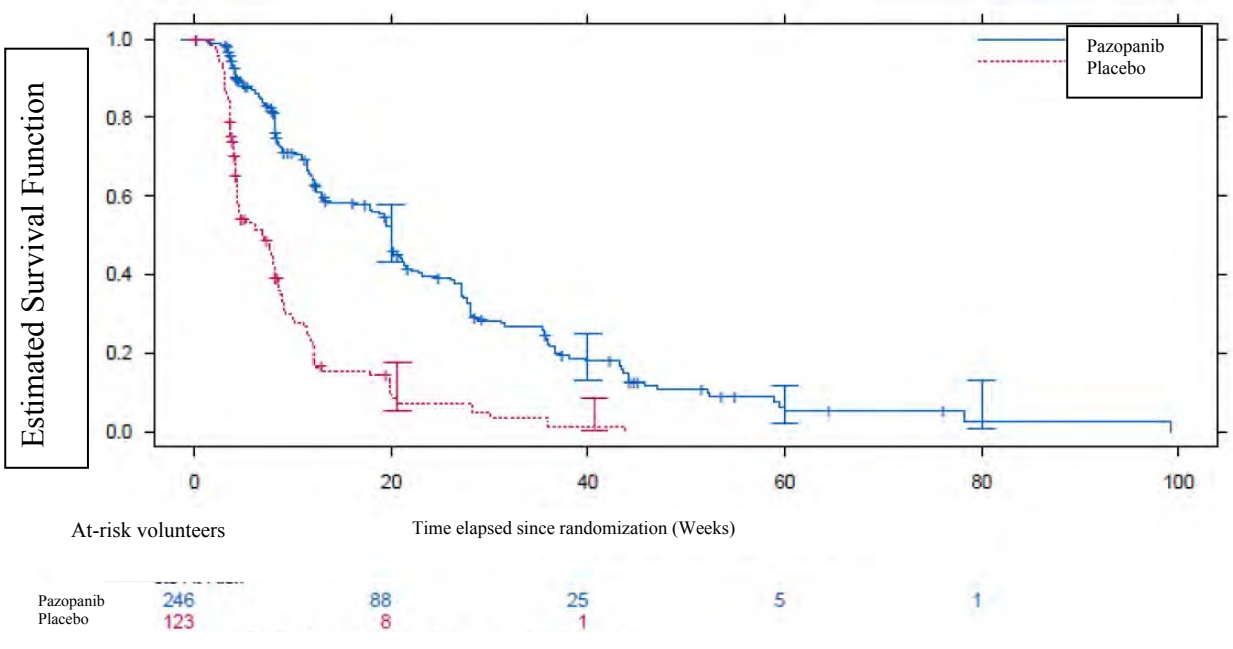
Table 6. Overall efficacy findings in STS with independent review (VEG110727)

Endpoints/study population	Pazopanib	Placebo	HR (95% CI)	P value (two-tailed)
PFS				
Overall ITT	N=246	N=123		
Median (months)	20	7	0.35 (0.26, 0.48)	<0.001
Leiomyosarcoma	N=109	N=49		
Median (months)	20.1	8.1	0.37 (0.23, 0.6)	<0.001
Subgroups of synovial sarcoma	N=25	N=13		
Median (months)	17.9	4.1	0.43 (0.19, 0.98)	0.005
'Other STS' subgroups	N=112	N=61		
Median (months)	20.1	4.3	0.39 (0.25, 0.6)	<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
Subgroups of synovial sarcoma*	N=25	N=13		
Median (months)	8.7	21.6	1.62 (0.79, 3.33)	0.115
	N=112	N=61		

Endpoints/study population	Pazopanib	Placebo	HR (95% CI)	P value (two-tailed)
Other STS subtypes* Median (months)	10.3	9.5	0.84 (0.59, 1.21)	0.325
Response Rate (CR+PR) % (95% CI) Response time Median (weeks) (95% CI)	4 (2.3, 7.9) 38.9 (16.7, 40)	0 (0, 3)		
HR = Hazard ratio; ITT = Intention-to-treat; PFS = Progression-free survival; CR = Complete response; PR = Partial response, CI = Confidence Interval; OS = Overall survival *Overall survival for relevant STS histologic subgroups (leiomyosarcoma, synovial sarcoma, and "Other" STS) should be interpreted with caution due to low case numbers and wide confidence intervals.				

Compared to the placebo arm, a similar improvement in PFS was observed in the pazopanib arm based on investigator assessment (HR: 0.39; 95% CI, 0.3 to 0.52, p <0.001 in the overall ITT population).

Figure 5. Kaplan-Meier curve for progression-free survival in the overall population based on independent review (VEG110727)



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

Pediatric population

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

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) in 57 pediatric patients with refractory solid tumors. The study was a single-agent, uncontrolled, open-label trial designed to determine the therapeutic activity of pazopanib in children and adolescents aged 1 to <18 years. Pazopanib was administered as a tablet at a daily dose of 450 mg/m²/dose or as an oral suspension at a dose of 225 mg/m²/dose. The maximum permitted daily dose was 800 mg for the tablet and 400 mg for the oral suspension. The median exposure duration was 1.8 months (range: 1 day to 29 months).

The results of this study did not show any meaningful anti-tumor activity in the relevant pediatric population. Therefore, pazopanib is not recommended for the treatment of these tumors in the pediatric population (for information on pediatric use, see Section 4.2).

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

5.2 Pharmacokinetic properties

General characteristics

Absorption:

Following oral administration of a single 800 mg dose of pazopanib to patients with solid tumors, a maximum plasma concentration (C_{max}) of approximately 19 ± 13 micrograms/mL and an $AUC_{0-\infty}$ of approximately 650 ± 500 micrograms.h/mL. Daily dosing results in a 1.23- to 4-fold increase in AUC_{0-T}.

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

Systemic exposure to pazopanib increases when administered with food. Administration of pazopanib with meals high or low in fat resulted in approximately a 2-fold increase in AUC and

C_{max} values. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after meals (see Section 4.2).

Compared to administration of the whole tablet, administration of a crushed single 400 mg pazopanib tablet increased $AUC_{(0-72)}$ by 46% and C_{max} by approximately 2-fold and decreased t_{max} by approximately 2 hours. These results indicate that bioavailability and the oral absorption rate of pazopanib increase when the tablets are administered crushed compared to when they are administered whole (see Section 4.2).

Distribution:
In vivo binding of pazopanib to human plasma protein is greater than 99% and is not concentration-dependent in the range of 10-100 micrograms/mL. *In vitro* studies suggest that pazopanib is a substrate for P-gp and BCRP.

Biotransformation:
In vitro studies indicate that CYP3A4 is primarily responsible for pazopanib metabolism, with minor contributions from CYP1A2 and CYP2C8 enzymes. Four major pazopanib metabolites account for only 6% of plasma exposure. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a potency similar to that of pazopanib, while the others are 10 to 20 times less active. Therefore, the activity of pazopanib is primarily based on exposure to the parent pazopanib.

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

Characteristic features in patients
Renal impairment:
The results indicate that less than 4% of the orally administered pazopanib dose is excreted in urine as pazopanib and its metabolites. Based on the results obtained from population pharmacokinetic modeling (data obtained from volunteers with baseline CLCR values ranging from 30.8 mL/min to 150 mL/min), renal impairment is not expected to have a clinically significant effect on the pharmacokinetics of pazopanib. No dosage adjustment is necessary in patients with creatinine clearance above 30 mL/min. In patients with creatinine clearance below 30 mL/min, caution is advised as there is no experience with pazopanib in this patient population (see Section 4.2).

Hepatic impairment:
Mild:
In patients with mild abnormalities in liver parameters (defined as normal bilirubin and any degree of ALT elevation or bilirubin levels up to 1.5 x ULN regardless of ALT value) after administration of 800 mg once daily, the median steady-state C_{max} and $AUC_{(0-24)}$ values are

similar to the median values in patients with normal liver function (see Table 5). Once-daily 800 mg pazopanib is the recommended dose in patients with mild abnormalities in serum liver tests (see Section 4.2).

Moderate:

In patients with moderate hepatic impairment (defined as an increase in bilirubin levels >1.5 x to 3 x ULN, regardless of ALT value), the maximum tolerated dose (MTD) of pazopanib was 200 mg once daily. Following once-daily administration of 200 mg, the median steady-state C_{max} and $AUC_{(0-24)}$ values of pazopanib in patients with moderate hepatic impairment were approximately 44% and 39%, respectively, of the corresponding median values following once-daily administration of 800 mg in patients with normal hepatic function (see Table 5).
Based on safety and tolerability data, the pazopanib dosage should be reduced to 200 mg once daily in patients with moderate hepatic impairment (see Section 4.2).

Severe:

Following once-daily administration of 200 mg, the median steady-state C_{max} and $AUC_{(0-24)}$ values of pazopanib in patients with severe hepatic impairment are approximately 18% and 15%, respectively, of the corresponding median values following once-daily administration of 800 mg in patients with normal hepatic function. Based on reduced exposure and limited hepatic reserve, pazopanib is not recommended in patients with severe hepatic impairment (total bilirubin level > 3 X ULN, regardless of ALT value) (see Section 4.2).

Table 7. Median steady-state pazopanib pharmacokinetics measured in patients with hepatic impairment

Group	Dose studied	C_max(micrograms/mL)	$AUC_{(0-24)}$ (micrograms x hours/mL)	Recommended dose
Normal hepatic function	800 mg once daily	52 (17.1–85.7)	888.2 (345.5–1482)	800 mg once daily
Mild liver dysfunction	800 mg once daily	33.5 (11.3–104.2)	774.2 (214.7–2034.4)	800 mg once daily
Moderate liver impairment	200 mg once daily	22.2 (4.2–32.9)	256.8 (65.7–487.7)	200 mg once daily
Severe liver dysfunction	200 mg once daily	9.4 (2.4–24.3)	130.6 (46.9-473.2)	Not recommended for use
OD-Once daily				

Pediatric population

When pazopanib 225 mg/m^2 (as an oral suspension) was administered to pediatric patients, pharmacokinetic parameters (C_{max}, T_{max} and AUC) were similar to those previously reported in adult patients treated with 800 mg pazopanib. The results showed no significant difference in pazopanib clearance normalized by body surface area between children and adults.

5.3 Preclinical safety data

The nonclinical safety profile of pazopanib was evaluated in mice, rats, rabbits, and monkeys. In repeated-dose studies in rodents, effects observed in various tissues (bone, teeth, nail beds, reproductive organs, hematological tissues, kidney, and pancreas) are thought to be related to VEGFR inhibition pharmacology and/or disruption of the VEGF signaling pathway, and most of these effects occurred at plasma exposure levels below those observed in clinical settings. Other observed effects include diarrhea and/or morbidity, which are secondary consequences of local gastrointestinal effects caused by high local mucosal drug exposure (in monkeys) or pharmacological effects (in rodents). Proliferative hepatic lesions (eosinophilic foci and adenomas) were observed in female rats at exposures 2.5 times the human AUC.

In toxicity studies in juvenile animals, when pazopanib was administered to rats from day 9 to day 14 postpartum before weaning, at a dose corresponding to approximately 0.1 times the clinical exposure based on the AUC value in adult humans, caused mortality and abnormal organ growth/maturation in the kidney, lung, liver, and heart. When dosing was administered to post-weaning rats starting on day 21 post-birth until day 62 post-birth, the toxicological findings were similar to those in adult rats at comparable exposures. Pediatric patients are at higher risk than adult patients for bone and dental effects due to growth suppression (shorter limbs), brittle bones, and tooth remodeling, among other changes, were observed in juvenile rats at doses ≥ 10 mg/kg/day (equivalent to approximately 0.1-0.2 times the AUC in adult humans) (see Section 4.4).

Reproduction, fertility, and teratogenic effects

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures > 300 times lower than human exposure (based on AUC). These effects included decreased fertility in females, increased preimplantation and postimplantation loss, early resorption, embryolethality, lethal body weight reduction, and cardiovascular malformations. Additionally, decreased corpus luteum, increased cysts, and ovarian atrophy were observed in rodents. In a male rat fertility study, there was no effect on mating or fertility, but at exposures 0.3 times the human exposure based on AUC, decreases in sperm production rate, sperm motility, and epididymal and testicular sperm concentrations were observed, along with decreases in testicular and epididymal weights.

Genotoxicity

Pazopanib did not cause genetic damage in genotoxicity tests (Ames test, human peripheral lymphocyte chromosome aberration test, and *in vivo* micronucleus test in rats). An intermediate product in pazopanib production, present in low amounts in the finished product, was not mutagenic in the Ames test but was genotoxic in the mouse lymphoma and *in vivo* mouse micronucleus tests.

Carcinogenicity

In two-year carcinogenicity studies conducted with pazopanib, an increase in the number of liver adenomas in mice and duodenal adenocarcinomas in rats was observed. Based on rodent-specific pathogenesis and the mechanism of these findings, these are not considered to pose a higher carcinogenic risk in patients receiving 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 Pink® YS-1-14762-A
Titanium Dioxide
Hypromellose 2910 (6 cps)
Hypromellose 2910 (3 cps)
Polyethylene glycol/Macrogol
Polysorbate 80
Iron oxide red (E172)

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 30 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

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Halkalı Merkez Mah. Basın Ekspres Cad. No:1 34303
Küçükçekmece/İSTANBUL/TÜRKİYE
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8. MARKETING AUTHORIZATION NUMBER

2021/500

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