Report on the Deliberation Results

September 11, 2012

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Votrient Tablets 200 mg
[Non-proprietary name]	Pazopanib Hydrochloride (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	December 13, 2011

[Results of deliberation]
In the meeting held on September 6, 2012, the Second Committee on New Drugs concluded that the product may be approved, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 10 years, and the drug substance and the drug product are both classified as powerful drugs.

[Conditions for approval]
Because of the very limited number of subjects treated in the Japanese clinical trials, the applicant is required to conduct all-case surveillance until data from a certain number of patients are accumulated after market launch, in order to identify the background information of patients treated with the product and collect safety and efficacy data on the product in the early post-marketing period, thereby take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

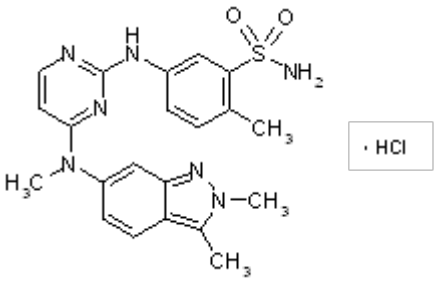
Review Report

August 28, 2012
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Votrient Tablets 200 mg
[Non-proprietary name]	Pazopanib Hydrochloride (JAN)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	December 13, 2011
[Dosage form/Strength]	Tablets; each tablet contains 216.7 mg of Pazopanib Hydrochloride (200 mg as pazopanib)
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{21}H_{23}N_7O_2S \cdot HCl$
Molecular weight: 473.98
Chemical name:
5-({4-[(2,3-Dimethyl-2*H*-indazol-6-yl)(methyl)amino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide monohydrochloride

[Items warranting special mention]	Orphan drug (Notification No. 1116-3 of Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 16, 2011)
[Reviewing office]	Office of New Drug V

Review Results

August 28, 2012

[Brand name]	Votrient Tablets 200 mg
[Non-proprietary name]	Pazopanib Hydrochloride (JAN)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	December 13, 2011

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with soft tissue sarcoma has been demonstrated and its safety is acceptable in view of its observed benefits. The following matters need to be further investigated via post-marketing surveillance: (1) the occurrence of hepatic function disorder, hypertension, cardiovascular events (including venous thromboembolic events), hemorrhagic events, pneumothorax, thyroid function abnormal, gastrointestinal perforations and gastrointestinal fistula, proteinuria and nephrotic syndrome, wound healing delayed, infections, posterior reversible encephalopathy syndrome, and interstitial lung disease and (2) further safety information on the product in the patients with hepatic impairment and patients with soft tissue sarcoma of tumor types not evaluated in clinical studies.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indications and dosage and administration, with the following conditions for approval.

[Indications]	Soft tissue sarcoma
[Dosage and administration]	The usual adult dosage is 800 mg of pazopanib orally administered once daily, at least 1 hour before or at least 2 hours after a meal. The dose may be adjusted according to the patient's condition.
[Conditions for approval]	Because of the very limited number of subjects treated in the Japanese clinical trials, the applicant is required to conduct all-case surveillance until data from a certain number of patients are accumulated after market launch, in order to identify the background information of patients treated with the product and collect safety and efficacy data on the product in the early post-marketing period, therby take necessary measures to ensure proper use of the product.

Review Report (1)

July 31, 2012

I. Product Submitted for Registration

[Brand name]	Votrient Tablets 200 mg
[Non-proprietary name]	Pazopanib Hydrochloride
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	December 13, 2011
[Dosage form/Strength]	Tablets; each tablet contains 216.7 mg of Pazopanib Hydrochloride (200 mg as pazopanib)
[Proposed indication]	Advanced soft tissue sarcoma
[Proposed dosage and administration]	The usual adult dosage is 800 mg of pazopanib orally administered once daily. The dose may be adjusted according to the patient's condition, but the daily dose should not exceed 800 mg.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.(1) Drug overview

Soft tissue sarcoma is a tumor that develops in the soft tissues of the body, including fibrous tissues, adipose tissues, muscular tissues, vascular tissues, and synovial membrane, which are of mesodermal origin, and peripheral nerves, which are of ectodermal origin, except such nonepithelial tissues as bones, teeth, endothelial system, glia and supporting tissues of parenchymatous organs, and there are a wide variety of tumor types. Signaling by receptor tyrosine kinases (RTKs), such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (c-Kit), seems to be involved in the proliferation of these tumors.

Pazopanib hydrochloride (hereinafter referred to as pazopanib) is a tyrosine kinase inhibitor discovered by GlaxoWellcome (currently, GlaxoSmithKline K.K.). Pazopanib is considered to suppress tumor proliferation by inhibiting the phosphorylation of RTKs, including VEGFR-1, -2, and -3, PDGFR-α and -β, and c-Kit.

Pazopanib was approved for the treatment of renal cell carcinoma in the United States and the EU in October 2009 and June 2010, respectively. As of June 2012, pazopanib has been approved in 76 countries/regions except Japan.

1.(2) Development history etc.

In foreign countries, a phase I study (Study VEG10003) in patients with solid tumors was started in December 2002, and a phase II study (Study VEG20002) in patients with soft tissue sarcoma (excluding gastrointestinal stromal tumor [GIST]) was started in October 2005. Then, a global phase III study (Study VEG110727) was carried out in chemotherapy-treated patients with soft tissue sarcoma (excluding adipocytic sarcoma and GIST) from October 2008 in 13 countries including Japan.

Including the above Study VEG110727, as a pivotal study, the registration application for an additional indication of pazopanib was filed in the US in June 2011 and in the EU in July 2011. In the US, Votrient was approved in April 2012 "for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy." and the application is under review in the EU.

As of June 2012, pazopanib has been approved in 4 countries for the treatment of soft tissue sarcoma.

In Japan, a phase I study (Study VEG109693) in patients with solid tumors was started in September 2007, approximately 2 years after the start of the above Study VEG20002, and then Study VEG110727 was started simultaneously as in foreign countries.

The approval application for pazopanib was submitted based on the results of the Study VEG110727 as pivotal data in December 2011.

Pazopanib was designated as an orphan drug in November 2011 with the expected indication of "advanced soft tissue sarcoma" (Designation No. [23 yaku] No. 257).

2. Data relating to quality

2.A. Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

Drug substance is a white to slightly yellow powder. The properties of the drug substance including description, solubility, hygroscopicity, melting point (thermal analysis), pH, dissociation constant, partition coefficient, polymorphism, and particle size have been determined. There are [redacted] crystalline forms including [redacted] and out of these, [redacted], and [redacted] ([redacted]) are the forms relevant to the proposed commercial manufacturing process. However, [redacted] ([redacted]) is selectively obtained by converting crystalline forms to [redacted] at the last step of the commercial manufacture.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry, ultraviolet-visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR) and X-ray crystallography.

2.A.(1).2) Manufacturing process

The drug substance is synthesized using [redacted], [redacted], [redacted] as the starting materials. Also, Quality by Design approach (QbD) is applied and primarily, the following investigations were performed:

- Identification of controls over Drug Substance Critical Quality Attributes (DS CQA), [redacted], and [redacted]

- Identification of Quality Critical Process Parameters (QCPP) and Quality Process Parameters (QPP) as well as their Proven Acceptable Ranges* (PAR) based on the risk assessment and Design of Experiments (DoE).

  *: PAR is defined as "the PAR for a given process parameter or attribute may be dependent upon the PAR values for one or more other process parameters or attributes (e.g. multivariate)," which

is different from the definition of PAR described in the "Revision of Guideline for Pharmaceutical Development" (PFSB/ELD Notification No.0628-1 dated June 28, 2010).

[redacted] step for pazopanib hydrochloride ([redacted]), [redacted] step for pazopanib hydrochloride ([redacted]), and [redacted] step for pazopanib hydrochloride ([redacted]) are identified as critical process steps.

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR[redacted]), purity (heavy metals, related substances [high performance liquid chromatography (HPLC)]), residual solvents (gas chromatography [GC]), [redacted], residue on ignition, [redacted], and assay (HPLC).

2.A.(1).4) Stability of drug substance

The stability study of the drug substance is summarized in the table below. Also, a photostability test indicates that the drug substance is stable to light.

Stability study for drug substance

Test type	Primary batches	Temperature	Humidity	Storage container	Storage period
Long-term	Commercial 3 batches	30°C	65% RH	Polyethylene bag (double)	36 M
Accelerated	Commercial 3 batches	40°C	75% RH		6 M

It was confirmed through the stability study above, drug substance is stable for 36 months at room temperature when stored in double polyethylene bags. However, slightly [redacted] than typical [redacted] profile was observed for some batches of pazopanib [redacted] mg tablet [redacted] which uses the drug substance batches stored for [redacted] months [Note by PMDA: Only 200 mg strength is filed for Japan]. Root cause investigation by the applicant revealed that there were [redacted] and [redacted]. The applicant considered that [redacted] affected the [redacted] leading to [redacted] than typical [redacted]. Therefore, the applicant is performing further studies to evaluate the impacts of storage period and storage condition [redacted] and to clarify the potential relationship between drug product [redacted]. In the meantime, the retest period of [redacted] months has been proposed for the drug substance and the drug substance package configuration is to be [redacted].

2.A.(2) Drug product

2.A.(2).1) Drug product, formulation and formulation development

The drug product is a film-coated tablet containing 216.7 mg of pazopanib hydrochloride (200 mg as pazopanib) per tablet. The drug product contains the following as excipients: microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, polysorbate 80, and red iron oxide.

2.A.(2).2) Manufacturing process

The manufacturing process of the drug product consists of granulation, drying/milling, blending, tableting, and film-coating. [redacted] and [redacted] are defined as the critical process steps and process parameters and control values are established for these manufacturing processes. Also, QbD is applied and primarily the following studies were performed:

- Identification of controls over Drug Product Critical Quality Attributes (DP CQA) [redacted]
- Optimization of formulation based on DoE analysis
- Identification of QCPP and QPP as well as their PAR based on risk assessment and DoE analysis
- Study of [redacted] conditions using a model
- Control of [redacted] via [redacted] between [redacted] and [redacted]
- Application of Real Time Release Testing (RTRT) to [redacted]

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include content, description (appearance), identification (UV/VIS), uniformity of dosage unit ([redacted]), dissolution (UV/VIS), and assay (HPLC). Following RTRT approach is proposed for [redacted]. If RTRT cannot be applied, the batch release will be determined on a batch to batch basis by performing an investigation including specification testing.

- [redacted]:
  In addition to manufacturing controls ([redacted]), [redacted] film coating [redacted], and inspect [redacted] to ensure that the tablet is a modified capsule-shaped, pink, film-coated tablet.

- [redacted]:
  In addition to manufacturing controls, perform an [redacted] using near-infrared (NIR) for a [redacted].

- [redacted] and [redacted] ([redacted]):
  In addition to manufacturing controls, confirm [redacted] by NIR (alternatively, [redacted]), and measure, [redacted] and [redacted] (by NIR) [redacted].

2.A.(2).4) Stability of drug product

Stability study of the drug product is summarized in the table below. Also, a photostability test indicates that drug product is stable to light.

Stability study for drug product

Test type	Primary batches	Temperature	Humidity	Storage container	Storage period
Long-term	Pilot 3 batches	25°C	60% RH	PTP blister	24 M
Accelerated	Pilot 3 batches	40°C	75% RH		6 M
Stressed (temperature)	Pilot 3 batches	50°C	-		3 M

It was confirmed through the stability study above, and based on the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003), the shelf life of 36 months has been proposed for the drug product when stored in press through package (PTP,

polyvinyl chloride/polyvinylidene chloride-laminated film and aluminum foil) at room temperature. The long-term stability test is still ongoing and will be continued up to 36 months.

2.B. Outline of the review by PMDA

PMDA concluded the quality of drug substance and drug product is appropriately controlled based on the submitted data and the following discussions.

Uniformity of dosage units

PMDA asked the applicant to explain how the uniformity of dosage units is assured by [redacted].

The applicant responded as follows:

The commercial tablet is film coated tablets [redacted], therefore [redacted] is set as specification test method for uniformity of dosage units. In tableting process, [redacted] is performed to meet the specification of [redacted]. To explain in detail, in-process control [redacted] are taken [redacted] and [redacted] are [redacted] to confirm [redacted]. It is also [redacted] that [redacted] are [redacted] by NIR [redacted]. [redacted] by NIR will be reported as [redacted] taken [redacted] throughout the tableting run ([redacted]: [redacted]).

For 3 batches manufactured at the commercial scale, the standard deviation (SD) of the individual NIR [redacted] is calculated for [redacted] obtained during tableting run. As shown in the table below, the results demonstrated that variation within and between batches are significantly small.

[redacted] by NIR and its standard deviation

Batch number	No. of tablets	[redacted]			SD
		Mean	Max.	Min.	
[redacted]9818	58	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]8560	69	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]8564	68	[redacted]	[redacted]	[redacted]	[redacted]

In addition, content uniformity was evaluated for the batch having the largest SD among the 3 batches ([redacted]8560). [redacted] was tested for content and separated into 10 and 30 tablets, and the mean of individual contents and SD are calculated for each 10 and 30 tablets. Acceptance values for content uniformity are also calculated. The result demonstrated that the tablets meet both $L1$ and $L2$ criteria*.

*: Acceptance criteria for uniformity of dosage units in the Japanese Pharmacopoeia 16th Edition ($L1 = 15.0$, $L2 = 25.0$)

Furthermore, the control strategy for commercial tablets introduces [redacted] which (1) [redacted] when [redacted] from [redacted] and (2) when [redacted] is outside [redacted] of [redacted] (it means [redacted] is outside [redacted]), the [redacted] from [redacted]. As a result, [redacted] is controlled.

Based on the above, the applicant considers that [redacted] can be assured through [redacted] and the [redacted] by NIR in tableting process.

An overview of statistical analysis results which forms the basis of the above discussion is

described below.

[redacted] (5000 sets with a set of 10 tablets) were generated randomly from a normal distribution, and [redacted], [redacted], [redacted], [redacted], and [redacted] were calculated. For the Japanese Pharmacopoeia (JP) uniformity of dosage units method, the proportion of acceptance value results that met the requirements of the uniformity of dosage units was determined. For the current [redacted], the number of times [redacted] was [redacted] and the number of times [redacted] or [redacted] weight was [redacted] was determined. As a result, it was demonstrated that the 99.9% acceptable zone for current [redacted] is well within the 99.9% acceptable zone for JP uniformity of dosage units [the figure below]. When true [redacted] and [redacted] [redacted] of those batches lie directly on the boundary lines of the JP acceptance value test, the probability of meeting the in-process [redacted] control requirements was <2.0%. The comparison of the two acceptance criteria indicates that the current [redacted] is more stringent than the requirements of the JP uniformity of dosage units.

[redacted]

Acceptance diagram comparing the performance of the current [redacted] and JP uniformity of dosage units

This is a graphical illustration of the probability of a batch meeting specified acceptance criteria as a [redacted] (typically batch [redacted] and batch [redacted])

Based on the submitted data and the discussions above, PMDA concluded that the uniformity of dosage units can be controlled by [redacted].

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A. Summary of the submitted data

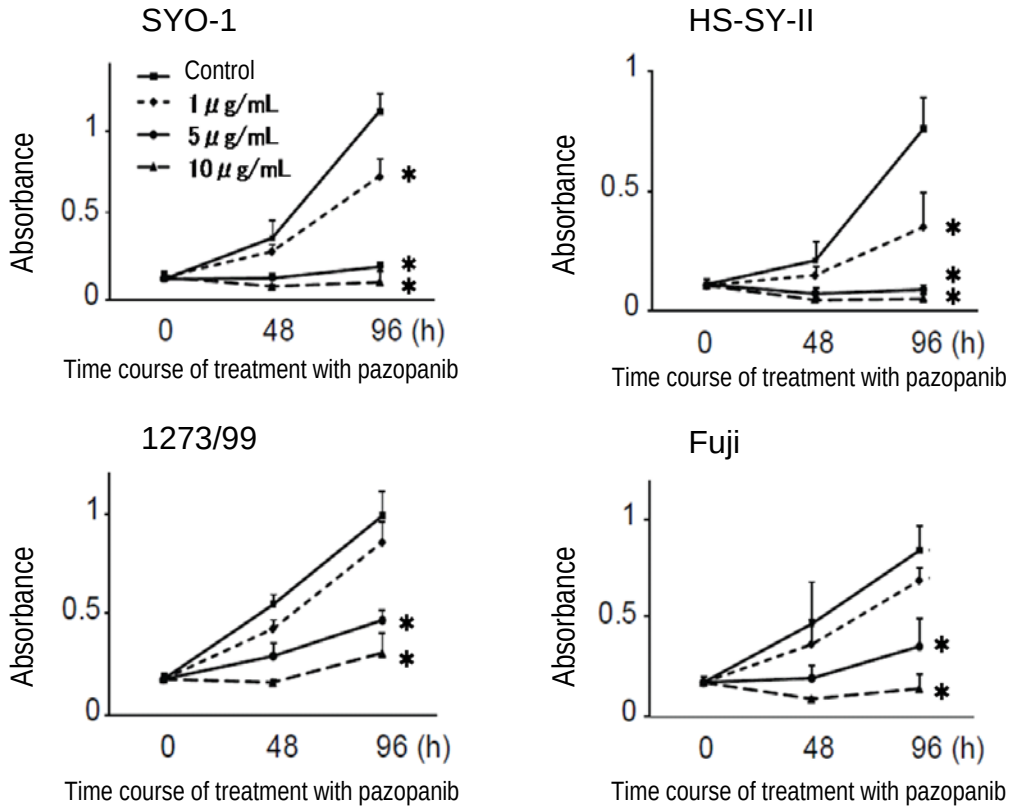
Pharmacology studies were conducted with the monohydrochloride salt of pazopanib, and some secondary pharmacodynamics studies with the dihydrochloride salt. In the pharmacology study section, all doses and concentrations of the test and control drugs are expressed in terms of the free base. The monohydrochloride salt and dihydrochloride salt of pazopanib are expressed as “pazopanib”.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Tumor growth inhibition (Report [redacted], 2011N112362_00)

***In vitro*:**

The effect of pazopanib (1-10 μg/mL) to inhibit tumor growth was evaluated in human synovial sarcoma SYO-1, HS-SY-II, 1273/99, and Fuji cells in terms of the absorbance of crystal violet-stained cells [the figures below].



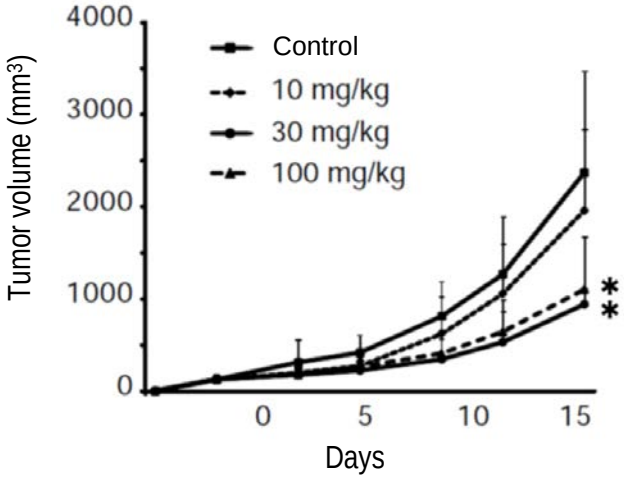
Tumor growth inhibition of pazopanib

Mean ± SD, n = 4 (SYO-1 and HS-SY-II cell lines), n = 3 (1273/99 and Fuji cell lines), *: $P < 0.05$ for the control (vehicle) group (Student's t-test)

***In vivo*:**

i) Inhibition of tumor growth in synovial sarcoma cells

The effect of pazopanib to inhibit tumor growth was evaluated in athymic mice subcutaneously implanted with human synovial sarcoma SYO-1 cells. Pazopanib was administered orally at 10, 30, or 100 mg/kg twice daily (BID) from 18 days after implantation (Day 1), when the implanted tumor grew up to the pre-specified size (≥100-200 mm^3), for 14 days consecutively and the tumor size was measured during the administration period [the figure below].

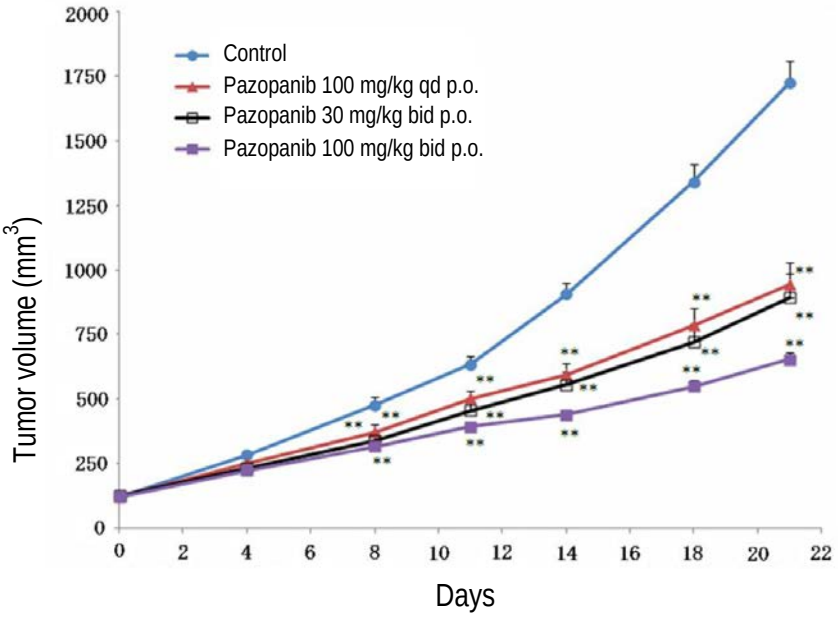


Tumor growth inhibition of pazopanib (SYO-1 cell line)
Mean ± SD, n = 8, *: $P < 0.05$ for the control (vehicle) group (Dunnett's test)

In the pazopanib 30 and 100 mg/kg groups, statistically significant tumor growth inhibition was observed compared with the vehicle control group. The applicant explained the mechanism of this activity as follows: pazopanib seems to inhibit tumor cell growth directly in addition to inhibition of angiogenesis because pazopanib was shown to stop cell cycles and inhibit AKT phosphorylation [see "3.(i).A.(1).2).iii).a Effect on phosphorylation signaling pathway," and "3.(i).A.(1).2).iii).b Effect on cell cycle and apoptosis induction"].

ii) Inhibition of tumor growth in liposarcoma cells

The effect of pazopanib to inhibit tumor growth was evaluated in severe combined immunodeficiency (SCID) mice subcutaneously implanted with human liposarcoma SW-872 cells. Pazopanib was administered orally at 100 mg/kg once daily (QD) or at 30 or 100 mg/kg BID from 13 days after implantation (Day 0), when the implanted tumor grew up to the pre-specified size (approximately ≥100-200 mm^3), for 21 days consecutively and the tumor size was measured during the administration period [the figure below].



Tumor growth inhibition of pazopanib (SW-872 cell line)
Mean ± SD, n = 10, **: $P < 0.01$ for the control (vehicle) group (Dunnett's test)

In all pazopanib groups, statistically significant tumor growth inhibition was observed compared with the vehicle control group. The applicant explained the mechanism of this activity as follows: this activity is primarily due to inhibition of angiogenesis because the direct tumor growth inhibition activity of pazopanib is weak in SW-872 cells [see "3.(i).A.(1).2).iii).c Inhibition of tumor growth in various tumor cell lines"].

3.(i).A.(1).2) Mechanism of action

i) Inhibition of phosphorylation

***In vitro*:**

a. Inhibition of various receptor tyrosine kinases (Report RR2002/00010/01, RH2003/00076/00)

The effect of pazopanib to inhibit recombinant tyrosine kinases (TKs) of various receptor tyrosine kinases (RTKs) (vascular endothelial growth factor receptor [VEGFR]-1, -2 and -3, platelet-derived growth factor receptor [PDGFR]-α and -β, stem cell factor receptor [c-Kit], and fibroblast growth factor receptor [FGFR]-1 and -3) was evaluated in terms of the level of auto-phosphorylated enzyme (Study 1) or incorporation of γ-^{33}P-ATP into substrate peptide (Study 2). The IC_{50} of pazopanib for each enzyme is shown in the following table.

Inhibitory effects of pazopanib on kinase activities

Enzyme	IC_{50} (nmol/L)	
	Study 1	Study 2*2
VEGFR-1	10 ± 4*1	13
VEGFR-2	30 ± 13*1	12
VEGFR-3	51, 43	-
PDGFR-α	-	71
PDGFR-β	-	84
c-Kit	-	80
FGFR-1	-	140
FGFR-3	-	130

Mean ± SD, *1: n = 3, *2: n = 1

b. Comparison with other kinase inhibitors (Report UH2008/00035/00)

Using the recombinant proteins of various TKs (VEGFR-1, -2 and -3, PDGFR-α and -β, c-Kit, Fms-like tyrosine kinase 3 receptor (Flt-3), B-Raf (wild type), B-Raf V600E (mutated type), and C-Raf), the effect of pazopanib, sunitinib and sorafenib to inhibit each kinase was evaluated. The apparent inhibition constant (K_i^{app}) is shown in the following table.

Inhibitory effects of pazopanib on kinase activities and comparison with sunitinib and sorafenib

Enzyme	K_i^{app} (nmol/L)			Index
	Pazopanib	Sunitinib	Sorafenib	
VEGFR-1	15 ± 6	229 ± 76	6.5, 14	Incorporation of γ-^{33}P-ATP into substrate peptide
VEGFR-2	8 ± 3	51 ± 13	4 ± 2	
VEGFR-3	10 ± 0.6	30 ± 14	6 ± 2	
PDGFR-α	30 ± 9	28 ± 9	2 ± 1	
PDGFR-β	14 ± 8	7 ± 5	5 ± 2	
Flt-3	230 ± 113	0.60 ± 0.2	22 ± 12	
c-Kit	2.40 ± 1	0.45 ± 0.07	15 ± 5	Incorporation of ATP into substrate peptide
B-Raf (wild type)	68 ± 6	470 ± 50	1.90, 2.04	Oxidative reaction of NADH
B-Raf V600E (mutated type)	160 ± 30	3000 ± 300	4.86, 7.56	
C-Raf	109 ± 9	2000 ± 200	1.90, 1.82	

Mean ± SD, n = 2-7

c. Inhibition of phosphorylation in various cells (Report UH2008/00016/01)

The effect of pazopanib to inhibit the phosphorylation of VEGFR-2, c-Kit, and PDGFR-β was evaluated using human umbilical vein endothelial cells (HUVEC), human small cell lung carcinoma NCI-H526 cells and human foreskin fibroblast (HFF) cells by immunoprecipitation/Western blot (IP/IB) assay. Treatment with pazopanib inhibited the phosphorylation of VEGFR-2, c-Kit, and PDGFR-β in HUVEC, NCI-H526 cells, and HFF, respectively, and IC_{50} values were 8, 3, and 3 nmol/L, respectively.

***In vivo*:**

Inhibition of VEGFR-2 (Report RH2003/00005/00)

Mice were given a single oral dose of pazopanib at 3, 10, 30, or 100 mg/kg, and 2 hours later an intravenous dose of vascular endothelial growth factor $(VEGF)_{121}$, ligand for VEGFR (15 μg/mouse). The phosphorylation of VEGFR-2 in the lungs at 5 minutes after $VEGF_{121}$ administration was evaluated by IP/IB assay. In the 10, 30, and 100 mg/kg groups, the phosphorylation of VEGFR-2 was inhibited compared with the vehicle control group. The plasma concentrations of unchanged pazopanib at 2 hours after dosing in the 3, 10, 30, and 100mg/kg groups were 14.2, 38.4, 50.3, and 180.1 μmol/L, respectively.

In another study, mice were given a single oral dose of pazopanib at 30 mg/kg, and 1, 4, 8, 16 and 24 hours later, an intravenous dose of $VEGF_{121}$ (15 μg/mouse). The phosphorylation of VEGFR-2 in the lungs at 5 minutes after $VEGF_{121}$ administration was evaluated by IP/IB assay. The inhibition of VEGFR-2 phosphorylation by pazopanib lasted for 8 hours after dosing. The plasma concentrations of unchanged pazopanib at 1, 4, 8, 16, and 24 hours after dosing were 153.9, 47.5, 41.1, 17.3, and 4.3 μmol/L, respectively.

The applicant explained as follows: pazopanib is expected to inhibit VEGFR phosphorylation when used clinically, because phosphorylation was inhibited when the plasma concentration of pazopanib was ≥40 μmol/L (17.5 μg/mL) and the trough plasma concentration of unchanged pazopanib is 22.0 μg/mL when the intended clinical dose is orally administered daily [see "4.(ii).A.(2).1) Phase I study in Japan"].

ii) Inhibition of angiogenesis

a. Effect on HUVEC (Report RH2002/00042/00, UH2007/00096/00)

The effect of pazopanib on the proliferation of HUVEC in the presence of VEGF or basic fibroblast growth factor (bFGF) was evaluated by enzyme-linked immunosorbent assay (ELISA) in terms of the uptake of bromodeoxyuridine (BrdU). IC_{50} values are shown in the following table.

Inhibitory effects of pazopanib on proliferation of HUVEC

Cell	Stimulants	IC_{50} (nmol/L)	n
HUVEC	VEGF	21.3 ± 4.5	15
HUVEC	bFGF	720.9 ± 239.5	11
HFF (control)	-	1012.3 ± 153.3	5

Mean ± standard error (SE)

As the major metabolites of pazopanib in human plasma, M24 (mono-oxygenation), M26 (mono-oxygenation), M27 (desmethylation) and M28 (desmethylation) have been identified. The effect of each metabolite on the proliferation of HUVEC in the presence of VEGF was also evaluated by ELISA in terms of the uptake of BrdU. IC_{50} values are shown in the following table.

Inhibitory effects of pazopanib and metabolites on proliferation of HUVEC

Compound	IC_{50} (nmol/L)
Pazopanib	38, 40
M24 (mono-oxygenation)	500, 254
M26 (mono-oxygenation)	20, 51
M27 (desmethylation)	620, 803
M28 (desmethylation)	300, 910

n = 2

b. Effect on CNV formation (Report UH2006/00101/00, UH2006/00062/01)

In mice with laser-induced retinal neovascularization, the preventive effect (Study 1) and treatment effect (Study 2) of pazopanib on neovascularization were evaluated. In Study 1, the mice were given pazopanib orally at 100 mg/kg BID for 13 days starting on the day of laser injury, and in Study 2, they were given pazopanib orally at 4, 20, or 100 mg/kg BID for 7 days starting 7 days after laser injury. In both studies, the mice were perfused with fluorescein-labeled dextran 14 days after laser injury, and the size of choroidal neovascularization (CNV) lesion was measured using fluorescence intensity [the tables below].

Prevention effect on laser-induced choroidal neovascularization in mice (Study 1)

Treatment	CNV lesion ($mm^2 \times 10^{-2}$)	n
Control (vehicle)	2.17 ± 0.16	8
Pazopanib	0.14 ± 0.03	10

Mean ± SE, $P < 0.0001$ by comparison between groups (Kruskal-Wallis test)

Therapeutic effect on laser-induced choroidal neovascularization in mice (Study 2)

	Dose (mg/kg/day)	CNV lesion ($mm^2 \times 10^{-2}$)	n
Day 7 post laser	0	0.96 ± 0.1	9
Day 14 post laser*	0 (vehicle control)	1.91 ± 0.13	9
	8	1.10 ± 0.09	7
	40	0.40 ± 0.05	6
	200	0.28 ± 0.04	8

Mean ± SE, *: $P < 0.001$ by comparison between groups (Kruskal-Wallis test)

In rabbits implanted with a hydron pellet containing VEGF and bFGF into suprachoroidal space (surgically created space between the choroid and the sclera) to induce choroidal neovascularization, pazopanib and gsk001 (related substance) were administered orally at 20 mg/kg BID for 26 days starting 48 hours after implantation. Fluorescein angiography (FA) was performed weekly for up to 4 weeks after pellet implantation. The inhibition of angiogenesis by pazopanib was determined by scoring the extent of fluorescein leakage (FA score) [the table below].

Anti-angiogenic effect in VEGF/bFGF pellet rabbit model (FA score*)

Treatment	Weeks after implantation of the pellet			
	Week 1	Week 2	Week 3	Week 4
Control (vehicle)	0.63 ± 0.18	1.00 ± 0.19	1.50 ± 0.38	1.38 ± 0.42
Pazopanib	0.13 ± 0.13	0.13 ± 0.13	0.13 ± 0.13	0.25 ± 0.25
gsk001	0.25 ± 0.16	0	0	0

Mean ± SE, n = 8, *: The index was scored in 4 levels, which were defined as 0 (no leakage), 1 (mild), 2 (moderate) and 3 (severe).

iii) Mechanism of inhibition of cell proliferation

a. Effect on phosphorylation signaling pathway (Report [redacted])

The effect of pazopanib on PI3K-AKT signaling pathway was evaluated using SYO-1, HS-SY-II, 1273/99 and Fuji cells by Western blot (IB) assay. Treatment with pazopanib (5 μg/mL) inhibited the phosphorylation of AKT in all cell lines tested.

b. Effect on cell cycle and apoptosis induction (Report [redacted])

The effect of pazopanib on cell cycles was evaluated using SYO-1 and HS-SY-II cells by flow cytometry. Treatment with pazopanib (1, 5 μg/mL) increased the percentage of cells in G1 phase.

The effect of pazopanib on apoptosis induction was also evaluated using SYO-1 and HS-SY-II cells by TUNEL staining. Treatment with pazopanib (5 μg/mL) did not change the number of TUNEL-positive cells.

c. Inhibition of tumor growth in various tumor cell lines (Report UH2008/00110/00, UH2008/00109/00, UH2008/00014/00, RH2002/00043/00, CH2009/00015/00, CH2009/00064/00)

***In vitro*:**

The ability of pazopanib to inhibit cell proliferation was evaluated using a panel of 281 human tumor cell lines in high and low cell density cultures. IC_{50} values for 18 soft tissue sarcoma cell lines are shown in the following table. In addition to these soft tissue sarcoma cell lines, pazopanib inhibited the proliferation of acute myelocytic leukemia GDM-1, melanoma ARH-77, colon cancer NCI-H716, renal leiomyoblastoma G402, thyroid cancer CGTH-W-1, and chronic myelocytic leukemia CML-T1 cells (IC_{50}: 0.01-0.79 μmol/L).

Anti-proliferative activity of pazopanib on human soft tissue sarcoma-derived cell lines

Cell line	Histology	IC_{50} (μmol/L)	
		High cell density*1	Low cell density*2
A204	Rhabdomyosarcoma	0.26	0.27
A673	Rhabdomyosarcoma	9.1	>10
GCT	Giant cell tumor	>10	6.4
HOS	Osteosarcoma	6.2	6.2
HT-1080	Fibrosarcoma	>10	5.1
KHOS-240S	Osteosarcoma	4.8	4.6
MES-SA	Uterine sarcoma	>10	7.0
RD-ES	Ewing's sarcoma	>10	8.2
SJRH30	Rhabdomyosarcoma	6.4	9.5
TE381.T	Rhabdomyosarcoma	5.3	5.2
U-2OS	Osteosarcoma	5.2	>10
RD	Osteosarcoma	>10	
Saos-2	Osteosarcoma		
SK-LMS-1	Leiomyosarcoma		
SK-UT-1	Leiomyosarcoma		
SW1353	Chondrosarcoma		
SW684	Fibrosarcoma		
SW-872	Liposarcoma		

n = 1, *1: 300-3600 cells/well (384 well), *2: A low density which had half the number of cells compared with the high density

The applicant explained as follows: pazopanib is likely to inhibit the proliferation of A204 cells directly by inhibiting VEGFR-1 because VEGFR-1 is expressed in A204 cells (*Int J Oncol*. 2005; 27: 791-8), and VEGFR-1 is likely to be involved in the proliferation of A204 cells.

***In vivo*:**
In mice subcutaneously implanted with human renal cell carcinoma (CAKI-2, ACHN, 786-O cells), human ovarian cancer OVCAR-3 cells, human colon cancer HT29 cells, human head and neck epidermoid cancer HN5 cells, human stomach cancer MKN-45 cells, and human hepatocellular carcinoma Hep3B cells, the ability of pazopanib to inhibit tumor growth was evaluated. Pazopanib inhibited tumor growth in all tumor-implanted mice.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Inhibition of receptors, channels, and transporters (Report RD2002/00946/00)

The effect of pazopanib on radioligand binding with a total of 49 types of receptors, channels, and transporters was evaluated. Pazopanib, up to 10 μmol/L, inhibited the binding of the radioligands to a total of 8 receptors including adrenoceptor β1 by ≥50%.

The applicant explained as follows: there is a concern that pazopanib may affect physiological functions associated with these receptors because the plasma C_{max} of unchanged pazopanib was 92.8 μmol/L (40.6 μg/mL) when used clinically [see "4.(ii).A.(2).1) Phase I study in Japan"]. However, pazopanib is unlikely to cause adverse effects on the central nervous, cardiovascular, or pulmonary system when used clinically, because pazopanib showed no significant effect on these systems in the safety pharmacology studies described below.

3.(i).A.(2).2) Inhibition of various kinases (Report UH2008/00089/00)

The inhibitory effects of pazopanib on 242 kinases was evaluated based on the amount of γ-^{33}P-ATP uptake. IC_{50} values for 5 out of 242 kinases (Aurora-A, C-Raf, mixed lineage kinase 1 [MLK1], protein tyrosine kinase 5 [PTK5], thousand and one amino acid kinase 3 [TAO3]) were 64, 92, 21, 97, and 181 nmol/L, respectively, which were within 10 times the IC_{50} values for VEGFR-2 (12, 30 nmol/L) [see "3.(i).A.(1).2).i).a Inhibition of various receptor tyrosine kinases"].

3.(i).A.(2).3) Effect on β adrenoceptor function (Report CH2002/00003/00)

The effect of pazopanib on β adrenoceptor function was evaluated using isolated rat atrium since pazopanib may have a potential to bind to β adrenoceptors [see "3.(i).A.(2).1) Inhibition of receptors, channels, and transporters"]. Pazopanib increased the contractile force of atrium dose-dependently, but this effect was not inhibited by propranolol, β adrenoceptor antagonist.

The applicant explained that the concentration-dependent increase in the contractile force of atrium is not a β adrenoceptor-mediated reaction.

When isoproterenol, β adrenoceptor agonist, was added after treatment with pazopanib, the maximum contraction induced by isoproterenol was reduced but atrial rate was not affected.

The applicant explained as follows: there is a concern that pazopanib may inhibit β adrenoceptor function, but pazopanib is unlikely to affect β adrenoceptor when used clinically, because pazopanib showed no cardiovascular events that raised concerns in the safety pharmacology studies described below, where the plasma concentration of unchanged pazopanib was similar to the C_{max} observed in clinical settings.

3.(i).A.(2).4) Effect on bone marrow progenitor cell (Report UH2008/00019/00)

Since pazopanib inhibits the TK activity of c-Kit [see "3.(i).A.(1).2).i).a Inhibition of various receptor tyrosine kinases"], the effects of pazopanib on the proliferation and differentiation of human bone marrow progenitor cells involving c-Kit and Flt-3 were evaluated by colony forming assay. Pazopanib, sorafenib, and sunitinib inhibited colony formation induced by GM-CSF or Flt-3 concentration-dependently (IC_{50} values of pazopanib, sorafenib, and sunitinib were 1079, 1671, 32.7 nmol/L for GM-CSF, or 8984, 795, 14.8 nmol/L for Flt-3, respectively).

The applicant explained as follows: comparison of IC_{50} values for colony formation indicates that the bone marrow suppression activity of pazopanib is weaker than that of sorafenib and sunitinib, possibly because of the difference in the ability to inhibit c-Kit and Flt-3.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effect on the central nervous system (Report RD2002/00060/00)

A single oral doses of 3, 10, 100, or 300 mg/kg of pazopanib was administered to female rats (6 per group). General signs were observed and the effects on the nervous system were evaluated by landing foot splay method. There were no effects of pazopanib in any parameters.

3.(i).A.(3).2) Effect on the cardiovascular system

i) Effect on hERG current (Report FD2002/00125/00)

Using human embryonic kidney HEK293 cells expressing human ether-a-go-go related gene (hERG), the effect of pazopanib on hERG potassium ion current was evaluated by whole-cell patch clamping. The percent inhibition of hERG current by pazopanib (mean ± standard error [SE]) was 19.5% ± 2.3% at 1.241 μmol/L (n = 5) and 18.5% ± 3.4% at 4.137 μmol/L (n = 6).

ii) Effect on action potential of purkinje fibers (Report FD2002/00060/00)
Using Purkinje fibers isolated from the canine heart, the effect of pazopanib (40, 80 nmol/L) on cardiac action potential was evaluated at 0.5 and 1 Hz based on resting membrane potential, action potential amplitude, maximum depolarization speed, and action potential duration (APD_{60}, APD_{90}). Pazopanib showed no statistically significant effect on cardiac action potential at either concentration (n = 4).

iii) Effect on cardiovascular system (Report CD2002/00099/00, CD2006/00750/00)
A single oral doses of 5, 50, or 500 mg/kg of pazopanib was administered to male cynomolgus monkeys (n = 4) by cross-over method to evaluate the effects of pazopanib on blood pressure, heart rate, and electrocardiogram (including PR and QT intervals). Pazopanib showed no effect on the cardiovascular system.

A single intravenous dose of 3.75 mg/kg of pazopanib was administered to male cynomolgus monkeys (n = 4) to evaluate the effects of pazopanib on blood pressure, heart rate, and electrocardiogram (including PR and QT intervals). Heart rate decreased from 75 minutes after dosing, but there were no effects on other parameters.

The applicant explained that the decrease in heart rate is not a clinical concern, because there was only a slight decrease in the rate (26% reduction at maximum) and it tended to resolve after 24 hours of dosing.

3.(i).A.(3).3) Effect on respiratory system (Report RD2001/01691/00)
A single oral doses of 3, 10, 100, or 300 mg/kg of pazopanib was administered to male rats (6 rats per group), and the effects on respiratory rate, tidal volume, and respiratory minute volume were evaluated by whole body plethysmography. Pazopanib showed no effect on the respiratory system.

3.(i).A.(4) Pharmacodynamic drug interactions (Report UH2008/00107/00)
There is a hypothesis that angiogenesis inhibitors can increase the concentration of concominantly administered chemotherapeutic drug within the tumor (*Science* 2005; 307: 58-62), the effects of pazopanib on the concentrations of chemotherapeutic agents administered concomitantly were evaluated in the tumors in mice implanted with HT29 cells and human non-small cell lung cancer NCI-H460 cells. Pazopanib showed no effect on the concentration of any chemotherapeutic agent administered concomitantly in the tumor tissue in this study.

3.(i).B Outline of the review by PMDA
Based on the submitted data and the following review, PMDA concluded that the efficacy of pazopanib in synovial sarcoma and liposarcoma, which are tumor types evaluated in the primary pharmacodynamics studies, has been demonstrated.

Mechanism of action and efficacy of pazopanib in soft tissue sarcoma with various tumor types
In this application, the proposed indication is “advanced soft tissue sarcoma.” Since soft tissue sarcoma has various tumor types, PMDA asked the applicant to explain the mechanism of action and efficacy of pazopanib in tumor types of soft tissue sarcoma other than synovial sarcoma and liposarcoma evaluated in the primary pharmacodynamics studies.

The applicant responded as follows:
Based on the study using human synovial sarcoma SYO-1 cells [see “3.(i).A.(1).1).i) Inhibition of tumor growth in synovial sarcoma cells”], pazopanib directly inhibits tumor growth in some tumor types.

However, pazopanib did not directly inhibit cell proliferation in most of the human soft tissue

sarcoma cell lines tested [see "3.(i).A.(1).2).iii).c Inhibition of tumor growth in various tumor cell lines"]. Considering the points described below, pazopanib is expected to be also effective against tumor types other than synovial sarcoma and liposarcoma which were not evaluated in the primary pharmacodynamics studies, since the major mechanism of action of pazopanib is considered to be the inhibition of angiogenesis.

- Pazopanib inhibited the phosphorylation of VEGFR-1, -2 and -3 RTKs [see "3.(i).A.(1).2).i) Inhibition of phosphorylation"].

- Pazopanib strongly inhibited the proliferation of VEGF-stimulated HUVEC [see "3.(i).A.(1).2).ii) Inhibition of angiogenesis"].

- The results of evaluation for VEGF, VEGFR, platelet-derived growth factor (PDGF), PDGFR, mast cell density (MCD), microvessel density (MVD/VD), intratumoral microvessel density (IMD), etc., indicate that angiogenesis is the common clinical feature in the following tumor types: malignant fibrous histiocytoma, leiomyosarcoma, synovial sarcoma, fibrosarcoma, myxofibrosarcoma, malignant peripheral nerve sheath tumor, epithelioid hemangioendothelioma, angiosarcoma, alveolar soft part sarcoma, and extrarenal rhabdoid tumor (*Anticancer Res.* 2005; 25: 3591-6, *Cancer Res.* 1994; 54: 560-4, *Rom J Morphol Embryol.* 2005; 46: 323-7, etc.).

PMDA considers as follows:
Direct inhibition of cell proliferation could be the major mechanism of action of pazopanib to exert its efficacy in some tumor types of soft tissue sarcoma. However, the applicant explained that angiogenesis inhibition is the major mechanism of action from the reason that pazopanib did not directly inhibit the proliferation of most of the human soft tissue sarcoma cell lines tested. This explanation is merely an inference based on the fact that pazopanib has demonstrated effectiveness against various tumor types of soft tissue sarcoma.

The efficacy of pazopanib in tumor types other than synovial sarcoma and adipocytic sarcoma has not been evaluated nonclinically and remains unknown. It is recommended to continue to study the mechanism of action of pazopanib and its efficacy profile in various tumor types nonclinically, as such information may be important to estimate the clinical efficacy of pazopanib and to select patients suitable for pazopanib treatment.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Pharmacokinetic studies were conducted with the monohydrochloride salt of pazopanib, and some pharmacokinetic studies with the dihydrochloride salt. In the pharmacokinetic study section, all doses and concentrations of the study drug are expressed as the free base. The monohydrochloride salt and dihydrochloride salt of pazopanib are expressed as "pazopanib," unless otherwise specified. The pharmacokinetics (PK) of pazopanib was evaluated in mice, rats, dogs, and cynomolgus monkeys. The plasma protein binding of pazopanib, drug metabolizing enzyme induction and inhibition, and interaction with transporters were evaluated using human or animal specimens.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single dose

The plasma pazopanib concentrations were determined after a single oral administration of pazopanib (monohydrochloride salt) at 100 mg/kg to male albino mice, a single oral administration of pazopanib (monohydrochloride salt) at 4 or 100 mg/kg to female pigmented mice, and a single oral administration of pazopanib (dihydrochloride salt) at 10, 30, or

100 mg/kg to female albino mice [the table below].

PK parameter of pazopanib (male and female mice, oral single dose)

Test substance	Dose (mg/kg)	Sex	t_{max} (h)	C_{max} (μg/mL)*2	AUC_{0-t} (μg·h/mL)
Pazopanib (monohydrochloride salt)	100	Male*1 (albino)	0.475	120 ± 3.80	1017
	4	Female (pigmented)	2.05	13.5 ± 4.44	130
	100		2.03	91.4 ± 29.4	753
Pazopanib (dihydrochloride salt)	10	Female (albino)	6	19.5 ± 1.77	220*3
	30		2	58.0 ± 6.84	657*3
	100		0.5	128 ± 9.65	1141*3

Mean, n = 3/timepoint, *1: n = 4/time point, *2: Mean ± SD, *3: $AUC_{0-\infty}$

In male rats, the plasma pazopanib concentrations were determined after a single oral administration of pazopanib at 10 mg/kg or after a 60-minute continuous intravenous infusion of pazopanib at 2 mg/kg [the table below]. There was a large individual variation in the systemic exposure to pazopanib after single oral dosing. The applicant explained as follows: because the plasma clearance (CL) of pazopanib was low and the volume of distribution at steady state (V_{ss}) was similar after intravenous administration compared with the hepatic plasma flow and total body water reported for rats (approximately 1790 mL/h/kg, approximately 668 mL/kg, respectively, *Pharm Res.* 1993; 10: 1093-5), pazopanib is distributed widely into tissues and plasma after intravenous administration in rats.

PK parameter of pazopanib (male rat, oral or IV single dose)

Route	Dose (mg/kg)	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	V_{ss} (mL/kg)	$t_{1/2}$ (h)	CL (mL/h/kg)	F (%)
PO	10	18.8 ± 19.7	2.43 ± 1.93	104 ± 150	ND	ND	ND	61.4 ± 87.7
IV	2	9.47 ± 5.29*	ND	35.3 ± 21.6	582 ± 627	4.08 ± 0.43	129 ± 157	-

Mean ± SD, n = 4, ND: not determined, *: at the end of 60-min. continuous intravenous infusion

The applicant explained that the difference in salt form has a minor effect on exposure because C_{max} was 41.3 ± 6.7 or 33.5 μg/mL, and AUC_{0-t} was 388 ± 73 or 406 μg·h/mL after a single oral administration of pazopanib (monohydrochloride salt) or pazopanib (dihydrochloride salt) at 30 mg/kg to female rats.

The plasma pazopanib concentration was determined after a single oral administration of pazopanib (monohydrochloride salt) at 5, 10, or 50 mg/kg or pazopanib (dihydrochloride salt) at 5 or 50 mg/kg, after a 60-minute continuous intravenous infusion of pazopanib (monohydrochloride salt) at 2 mg/kg, or after a single intravenous administration of pazopanib (dihydrochloride salt) at 5 mg/kg to male cynomolgus monkeys [the table below]. There was a large individual variation in the systemic exposure to pazopanib (monohydrochloride salt) and pazopanib (dihydrochloride salt) after single oral dosing. CL and V_{ss} after intravenous administration were low compared with the hepatic plasma flow and total body water reported for cynomolgus monkeys (approximately 1540 mL/h/kg, approximately 693 mL/kg, respectively; *Pharm Res.* 1993; 10: 1093-5). Based on these findings, the applicant explained that the difference in salt form has a minor effect on the exposure to pazopanib and the tissue distribution of pazopanib was low in cynomolgus monkeys.

PK parameter of pazopanib (male cynomolgus monkeys, oral or intravenous single dose)

Test substance	Route	Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	V_{ss} (mL/kg)	$t_{1/2}$ (h)	CL (mL/h/kg)	F (%)
Pazopanib (monohydrochloride salt)	PO	5	4	7.80 ± 1.04	2.00*2	50.6 ± 21.2*3	-	-	-	-
		10	4	1.17 ± 0.165	7.43 ± 0.954	20.4 ± 4.64	-	-	-	16.1 ± 6.28
		50	4	30.3 ± 10.4	0.9 ± 0.3	141 ± 12.6	-	6.6 ± 2.8	-	30 ± 2
		50*2	3	20.9 ± 4.11	1.33 ± 0.58	76.3 ± 22.8*3	-	-	-	-
		50	4	33.4 ± 3.6	1.75 ± 0.5	177 ± 106	-	-	-	-
		50*2	3	21.9 ± 4.9	2.00*2	129 ± 31*3	-	-	-	-
	IV	2	4	10.3 ± 3.75*1	-	29.3 ± 9.48	268 ± 50.4	2.91 ± 0.428	81.2 ± 14.0	-
Pazopanib (dihydrochloride salt)	PO	5	4	8.0 ± 2.1	1.4 ± 1.1	28.4 ± 15.3	-	4.9 ± 2.5	-	49 ± 31
		50	4	33.7 ± 9.9	2.0 ± 1.2	174 ± 60.9	-	-	-	30 ± 9
	IV	5	4	-	-	58.9 ± 11.7	283 ± 24	4.7 ± 0.3	96 ± 18	-

Mean ± SD, *1: at the end of 60-min. continuous intravenous infusion, *2: Median, *3: AUC_{0-t}

3.(ii).A.(1).2) Repeat dose

The plasma pazopanib concentration was determined after 13-week repeated oral administration of pazopanib at 100, 300, or 1000 mg/kg QD to male and female mice [the table below]. In the dose range studied, there was no increase in C_{max} or AUC_{0-t} with increasing dose, and the systemic exposure to pazopanib tended to be higher in females than in males. During repeated administration at 100 mg/kg/day, C_{max} and AUC_{0-t} remained similar with no effect of repeat dosing.

PK parameter of pazopanib (male or female mice, oral repeated dose)

Timepoint	Dose (mg/kg)	C_{max} (μg/mL)*1		t_{max} (h)		AUC_{0-t} (μg·h/mL)	
		Male	Female	Male	Female	Male	Female
Day 1	100	120 ± 3.80	-	0.475	-	1017	-
Day 7	100	101 ± 8.24	-	2.00	-	987	-
Week 13*2	100	102 ± 8.92	132 ± 10.4	1.00	2.00	818	1434
	300	97.9*3	134 ± 22.0	2.00	4.00	1044	1463
	1000	80.7 ± 26.1	114 ± 0.986	2.00	8.00	932	1607

Mean, n = 4/time point, *1: Mean ± SD, *2: n = 3/time point, *3: n = 2/time point (only mean)

The plasma pazopanib concentration was determined after 7-day, 4-week, or 26-week repeated oral administration of pazopanib at 3 to 300 mg/kg/day to male and female rats. PK parameters during 26-week repeated administration are shown in the table below. In all studies, the C_{max} and AUC_{0-t} values increased at a lower rate than the dose increase, and individual variation in the systemic exposure to pazopanib was generally large. The exposure to pazopanib tended to be higher in females than in males. The study was terminated on Day 140 in the 300 mg/kg/day group because of toxicity.

PK parameter of pazopanib (male or female rat, oral repeated dose)

Timepoint	Dose (mg/kg)	C_{max} (μg/mL)*1		t_{max} (h)		AUC_{0-t} (μg·h/mL)	
		Male	Female	Male	Female	Male	Female
Week 4	3	6.48 ± 1.17	11.2 ± 2.20	4.00	0.51	63.5	90.0
	30	37.2 ± 2.69	66.1 ± 14.7	1.00	1.00	351	498
	300	72.8 ± 9.57	114 ± 22.6	4.00	4.00	877	1308
Week 13	3	8.40 ± 2.94	10.3 ± 1.46	1.00	4.00	72.2	89.7
	30	53.8 ± 14.0	58.1 ± 9.89	1.00	2.01	392	507
	300	67.5*2	94.1 ± 18.6	4.02	4.02	830	887
Week 26	3	8.59 ± 1.65	10.5 ± 0.72	4.00	0.50	76.6	100
	30	44.6 ± 8.30	60.9 ± 6.44	2.01	1.01	374	544

Mean, n = 3/time point, *1: Mean ± SD, *2: n = 2/time point (only mean)

The plasma pazopanib concentration was determined during 7-day, 4-week, or 52-week repeated oral administration of pazopanib at 5 to 500 mg/kg/day to male and female cynomolgus monkeys. PK parameters during 52-week repeated administration are shown in the table below. In all studies, the C_{max} and AUC_{0-t} values increased at a lower rate than the dose increase and individual variation in the systemic exposure to pazopanib was generally large. The exposure to pazopanib was generally similar in male and female monkeys, except AUC_{0-t}, which was approximately 2.7 times higher in females than in males in the 500 mg/kg/group at Weeks 13 and 26 in the 52-week repeat dose study. The dosing of 500 mg/kg/day group was terminated at Week 34 due to toxicity.

PK parameter of pazopanib (male or female cynomolgus monkeys, oral repeated dose)

Time point	Dose (mg/kg)	C_{max} (μg/mL)		t_{max} (h)*1		AUC_{0-t} (μg·h/mL)	
		Male	Female	Male	Female	Male	Female
Week 4	5	13.6 ± 3.25	10.2 ± 4.28	1.50 (1.00, 2.00)	1.50 (0.98, 2.00)	44.1 ± 10.9	33.1 ± 9.94
	50	28.0 ± 19.8	27.1 ± 8.43	1.50 (1.00, 2.00)	1.51 (0.98, 2.00)	151 ± 128	160 ± 79.2
	500	62.0 ± 35.3	48.6 ± 28.6	3.00 (1.00, 4.00)	1.25 (0.50, 3.97)	665 ± 615	345 ± 395
Week 13	5	12.1 ± 2.98*2	10.5 ± 6.29	1.02 (1.00, 2.00)	1.00 (0.52, 2.00)	40.6 ± 5.19	32.1 ± 13.6
	50	23.6 ± 5.16	21.9 ± 2.72	1.50 (1.00, 2.02)	1.50 (1.00, 2.00)	126 ± 52.3	112 ± 30.6
	500	44.5 ± 22.3	57.2 ± 36.7	2.01 (1.00, 4.03)	1.25 (0.50, 11.88)	252 ± 228	670 ± 939
Week 26	5	16.9 ± 3.65*2	9.20 ± 2.65	1.00 (1.00, 1.00)	1.54 (0.50, 2.05)	49.9 ± 10.2	30.0 ± 10.8
	50	24.1 ± 6.03	30.1 ± 5.32	1.00 (1.00, 1.00)	1.00 (0.50, 4.00)	129 ± 50.0	171 ± 51.2
	500	26.8*2	50.1 ± 25.5	NC	3.03 (1.00, 4.00)	172*3	456 ± 292
Week 39	5	14.7 ± 1.43*2	18.1 ± 4.18	2.00 (1.02, 2.00)	1.00 (0.50, 1.00)	49.2 ± 1.51	43.6 ± 13.8
	50	45.6 ± 16.2	29.4 ± 5.56	2.00 (2.00, 2.02)	1.50 (1.00, 2.00)	221 ± 127	142 ± 41.4
	500*4	NC	50.6 ± 14.9*2	NC	2.00 (1.00, 12.00)*3	NC	450 ± 413*2
Week 52	5	13.3 ± 1.87*2	12.8 ± 4.21	1.00 (1.00, 2.00)	0.75 (0.50, 1.00)	46.0 ± 13.2	36.3 ± 5.92
	50	31.8 ± 10.3	44.0 ± 17.1	2.01 (1.00, 2.02)	3.95 (0.52, 3.98)	235 ± 142	289 ± 100

Mean ± SD, n = 4, NC: Not calculated, *1: Median (range), *2: n = 3, *3: n = 2 (only mean), *4: Time point = Week 34

After 4-day repeated oral administration of pazopanib at 50, 100, or 150 mg/kg/day to male and female dogs, C_{max} on Day 1 and Day 4 were 8.45 to 33.3 and 10.6 to 23.8 μg/mL, and AUC_{0-24} were 41.1 to 165 and 37.6 to 118 μg·h/mL, respectively. Exposure to pazopanib did not increase with increased dose.

Based on the above results, the applicant explained the PK of pazopanib in animals as follows:

- The increase in exposure after repeated oral administration was not proportional to the increase in dose, and the exposure tended to increase at a lower rate than the dose increase at higher doses. The non-linear PK is probably due to the poor solubility of pazopanib; pazopanib dissolves poorly in the gastrointestinal tract and the absorption from the gastrointestinal tract is limited.

- The exposure to pazopanib tended to be higher in females than in males in mice and rats, but the reason for the discrepancy is unknown.

- Exposure to pazopanib is not considered to have accumulative property during repeat dosing.

- The exposure to pazopanib in dogs was lower than in mice, rats and cynomolgus monkeys.

As the drug substance is micronized in the final formulation, the effect of micronization on PK of pazopanib was evaluated by repeated oral administration of micronized pazopanib or non-micronized pazopanib at 30 mg/kg/day to male rats for up to 4 weeks. The PK parameters are shown below. On Day 1, C_{max} and AUC_{0-t} were similar between with or without micronization. The systemic exposure on Day 1 was similar to those on Day 7 and thereafter.

Based on the above results, the applicant explained that micronization of pazopanib does not affect the systemic exposure in rats.

PK parameter of pazopanib (male rats, oral repeated dose)

Test substance	Study period	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)
Non-micronized form*1	1 day	33.6 ± 0.8	261 ± 49
Micronized form		42.5 ± 10.9	450 ± 128
Micronized form	7 days	33.4 ± 1.7	317 ± 28
Non-micronized form*2	4 weeks	29.9	221
Non-micronized form*3		37.2 ± 2.69	351

Mean ± SD, n = 4, *1: n = 3, *2: n = 2 (only mean), *3: n = 3/time point

The plasma pazopanib concentration was determined during 42-day repeated oral administration of pazopanib at 10, 30, and 300 mg/kg/day to male and female juvenile rats (Postnatal Day 21) (In the 300 mg/kg/day group, as deaths and decreased body weight were observed around Postnatal Day 50 [Day 29 of dosing], the dose was reduced to 100 mg/kg/day after a dose interruption for 4 days) (the table below). The C_{max} and AUC_{0-t} values increased generally at a lower rate than the dose increase in both sexes, suggesting that the absorption of pazopanib from the gastrointestinal tract was limited. Comparison of exposure on Days 5, 15, and 42 of dosing indicates no accumulation of pazopanib by repeat dosing, and there was no marked gender difference in exposure. Although the systemic exposure to pazopanib was higher in females than in males in the repeated dose study in adult rats, there was no gender difference in exposure in juvenile rats. The applicant explained that the reason for the contradictory finding in exposure is unknown.

PK parameter of pazopanib (male and female juvenile rats, oral repeated dose)

Time point	Dose (mg/kg/day)	Sex	C_{max} (μg/mL)	t_{max} (h)*2	AUC_{0-t} (μg·h/mL)
Day 5*1	10	Male	6.93 ± 2.56	4.00	51.8
		Female	8.14 ± 2.79	1.00	51.4
	30	Male	23.7 ± 2.54	2.00	152
		Female	26.9 ± 5.94	1.00	158
	300	Male	73.9 ± 18.8	4.00	634
		Female	81.4 ± 10.9	2.00	547
Day 15	10	Male	9.64 ± 3.73	4.00 (4.00, 4.00)	85.5 ± 35.4
		Female	10.8 ± 3.58	4.00 (1.00, 4.00)	101 ± 54.6
	30	Male	28.4 ± 5.85	1.00 (1.00, 4.00)	216 ± 18.4
		Female	26.1 ± 4.98	2.00 (2.00, 2.00)	213 ± 89.7
	300	Male	70.0 ± 4.98	8.00 (2.00, 8.00)	762 ± 62.2
		Female	64.6 ± 8.06	2.00 (2.00, 4.00)	701 ± 106
Day 42	10	Male	13.3 ± 4.05	2.00 (2.00, 4.00)	96.5 ± 32.9
		Female	16.9 ± 4.26	1.00 (1.00, 8.00)	145 ± 16.0
	30	Male	27.1 ± 5.34	1.00 (1.00, 2.00)	214 ± 72.0
		Female	33.7 ± 6.28	1.00 (0.50, 1.00)	191 ± 64.7
	100*3	Male	56.5 ± 13.4	4.00 (2.00, 8.00)	649 ± 176
		Female	34.7 ± 12.4	1.00 (0.50, 8.00)	314 ± 144

Mean ± SD, n = 3, *1: n = 3/timepoint, *2: Median (range), *3: Day 11 of 100 mg/kg administration after interruption

3.(ii).A.(1).3) *In vitro* membrane permeability

The permeability of pazopanib to human gastrointestinal membranes was evaluated using human colon cancer Caco-2 cells. The apparent permeability coefficients from the apical membrane to the basal membrane ($P_{appA \rightarrow B}$) for pazopanib were 12.2×10^{-6} cm/sec at 1 μmol/L, 7.25×10^{-6} cm/sec at 3 μmol/L, and 12.7×10^{-6} cm/sec at 10 μmol/L. The applicant explained that, when these results were compared with the positive controls (minoxidil and pindolol [$P_{appA \rightarrow B}$ values were 3.07-3.75 $\times 10^{-6}$ and 13.7-17.3 $\times 10^{-6}$ cm/sec, respectively]) and the negative control (atenolol [$P_{appA \rightarrow B}$ value was 0.184-0.265 $\times 10^{-6}$ cm/sec]), pazopanib is highly permeable.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution

The tissue distribution of radioactivity was determined by quantitative whole body autoradiography (WBA) after a single oral dose of ^{14}C-labeled pazopanib at 10 mg/kg to male and female pigmented rats.

In both sexes, radioactivity was widely distributed throughout the body and reached the maximum at 2 hours after dosing in most of the tissues evaluated. At 2 hours after dosing, the highest radioactivity was observed in the gastrointestinal content in both sexes, followed in descending order by bile, blood, liver, lungs, adrenal gland, renal medulla, uvea, renal cortex, brown fat, heart, bladder, meninges, and small intestine in males (21.2, 8.57, 8.23, 7.23, 5.45, 5.24, 4.52, 4.11, 4.08, 3.92, 3.89, 3.54, 3.05 μg eq/g, respectively), and meninges, uvea, blood, liver, adrenal gland, lungs and aortas (11.9, 11.8, 11.2, 11.2, 9.92, 9.70, 9.40 μg eq/g, respectively) in females. Tissue radioactivity disappeared rapidly in both sexes, and radioactivity decreased to below the lower limit of quantification (0.037 μg eq/g for male, 0.044 μg eq/g for female) in most tissues except melanin containing tissues (uvea, skin, meninges) at 3 days post dose. On the other hand, melanin containing tissues still had quantifiable levels of radioactivity after 35 days, and excretion of radioactivity from melanin containing tissues was slow. Radioactivity was found in the central nervous system (CNS), but concentrations were lower than

that in blood, except in meninges and male pituitary.

Following 7-day repeated oral administration of ^{14}C-labeled pazopanib at 100 mg/kg QD to pigmented male rabbits, radioactivity concentrations in the eye were high in melanin containing tissues such as choroids, and iris and ciliary body, and radioactivity was also widely distributed to other tissues throughout the body. Radioactivity concentrations reached a steady state by Day 7 in the eye tissues where radioactivity was detected, and declined over time after the final dose in all these tissues.

Based on the above findings, the applicant explained that pazopanib is widely distributed throughout the body in male and female pigmented rats, but the CNS penetration is low and the affinity of pazopanib and its metabolites for melanin containing tissues is high.

3.(ii).A.(2).2) Plasma protein binding and distribution to blood cells

Pazopanib (10-100 μg/mL) was incubated with plasma of mouse, rat, dog, monkey, and human and the plasma protein binding of pazopanib was evaluated by equilibrium dialysis. As a result, the plasma protein binding of pazopanib was as high as approximately 99% in all animal species tested, and was consistent regardless of the concentration. The binding rates of pazopanib to human serum albumin and α1-acid glycoprotein were >99% and >96%, respectively. The applicant explained as follows: the plasma protein binding rate of pazopanib is high and the distribution volume is small, but concomitant use of pazopanib with other drugs is unlikely to cause a pharmacokinetic drug interaction due to displacement of binding to plasma protein, as shown by the results of the pharmacokinetic drug interaction studies with other drugs with high protein binding property (lapatinib tosilate hydrate [lapatinib], potassium warfarin, omeprazole) [see "4.(ii).A.(3) Drug-drug interaction studies"], and the results of foreign clinical studies demonstrating no differences in the adverse event profile with or without concomitant use of lapatinib.

The applicant explained that the distribution of pazopanib and its metabolites in blood cells is low, since the blood/plasma radioactivity concentration ratio was approximately 0.63 to 0.71 after a single oral dose of ^{14}C-labeled pazopanib at 5 mg/kg to male and female cynomolgus monkeys.

3.(ii).A.(2).3) Placental transfer and fetal distribution

The applicant explained as follows: although the placental transfer and fetal distribution of pazopanib have not been evaluated, pazopanib is considered to pass through the placenta to fetuses because teratogenicity was detected in the embryo-fetal development study in rats.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* metabolism

The metabolism of pazopanib was evaluated following incubation of ^{14}C-labeled pazopanib (10 μmol/L) with hepatic microsomes from mice, rats, rabbits, dogs, cynomolgus monkeys, and humans at 37°C for 30 minutes. The unchanged compound was detected at the highest concentration in all animal species except in rabbits, and the major metabolites were M24 (mono-oxygenation) and M26 (mono-oxygenation) in animals and humans. M12 (di-oxygenation) was also detected in rabbits, cynomolgus monkeys, and humans, M28 (desmethylation) in rabbits, and M8 (carboxylation) in humans.

The metabolism of pazopanib was evaluated following incubation of ^{14}C-labeled pazopanib (10 μmol/L) with hepatocytes from mice, rats, rabbits, dogs, cynomolgus monkeys, and humans at 37°C for 4 or 24 hours. The unchanged compound was detected at the highest concentration in rats, cynomolgus monkeys, and humans. Other metabolites detected were M24 and M26 (except in rabbits), M20 (desmethylation of a mono-oxygenated metabolite [except in rabbits and humans]), M12 (except in rats and rabbits), M8 (except in rats, dogs, and cynomolgus monkeys),

and M15 (glucuronidation of a mono-oxygenated metabolite [except in dogs]). M9 (glucuronidation of a carboxylated metabolite) was detected only in humans.

^{14}C-labeled pazopanib (5, 50 μmol/L) was incubated with human hepatic microsomes in the presence of an inhibitor of each CYP coenzymes (CYP1A2, 2D6, 2C8, 2C9, 2C19, 3A4). CYP3A4 inhibitor inhibited the metabolism of pazopanib (5 μmol/L) to M24 and M26 by 100% and the metabolism of pazopanib (50 μmol/L) to M24, M26, and M27 (desmethylation) by approximately 77%, 85%, and 100%, respectively. CYP2C8 inhibitor inhibited the metabolism of pazopanib (5 μmol/L) to M24 and M26 by approximately 62% and 47%, respectively and the metabolism of pazopanib (50 μmol/L) to M24, M26, and M27 by approximately 28%, 23%, and 17%, respectively. The metabolism of pazopanib was unaffected in the presence of CYP1A2, 2C9, 2D6, or 2C19 inhibitor.

CYP isozymes involved in the metabolism of pazopanib were studied by incubating ^{14}C-labeled pazopanib (5 or 50 μmol/L) with human recombinant CYP (CYP1A2, 2D6, 2C8, 2C9, 2C19, 3A4). In the CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 expression systems, pazopanib (50 μmol/L) was metabolized to M24 (13.44%, 2.19%, 0.63%, 0.73%, 2.07%, 4.50% of total radioactivity, respectively) and M26 (1.82%, 0.45%, 0.23%, 0.41%, 0.18%, 4.79% of total radioactivity, respectively) and in the CYP1A2, 2D6, and 3A4 expression systems, it was metabolized to M27 (0.84%, 0.46%, 0.81% of total radioactivity, respectively). On the other hand, pazopanib (5 μmol/L) was not metabolized to M26 in the CYP2C9 and 2C19 expression systems, and M24 in the CYP2C19 expression system. In the CYP3A4 expression system, pazopanib was metabolized to the di-oxygenated metabolites, M12 and M16, and to 2 unidentified components in the CYP1A2 expression system.

Based on the above findings, the applicant explained that pazopanib is not readily metabolized in hepatic microsomes or hepatocytes, but a part of pazopanib is oxygenated primarily by CYP3A4 and partly by CYP1A2 and CYP2C8.

3.(ii).A.(3).2) ***In vivo*** **metabolism**

The plasma metabolites of pazopanib were determined after a single oral administration of ^{14}C-labeled pazopanib at 100 or 1000 mg/kg to male and female mice, at 10 mg/kg to male and female rats, and at 5 mg/kg to male and female cynomolgus monkeys. In the plasma of rats, cynomolgus monkeys, and male mice, pazopanib was mainly found as unchanged drug. The metabolites detected in human plasma (M24, M26, M27) were also detected in animals, and the plasma concentrations of M24, M26, and M27 were lower than that of unchanged pazopanib. There was no marked gender difference in plasma metabolites in any animal species.

After 7-day repeated oral administration of pazopanib (QD) at 100 mg/kg to male mice, at 3 or 30 mg/kg to male rats, and at 50 mg/kg to male and female cynomolgus monkeys, pazopanib in the plasma was mainly found as unchanged drug. In the animals, the plasma concentrations of the major metabolites detected in human plasma (M24, M26, M27, M28) were lower than that of unchanged pazopanib.

After a single oral administration of ^{14}C-labeled pazopanib at 10 or 5 mg/kg to male and female rats and cynomolgus monkeys, urinary and fecal metabolites were determined in rats and fecal metabolites in cynomolgus monkeys. In the rat urine and feces and cynomolgus monkey feces, pazopanib was mainly found as unchanged drug.

The metabolites of pazopanib in bile were determined after a single oral administration of ^{14}C-labeled pazopanib to bile duct cannulated male rats and male cynomolgus monkeys at 10 and 5 mg/kg, respectively. In rats, the abundance values (% of administered dose) recovered in bile were highest for unchanged pazopanib (1.3%), followed by M15 (1.2%). In cynomolgus monkeys,

the abundance values (% of administered dose) recovered in bile were highest for M8 and M9 in total (3.8%), followed by M18 (2.4%), M14 (glucuronidation) and M15 in total (1.4%), and M16 and M17 (glucuronidation of a mono-oxygenated metabolite) in total(1.4%). Several other metabolites including unchanged pazopanib were also detected, but either metabolite accounted for 1.1% or less.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Urinary and fecal excretion

The urinary and fecal excretions of radioactivity (% of administered radioactivity) were determined after a single oral administration of ^{14}C-labeled pazopanib at 10 mg/kg to male and female rats. The total recovery of radioactivity by 96 hours after dosing was approximately 90% in males and approximately 94% in females. The urinary and fecal excretions of radioactivity were 15% and 61% in males and 17% and 52% in females, respectively. Because of loose stool caused by pazopanib, 25% and 14% of administered radioactivity were recovered in cage washing in males and females, respectively.

The urinary and fecal excretions of radioactivity were determined after a single oral administration of ^{14}C-labeled pazopanib at 5 mg/kg to male and female cynomolgus monkeys. The total recovery of radioactivity by 168 hours after dosing was 89% in males and 93% in females, and the urinary and fecal excretions of radioactivity were 2% and 85% in males and 3% and 87% in females, respectively.

Based on the above findings, the applicant explained that the major excretion route of pazopanib after single oral administration was via the feces in rats and cynomolgus monkeys, and there was no marked gender difference in the excretion of pazopanib.

3.(ii).A.(4).2) Biliary excretion

The biliary, urinary, and fecal excretions of radioactivity were determined after a single oral administration of ^{14}C-labeled pazopanib at 10 and 5 mg/kg to bile duct cannulated male rats and male cynomolgus monkeys.

In rats, the total recovery of radioactivity by 96 hours after dosing was approximately 92%, and the biliary, urinary, and fecal excretions of radioactivity were approximately 8%, 25%, and 43%, respectively. Because of loose stool caused by pazopanib, approximately 14% of administered radioactivity was recovered in cage washing.

In cynomolgus monkeys, the biliary, urinary, and fecal excretions of radioactivity by 96 hours after dosing were approximately 23%, 2%, and 60%, respectively.

Based on the above findings, the applicant explained as follows:
In rats, the majority of pazopanib was primarily excreted via the feces, secondarily via the urine, and slightly via the bile. In cynomolgus monkeys, the urinary excretion of pazopanib was small, and the majority was excreted via the feces as unchanged pazopanib, and partly via the bile. In rats and cynomolgus monkeys, at least 35% and 25%, respectively, of administered radioactivity were absorbed.

A potential for enterohepatic circulation of pazopanib and its metabolites was not studied since the blood pazopanib concentrations did not show a bimodal curve to suggest enterohepatic circulation. The applicant explained that, because pazopanib is metabolized by oxygenation and glucuronide conjugation in the liver, and excreted in the bile, unchanged pazopanib or the deconjugated product formed, by the hydrolysis of glucuronide conjugates by enteric bacteria, may get trapped in enterohepatic circulation.

3.(ii).A.(4).3) Excretion into milk

A potential for pazopanib excreted into milk was not studied. The applicant explained that pazopanib is considered to be excreted into milk because it has been reported that breast cancer resistance protein (BCRP) is involved in milk excretion of drugs (*Nat Med.* 2005; 11: 127-9) and pazopanib is a substrate for mouse Bcrp and human BCRP.

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1) Enzyme inhibition

The substrates of various CYP coenzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) were incubated with human liver microsomes in the presence of pazopanib (0.1-100 μmol/L). Pazopanib inhibited the metabolism of each substrate with IC_{50} values of 16, 15, 10, 7.9, 11, 18, 17, and 11 to 14 μmol/L, respectively.

Pazopanib (0.1-100 μmol/L) was incubated with human CYP expression systems (CYP1A2, 2C9, 2C19, 2D6, 3A4). IC_{50} values for CYP1A2, 2C9, 2C19, 2D6, and 3A4 were 11.7, 1.7, 12.5, 85, and 12.0 to 50 μmol/L, respectively. When pazopanib (0.25-250 μmol/L) was added to human UGT1A1 expression system, IC_{50} was 1.2 μmol/L.

The above results indicate that pazopanib inhibits CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, as well as UGT1A1. The applicant explained that pazopanib is likely to cause pharmacokinetic drug interactions with drugs metabolized by these CYP coenzymes or UGT1A1, as the C_{24} of unchanged pazopanib was approximately 22 μg/mL when Japanese patients with solid tumors received multiple oral doses of pazopanib 800 mg [see "4.(ii)A.(2).1) Phase I study in Japan"].

3.(ii).A.(5).2) Enzyme induction

(i) ***In vitro***

The induction of CYP3A4 by pazopanib (0.01-10 μmol/L) was investigated using HuH7 cells expressing human pregnane X receptor (PXR). Pazopanib activated PXR at 10 μmol/L similarly (1.07 times) to the positive control, rifampicin (10 μmol/L).

Human primary hepatocytes in culture were treated with pazopanib (1-100 μmol/L) for 2 days, and mRNA expression and enzyme activity were determined for CYP1A2, 2B6, and 3A4. Compared with the vehicle control group, mRNA expression and enzyme activity were 2.0 to 9.5 and 0.84 to 2.3 times higher for CYP3A4, 1.3 to 5.6 and 1.2 to 3.1 times higher for CYP2B6, and 1.1 to 3.2 and 0.57 to 2.2 times higher for CYP1A2, respectively, but these changes were not dependent on the concentration of pazopanib.

(ii) ***In vivo***

After 4-week repeated oral administration of pazopanib at 3, 10, 30, 100, or 300 mg/kg/day to male and female rats, and at 5, 50, or 500 mg/kg/day to male and female cynomolgus monkeys, total CYP content and enzyme activity for CYP1A, 2B, 2E, 3A, and 4A were determined. Pazopanib did not affect total CYP content or CYP activity in male and female rats and male and female cynomolgus monkeys, except that total CYP content was higher in male rats in the 300 mg/kg/day group than in the vehicle control group.

Based on the above results, the applicant explained as follows:
Pazopanib has a potential to induce CYP3A4 and 2B6 in humans, but pazopanib is unlikely to induce CYP in clinical settings because (1) repeated oral administration of pazopanib at 300 mg/kg in rats and 500 mg/kg in cynomolgus monkeys did not induce CYP, and (2) the PK of CYP substrates was not affected by CYP induction in the drug-drug interaction studies of pazopanib with various CYP substrates [see "4.(ii).A.(3).4) Drug-drug interaction study with various CYP substrates"].

3.(ii).A.(5).3) Transporters

The permeability of pazopanib to membranes via P-glycoprotein (P-gp) was evaluated at 1, 3, and 10 μmol/L using Caco-2 cells. The apparent flux ratios ($P_{appB\rightarrow A}/P_{appA\rightarrow B}$) for pazopanib were 4.93, 4.40, and 1.65, respectively, and decreased to 1.38, 1.03, and 0.613, respectively, in the presence of GF120918 (P-gp inhibitor).

The permeability of ^{14}C-labeled pazopanib to membranes via P-gp was evaluated at 3 μmol/L using MDCKII-MDR1 cells expressing human P-gp. The $P_{appB\rightarrow A}/P_{appA\rightarrow B}$ for pazopanib was 19.5 and decreased to 1.0 in the presence of GF120918.

In MDCKII cells expressing mouse Bcrp (MDCKII-Bcrp cells) and MDCKII cells expressing human BCRP (MDCKII-BCRP cells), $P_{appB\rightarrow A}/P_{appA\rightarrow B}$ for ^{14}C-labeled pazopanib (3 μmol/L) were 12.9 and 7.6, respectively, and decreased to 1.04 and 0.84, respectively, in the presence of GF120918 (BCRP inhibitor).

A potential for pazopanib (0.1-30 μmol/L) and its major human metabolites, M24 and M26 (0.1-100 μmol/L) to inhibit digoxin transportation via P-gp was investigated using MDCKII-MDR1 cells. Pazopanib, M24, and M26 did not inhibit P-gp even at the highest concentration tested.

A potential for pazopanib (0.3-100 μmol/L) to inhibit prazosin transportation via mouse Bcrp was investigated using MDCKII-Bcrp cells. Pazopanib did not inhibit Bcrp at 100 μmol/L where pazopanib was precipitated. Pazopanib did not inhibit Bcrp at 30 μmol/L, the highest concentration where pazopanib was not precipitated. A potential for pazopanib (0.3-10 μmol/L), M24 and M26 (0.3-100 μmol/L) to inhibit cimetidine transportation via human BCRP was investigated using MDCKII-BCRP cells. Pazopanib did not inhibit BCRP even at the highest concentration tested, while both M24 and M26 inhibited BCRP with an IC_{50} value of 10 μmol/L

A potential for pazopanib (0.1-100 μmol/L) to inhibit estradiol 17β-D glucuronide transportation via OATP1B1 was investigated using Chinese hamster ovarian cells expressing human OATP1B1. An IC_{50} value for pazopanib was 0.79 μmol/L for OATP1B1. Data for 0.1 to 30 μmol/L of pazopanib were analyzed since pazopanib was precipitated at 100 μmol/L.

A potential for pazopanib, M24, and M26 (0.3-30 μmol/L) to inhibit the transcellular transport of sodium taurocholate via the hepatic uptake transporter, Na^+-taurocholate-cotransporting polypeptide (Ntcp) and the hepatic efflux transporter, bile salt export pump (Bsep) was investigated using rat hepatocytes (B-CLEAR Kit, CellzDirect). Pazopanib, M24, and M26 hardly affected the efflux coefficient to the bile duct (95%, 95%, 88% of the vehicle control, respectively) and accumulation in hepatocytes (60%, 85%, 86% of the vehicle control, respectively) for sodium taurocholate even at the highest concentration tested. On the other hand, pazopanib, M24, and M26 (30 μmol/L) reduced the hepatic uptake of sodium taurocholate by 44%, 33% and 42% of the vehicle control, respectively. These findings indicate that pazopanib, M24, and M26 inhibit rat Ntcp but not rat Bsep.

A potential for pazopanib, M24, and M26 (0.3-30 μmol/L) to inhibit the transcellular transport of sodium taurocholate was investigated using human hepatocytes (B-CLEAR Kit, CellzDirect). Pazopanib, M24, and M26 hardly affected the efflux coefficient to the bile duct (100%, 93%, 91% of the vehicle control, respectively), accumulation in hepatocytes (100%, 150%, 120% of the vehicle control, respectively) and hepatic uptake (100%, 110%, 93% of the vehicle control, respectively) for sodium taurocholate even at the highest concentration tested. These findings indicate that pazopanib, M24, and M26 do not inhibit human NTCP or human BSEP.

A potential for pazopanib (2.3-133 μmol/L) to inhibit estradiol 17β-D glucuronide transportation via human multidrug resistance protein 2 (MRP2) was investigated using membrane vesicles of

Sf9 insect cells expressing MRP2. Pazopanib did not inhibit MRP2 even at the highest concentration tested.

Based on the above findings, the applicant explained as follows:
Pazopanib is likely to cause pharmacokinetic drug interactions clinically in concomitant use with a P-gp or BCRP inhibitor, or an OATP1B1 substrate drug, taking into account that pazopanib is a substrate for P-gp and BCRP, pazopanib inhibits OATP1B1 (IC_{50}, 0.79 μmol/L [0.3 μg/mL]), and the C_{24} of unchanged pazopanib was approximately 22 μg/mL when Japanese patients with solid tumors received multiple oral dose of pazopanib 800 mg. On the other hand, M24 and M26 inhibit BCRP, but these metabolites are unlikely to cause pharmacokinetic drug interactions via BCRP clinically, because of the plasma concentrations of M24 and M26 observed when Japanese patients with solid tumors received multiple oral dose of pazopanib 800 mg.

3.(ii).B Outline of the review by PMDA
Based on the submitted data and the following review, PMDA concluded that the applicant's explanation on absorption, distribution, metabolism, and excretion and pharmacokinetic interactions of pazopanib are acceptable.

3.(ii).B.(1) Tissue distribution
The applicant explained that pazopanib has a high affinity for melanin. PMDA asked the applicant to explain potential issues resulting from the distribution of pazopanib or its metabolites to melanin containing tissues from a safety point of view when pazopanib is used clinically.

The applicant responded as follows:
The single dose study of pazopanib in pigmented rats suggested a selective association of pazopanib-related material with melanin, but the 7-day repeat dose study in pigmented rabbits indicated that pazopanib and its metabolites are unlikely to accumulate in melanin containing tissues.

Adverse events and adverse drug reactions of skin and subcutaneous tissue disorders and ocular events (≥5% in either population) in a global phase III study (Study VEG110727), reported from Japanese (31 subjects), Asian (a total of 57 subjects including 31 Japanese and 26 Korean patients) and non-Asian (183 subjects) patients with soft tissue sarcoma treated with pazopanib, were investigated. There was no clear difference in the incidence of adverse events between Japanese and Asian patients, but some adverse events of skin and subcutaneous tissue disorders tended to occur more frequently in Asian patients. The incidences of the following adverse events were ≥10% higher in Asian patients than in non-Asian patients: hair colour changes (Asian, 54%; non-Asian, 34%), exfoliative rash (30%, 15%), alopecia (19%, 9%), and skin disorder (28%, 6%). The reason for this difference is unknown, but it is not considered to be clinically significant because none of these events led to treatment withdrawal. In Study VEG105192, Study VEG102616, and Study VEG107769 in patients with renal cell carcinoma, the types and incidences of adverse events reported by ≥15% of subjects were similar in East-Asian (51 patients), Asian (89 patients), and Caucasian (489 patients) patients. These results indicate no ethnic difference in the safety of pazopanib.

Moreover, in Study VEG110727, adverse events and adverse drug reactions of skin and subcutaneous tissue disorders and ocular events reported by ≥2 patients were analyzed by the time of onset (i.e., <6 months, 6 months to <1 year, ≥1 year). Most of the adverse events and adverse drug reactions were reported within 6 months of the first dose of pazopanib, which indicates that there were no clinically significant events observed during long-term treatment with pazopanib.

Based on the above, pazopanib is unlikely to cause any safety issue resulting from the distribution of pazopanib or its metabolites to melanin containing tissues.

PMDA considers as follows:
It is necessary to monitor adverse events suggestive of the distribution of pazopanib to melanin containing tissues when pazopanib is used clinically, because non-clinical data indicated the long-term distribution of pazopanib or its metabolites in melanin containing tissues including uvea. In addition, it is necessary to appropriately provide the information about such adverse events as skin disorder and hair colour changes, which were reported more frequently in Japanese patients than in foreign patients in Study VEG110727 [see "4.(iii).B.(3).1) Safety profile of pazopanib and difference in safety between Japan and other countries"], to the medical practice.

3.(ii).B.(2) Pharmacokinetic drug interactions via transporters
The applicant explained that pazopanib did not inhibit P-gp, BCRP, NTCP, or BSEP in the concentration range up to 10 or 30 μmol/L tested. PMDA asked the applicant to explain the potential for pazopanib to cause pharmacokinetic drug interactions via transporters when used by the proposed dosage and administration, based on the finding that the geometric mean of C_{max} was approximately 41 μg/mL (94 μmol/L) when Japanese patients with solid tumors received multiple oral dose of pazopanib 800 mg [see "4.(ii).A.(2).1) Phase I study in Japan"].

The applicant responded as follows:
Higher concentration of pazopanib should have been investigated in non-clinical studies since the maximum concentrations tested in the non-clinical studies were lower than the C_{max} of pazopanib found in clinical studies. However, from the result that pazopanib was precipitated at 100 μmol/L in the studies to investigate a potential for pazopanib to inhibit mouse Bcrp and human OATP1B1 [see "3.(ii).A.(5).3) Transporters"], concentrations above 30 μmol/L were not tested in the subsequent studies. Therefore it is unknown whether pazopanib causes any pharmacokinetic drug interaction via a transporter in clinical use.

As it remains to be elucidated whether pazopanib causes any pharmacokinetic drug interaction via a transporter in clinical use, PMDA considers that it is necessary to continuously collect relevant information, including findings from further investigation by the applicant, and appropriately provide information to the medical practice when new findings become available.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies were conducted with the monohydrochloride salt of pazopanib, and some toxicity studies with the dihydrochloride salt. In the toxicity study section, all doses and concentrations of the study drug are expressed in terms of the free base. The monohydrochloride salt and dihydrochloride salt of pazopanib are expressed as "pazopanib."

3.(iii).A.(1) Single dose Toxicity
No single dose toxicity was conducted, but the acute toxicity of pazopanib was evaluated in a 4-day oral repeat dose study in rats and an 8-day oral repeat dose study in monkeys.

3.(iii).A.(1).1) Four-day oral dose toxicity study in rats
In SD rats (6 females per group), repeat oral dose of pazopanib was administered at 0 (vehicle control), 30, 100, or 300 mg/kg/day for 4 days. There were no deaths at up to 300 mg/kg/day, and the approximate lethal dose was considered to be >300 mg/kg/day.

3.(iii).A.(1).2) Eight-day oral dose toxicity study in monkeys
In cynomolgus monkeys (1 each of male and female per group), repeat oral dose of pazopanib

was administered via a transnasal catheter at 0 (vehicle control), 100, 300, or 1000 mg/kg/day for 8 days. There were no deaths at up to 1000 mg/kg/day, and the approximate lethal dose was considered to be >1000 mg/kg/day.

3.(iii).A.(2) Repeat dose toxicity

3.(iii).A.(2).1) Thirteen-week oral dose toxicity study in mice

In mice (ICR, 12 each of males and females per group), pazopanib was administered orally at 0 (vehicle control), 100, 300, or 1000 mg/kg/day for 13 weeks. Clinical signs observed were pale incisor teeth (males at ≥300 mg/kg/day, females in all pazopanib groups), overgrown and broken incisor teeth (≥300 mg/kg/day), overgrown and broken nails (all pazopanib groups), pale feces (males at 1000 mg/kg/day, females at ≥300 mg/kg/day), tendency to reduce body weight gain (males at 1000 mg/kg/day, females in all pazopanib groups), and reduced food consumption (females at 1000 mg/kg/day). Hematological findings included increased hematocrit and hemoglobin (males in all pazopanib groups), decreased red blood cell count (females in all pazopanib groups), increased monocyte count (males in all pazopanib groups, females at ≥300 mg/kg/day), increased eosinophil count (females at ≥300 mg/kg/day), increased basophil count (males in all pazopanib groups, females at 1000 mg/kg/day), increased leukocyte count (males at ≥300 mg/kg/day, females at 1000 mg/kg/day), increased lymphocyte count (males at ≥300 mg/kg/day, females at 1000 mg/kg/day), and increased neutrophil and large nonstained cell count (1000 mg/kg/day). In the clinical chemistry, increased plasma alanine aminotransferase (ALT) (males in all pazopanib groups, females at 1000 mg/kg/day) and aspartate aminotransferase (AST) (males at ≥300 mg/kg/day, females at 1000 mg/kg/day), decreased plasma glucose (females at ≥300 mg/kg/day), and decreased albumin concentrations (males at ≥300 mg/kg/day, females at 1000 mg/kg/day) were observed. Histopathological findings revealed basophilic change of renal cortical tubules and inflammatory cell infiltration in renal cortex (females at ≥300 mg/kg/day), atrophy and mineralization of glomerulus and pigmentation and mineralization of renal cortex (females at 1000 mg/kg/day) in the kidney, hepatocellular hypertrophy (males at ≥300 mg/kg/day, females at 1000 mg/kg/day), eosinophilic foci and adenomas (females at 1000 mg/kg/day), decreased cytoplasmatic density (all pazopanib groups), macrophage accumulation (≥300 mg/kg/day) in the liver, increased extramedullary hematopoiesis (all pazopanib groups) and hemosiderin deposition (males in all pazopanib groups) in the spleen, crystalline material and inflammatory cell infiltration in lumina propria, crystalline material in mesenteric lymph node, ulcer of duodenal mucosa (1000 mg/kg/day) in the small intestine, decreased number and loss of corpora lutea (females at ≥300 mg/kg/day) in the ovary, predentin thickening, dentin thinning, and irregular ameloblast layer (all pazopanib groups) in incisor teeth, growth plate hypertrophy, degeneration and partial fusion in the femur and sternum, osteoarthrosis in stifle joints (1000 mg/kg/day), complete fusion of tibia and femur joint surface (males at 1000 mg/kg/day), and subcutaneous inflammation, and incurving and erosion of distal phalanx (males in all pazopanib groups, females at ≥300 mg/kg/day) in fingers. There were no deaths in this study.

Based on the above, the no observed adverse effect level (NOAEL) was considered to be <100 mg/kg/day.

3.(iii).A.(2).2) Four-week oral dose toxicity study in rats

In rats (SD, 10 each of males and females per group), pazopanib was administered orally at 0 (vehicle control), 3, 10, 30, 100, or 300 mg/kg/day for 4 weeks. Recovery groups (5 each of males and females per group) with a 6-week washout period were included in the control group and 300 mg/kg/day group. There were tendency to reduce reticulocyte count (males at 300 mg/kg/day) in hematology, tendency to increase serum ALT, AST and alkaline phosphatase (ALP) (females at 300 mg/kg/day) in clinical chemistry, and decreased testicular weight (males at 300 mg/kg/day) in organ weights. Histopathological findings revealed epiphyseal growth plate hypertrophy in

sternum (300 mg/kg/day) and femur (≥100 mg/kg/day), hypoplasia of metaphyseal bone marrow in sternum (males at ≥300 mg/kg/day), and depletion of round spermatids in Stages I to V in seminiferous tubules (males at 100 mg/kg/day). During the washout period, reduced body weight gain, reduced food consumption, tendency to increase reticulocyte count, overgrown and fragile incisor teeth, and absent and broken nails (300 mg/kg/day) were observed, and the effects on body weight and food consumption were considered to be secondary effects of abnormal incisor teeth. After the washout period, the effects on teeth and nails remained, but changes in the clinical chemistry and histopathological changes in the testicle, epiphyseal growth plate and metaphyseal bone marrow completely or partially resolved. There were no drug-related deaths, exacerbation of clinical signs, ophthalmology, urinalysis, or necropsy findings.

Based on the above, the NOAEL was considered to be 30 mg/kg/day.

3.(iii).A.(2).3) Twenty-six-week oral dose toxicity study in rats

In rats (SD, 12 each of males and females per group), pazopanib was administered orally at 0 (vehicle control), 3, 30, or 300 mg/kg/day for 26 weeks. At the beginning of the study, recovery groups were included in the control group and 300 mg/kg/day group (6 each of males and females per group). However, recovery was not evaluated in this study, because 1 female in the 30 mg/kg/day group and 9 males and 9 females in the 300 mg/kg/day group died or were sacrificed moribund due to exacerbation of clinical signs, and because of serious toxicity, male survivors in the 300 mg/kg/day group and 6 males in the control group were necropsied on Day 98, and female survivors in the 300 mg/kg/day group and 6 females in the control group were necropsied on Day 140. In the clinical observation, overgrown and broken incisor teeth (both sexes in all pazopanib groups), exacerbation of clinical signs (emaciation, hunched posture, unkept coat, etc.), abnormal feces (watery feces, liquid feces, etc.), and decreased body weight and food consumption (≥30 mg/kg/day) were observed. Hematological findings included decreased red blood cell count, increased red cell distribution width and prolonged activated partial thromboplastin time (≥30 mg/kg/day), decreased platelet count (males at ≥30 mg/kg/day), increased leukocyte and lymphocyte counts (females at ≥30 mg/kg/day), increased neutrophil and monocyte counts, and decreased hematocrit (300 mg/kg/day). Clinical chemistry findings included increased serum globulin and ALT, and decreased albumin globulin ratio (males in all pazopanib groups, females at ≥30 mg/kg/day), increased serum ALP (males at 300 mg/kg/day, females in all pazopanib groups), increased serum cholesterol and bile acid, decreased serum albumin (≥30 mg/kg/day), increased serum urea nitrogen (males at 300 mg/kg/day, females at ≥30 mg/kg/day), increased serum bilirubin and inorganic phosphorus (females at ≥30 mg/kg/day), decreased serum total protein and increased serum triglyceride (300 mg/kg/day), and increased serum AST and γ-glutamyltranspeptidase (females at 300 mg/kg/day). Urinalysis findings included increased urinary protein excretion and urinary protein/creatinine ratio (≥30 mg/kg/day), increased urine volume and decreased specific gravity (females at 300 mg/kg/day), and decreased urinary creatinine excretion (males at 300 mg/kg/day). Necropsy and organ weight findings revealed decreased testes weight (males at ≥30 mg/kg/day), abnormal incisor teeth (absence, overgrowth, etc.), large lumen in gastrointestinal tract, absence of paws with crusted area or red foci (300 mg/kg/day), and increased adrenal weight (females at 300 mg/kg/day). Histopathological findings revealed chronic progressive nephropathy and adrenal cortex angiectasis (all pazopanib groups), pituitary basophil hypertrophy (males in all pazopanib groups), bone marrow hypoplasia in the femur and sternum, trabecular atrophy of the femur, granular lymphocyte count decreased in mucosal epithelium of trachea, nail dyskeratosis, and dentin and enamel thinning, degeneration, dental pulp necrosis, etc. in incisor teeth (≥30 mg/kg/day), growth plate hypertrophy of the femur, periosteal chondroid change in sternum, adrenal cortex necrosis, duodenal villous atrophy, pancreatic acinar atrophy, ameloblastic and odontoblastic necrosis in incisor teeth, periodontal edema, and deposit of crystalline material in mesenteric lymph node macrophages, duodenal lamina propria, and jejunal lamina

propria mucosae (300 mg/kg/day), testicular atrophy and degeneration, and changes in the epididymis (hypospermia, aspermia, and cribriform change) (males at ≥30 mg/kg/day), and ovarian atrophy (females at ≥30 mg/kg/day). There were no pazopanib-related findings in ophthalmology.

Based on the above, the NOAEL was considered to be <3 mg/kg/day. The systemic exposures (AUC_{0-t}) at this dose level were 76.6 (male) and 100 μg·h/mL (female) at Week 26, which were 0.11 and 0.15 times the clinical exposure*, respectively.

*: AUC_{0-24} was 677 μg·h/mL on Day 22, when Japanese patients with solid tumors received multiple oral dose of pazopanib 800 mg QD.

3.(iii).A.(2).4) Four-week oral dose toxicity study in monkeys

In cynomolgus monkeys (3 each of males and females per group), pazopanib was administered orally at 0 (vehicle control), 5, 50, or 500 mg/kg/day for 29 days. Discolored feces (brownish yellow) were reported as a change in clinical signs in the pazopanib groups, but this was due to pazopanib present in feces, and of no toxicological significance. There were no pazopanib-related changes in body weight, ophthalmology, electrocardiography, hematology, clinical chemistry, urinalysis, necropsy, organ weight, or histopathology.

Based on the above, the NOAEL was considered to be 500 mg/kg/day.

3.(iii).A.(2).5) Fifty-two-week oral dose toxicity study in monkeys

In cynomolgus monkeys (4 each of males and females per group), pazopanib was administered orally at 0 (vehicle control), 5, 50, or 500 mg/kg/day for 52 weeks. The following animals were sacrificed moribund: 1 male in the 5 mg/kg/day group due to diaphragmatic hernia on Day 52, 1 male in the 500 mg/kg/day group due to right forelimb fracture on Day 90, and 1 male in the 500 mg/kg/day group due to exacerbation of clinical signs (persistent diarrhea, decreased body weight, etc.), possibly caused by protozoal enteropathy, on Day 171. The administration of pazopanib was terminated at Week 34 in the 500 mg/kg/day group, because deposit of crystalline material in lamina propria of small-intestinal mucosae and mesenteric lymph node were observed histopathologically in the sacrificed animals, and 2 other animals in this group were withdrawn from pazopanib because of the exacerbation of clinical signs (abnormal feces including discolored feces and liquid feces, decreased body weight). Of the remaining animals in the 500 mg/kg/day group, 1 male and 1 female were necropsied on Day 234 to investigate the relationship between crystalline material and diarrhea. The other animals were withdrawn from pazopanib for approximately 19 weeks until Week 52 to investigate recovery. Clinical signs observed were discolored feces (green, orange, white, tan, yellow), mucous feces and liquid feces (males and females at ≥50 mg/kg/day), and decreased body weight and food consumption (males at 500 mg/kg/day). Clinical chemistry findings included decreased serum total protein and albumin (females at 500 mg/kg/day), and increased serum bilirubin (1 male and 1 female at 500 mg/kg/day). Decreased number of corpora lutea (females at 500 mg/kg/day) was observed in histopathology. In the 500 mg/kg/day group, abnormal feces were observed during the withdrawal period as well and decreased serum total protein and albumin were not reversible after the withdrawal period. Crystalline material in lamina propria of small-intestinal mucosae and mesenteric lymph node observed in the sacrificed animals in the 500 mg/kg/day group (2 males) was identified as pazopanib by IR spectroscopy, mass spectrometry, and nuclear magnetic resonancy. There were no pazopanib-related changes in ophthalmology, electrocardiogram, hematology, urinalysis, necropsy, or organ weight.

Based on the above, the NOAEL was considered to be 50 mg/kg/day. The systemic exposures (AUC_{0-t}) at this dose level were 235 (male) and 289 μg·h/mL (female) at Week 52, which were 0.35 and 0.43 times the clinical exposure*, respectively.

*: AUC_{0-24} was 677 μg·h/mL on Day 22, when Japanese patients with solid tumors received multiple oral dose of pazopanib 800 mg QD.

3.(iii).A.(3) Genotoxicity

Reverse mutation tests using *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and *Escherichia coli* (WP2*uvrA*pKM101), chromosomal aberration assay with human peripheral lymphocytes, and micronucleus assay with rat bone marrow were conducted with pazopanib. Genotoxicity assessments indicate that pazopanib is not genotoxic.

3.(iii).A.(4) Carcinogenicity

As pazopanib is an antineoplastic drugs for advanced malignant tumors, no carcinogenicity studies have been conducted with pazopanib.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Fertility and early embryonic development to implantation in rats

In male SD rats (25 per group), pazopanib were administered orally at 0 (vehicle control), 3, 30, or 100 mg/kg/day for 105 to 108 days from 10 days before mating. Following 10 days of treatment and 63 to 65 days of treatment, treated males were mated to untreated females. Female rats were caesarian sectioned on Gestation Day 20 (Gestation Day 0 was defined as the day when mating was confirmed), and fetuses were examined externally. Clinical signs observed in paternal animals were abnormal incisor teeth, loose feces, and decreased body weight gain and food consumption (≥30 mg/kg/day). Decreased organ weight was observed in testes, epididymides, and seminal vesicle (≥30 mg/kg/day). Sperm findings were decreased testicular and epididymal sperm concentrations and decreased sperm motility (100 mg/kg/day). During the study period, there were no pazopanib-related deaths. There were no pazopanib-related changes in mating, copulation/conception rate, the number of days between pairing and coitus, untreated female body weight after mating, fetal body weight, fetal viability, or fetal external examinations.

Based on the above, the NOAELs for male fertility and male reproductive organs were considered to be 100 and 3 mg/kg/day, respectively.

In female SD rats (25 per group), pazopanib were administered orally at 0 (vehicle control), 3, 30, or 300 mg/kg/day from 2 weeks before mating until Gestation Day 6. After mating with untreated male rats, the female rats were caesarian sectioned on Gestation Day 20 and fetuses were examined externally. Clinical signs observed in maternal animals were decreased body weight gain on Gestation Day 0 to Gestation Day 7 (all pazopanib groups) and Gestation Day 7 to Gestation Day 20 (300 mg/kg/day), and decreased food consumption on Gestation Day 14 to Gestation Day 20 (300 mg/kg/day). Effects on fertility and early embryonic development observed were increased rate of pre- and post-implantation loss (≥30 mg/kg/day), and decreased fertility rate and number of implantations (300 mg/kg/day). There were no live fetuses in the 300 mg/kg/day group. Fetal body weight was decreased (30 mg/kg/day). There were no pazopanib-related changes in the number of estrus cycle, number of days until mating, copulation rate, or fetal external examinations.

Based on the above, pazopanib was shown to be embryolethal, and the NOAEL for female fertility and early embryonic development was considered to be 3 mg/kg/day.

3.(iii).A.(5).2) Study of embryo-fetal development in rats

In pregnant rats (SD, 21-22 per group), pazopanib were administered orally at 0 (vehicle control), 1, 3, or 10 mg/kg/day on Gestation Day 6 to Gestation Day 17. The rats were caesarian sectioned on Gestation Day 21, and fetuses were examined. In maternal animals, body weight gain was decreased on Gestation Day 6 to Gestation Day 18 (10 mg/kg/day). Effects on embryofetal development were delayed ossification of centrum of thoracic and lumbar vertebra

(≥3 mg/kg/day), decreased number of live fetuses, increased rate of post-implantation loss, decreased fetal body weight, and fetal cardiovascular malformations (including retroesophageal right subclavian arteries, missing innominate artery) (10 mg/kg/day).

Based on the above, pazopanib was shown to be embryolethal and teratogenic, and the NOAEL for embryo fetal development was considered to be 1 mg/kg/day.

3.(iii).A.(5).3) Embryo-fetal development in rabbits (dose-finding study)

In pregnant rabbits (NZW, 6 per group), pazopanib were administered orally at 0 (vehicle control), 3, 10, 30, or 100 mg/kg/day on Gestation Day 7 to Gestation Day 19. The rabbits were caesarian sectioned on Gestation Day 29 and fetuses were examined externally. Because decreased food consumption (≥30 mg/kg/day) and decreased body weight (100 mg/kg/day) were observed in maternal animals as the effects on clinical signs, all animals in the 100 mg/kg/day group were sacrificed moribund on Gestation Day 18. Effects on embryofetal development were increased rate of post-implantation loss (10, 30 mg/kg/day), and decreased fetal weight (all pazopanib groups).

Based on the above, pazopanib was shown to be embryolethal. As pazopanib was shown to be embryolethal and teratogenic in the rat embryofetal developmental study, the definitive embryofetal developmental study using rabbits was not conducted.

3.(iii).A.(5).4) Study in neonatal animals

In the dose-range study in juvenile rats administered pazopanib orally at 0.3, 3, 30, 300, or 1000 mg/kg/day on Postnatal Day 9 to Postnatal Day 21, some rats died at ≥30 mg/kg/day from Day 5 and all rats in the ≥300 mg/kg/day group died or were sacrificed moribund by Day 8.

In juvenile rats (SD, 10 each of males and females per group), pazopanib were administered orally at 0 (vehicle control), 10, 30, or 300 mg/kg/day on Postnatal Day 21 to Postnatal Day 62. Recovery groups (10 each of males and females per group) with a 4-week washout period were included in the 0, 30, and 300 mg/kg/day groups. Two female rats in the 300 mg/kg/day group were sacrificed moribund because of a marked reduction in body weight gain on Postnatal Day 46. Dosing was interrupted in all male and female rats in the 300 mg/kg/day group for 4 days from Postnatal Day 49 to Postnatal Day 52 before dosing was resumed at 100 mg/kg/day (hereinafter "300/100 mg/kg/day"). Clinical signs observed were abnormal incisor teeth (overgrown, broken, etc.) and decreased body weight gain and food consumption (≥30 mg/kg/day). Hematology findings included increased mean red cell volume and mean red cell hemoglobin (all pazopanib groups), increased red cell distribution width and monocyte count (≥30 mg/kg/day), and increased neutrophil count (300/100 mg/kg/day). Clinical chemistry findings included increased serum ALT (all pazopanib groups), increased serum ALP (males in all pazopanib groups, females at 300/100 mg/kg/day), increased serum total bilirubin (males at 300/100 mg/kg/day, females in all pazopanib groups), increased cholesterol (males at 300/100 mg/kg/day), increased serum triglycerides (females at ≥30 mg/kg/day), increased serum AST and decreased serum creatinine, albumin, and total protein (300/100 mg/kg/day). Urinalysis findings were decreased urinary glucose excretion (all pazopanib groups) and decreased urinary protein excretion (males at 300/100 mg/kg/day). Decreased femur length was observed in necropsy (all pazopanib groups), and decreased organ weights were observed in liver (all pazopanib groups), testes (males in all pazopanib groups), kidneys (males at ≥30mg/kg/day, females in all pazopanib groups), heart (≥30 mg/kg/day), adrenal gland, spleen (males at 30 mg/kg/day), thymus (300/100 mg/kg/day), and prostate (males at 300/100 mg/kg/day). Histopathology findings revealed growth plate hypertrophy in the femur and tibia and cortical bone thinning, decreased granular lymphocyte count in mucosal epithelium of trachea, dentin degeneration in incisor teeth (≥30 mg/kg/day), adrenal angiectasis and necrosis, hyperplasia of mucous secreting cells in the pyloric region of the stomach, dilation of

duodenal Brunner's gland ducts, dilation and inflammation in the pancreas ducts, foreign body deposit within macrophages in the mesenteric lymph nodes, growth plate hypertrophy of the sternum, hypocellularity of germinal epithelium, decreased secretion in the prostate, inflammation in the vagina, increased mucus, etc. (300/100 mg/kg/day). After the 4-week washout period, body weight, and hematology, clinical chemistry, and urinalysis parameters showed a tendency for recovery. Histopathological changes observed in the femur and tibia, adrenal gland, Brunner's gland, and mesenteric lymph node showed no recovery, and partial or complete epiphyseal closure in the femur and tibia, and cartilaginous rest and osteonecrosis in the trabecular and cortical bones were observed after the washout period. Other histopathological changes tended to recover.

Based on the above, the NOAEL was considered to be <10 mg/kg/day.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Effects on incisor teeth and nails

In male rats (SD, 5 per group), pazopanib were administered orally at 0 (vehicle control), 10, 30, or 300 mg/kg/day for 4 weeks in order to investigate the reversibility of the effect on incisor teeth and nails observed in the 4-week repeat dose study in rats. As recovery test, 2-, 4-, 6-, and 10-week washout periods were set for the control group and 300 mg/kg/day group. At the end of the treatment period (Day 29), overgrown incisor teeth and short nails were observed (all pazopanib groups), and dentin and enamel degeneration, thinning, dental pulp necrosis, etc. in incisor teeth were observed in histopathology (≥30 mg/kg/day). The effects of pazopanib on incisor teeth and nails were observed until Day 71 (after 6-week recovery period), but not on Day 99 (after 10-week recovery period).

Based on the above, all changes observed with pazopanib reversed during the 10-week recovery period.

3.(iii).A.(6).2) Impurities

Genotoxicity studies were conducted for one impurity, gsk002, which has a genotoxic potential.

gsk002 was not mutagenic in reverse mutation assay with *S. typhimurium*, but positive in the mouse lymphoma TK assay and mouse bone marrow micronucleus test. gsk002 also induced micronuclei *in vitro* in a mouse lymphoma (L5178Y) cell micronucleus kinetochore assay, but through an aneugenic mechanism. Based on the method for calculating the exposure limit for a Class 2 solvent recommended in the "Guideline for Residual Solvents" (PMSB/ELD Notification No. 307 dated March 30, 1998), the Permitted Daily Exposure (PDE) level of gsk002 calculated from the no-effect dose level (25 mg/kg) in the mouse bone marrow micronucleus test was 0.1 mg/day. The content of gsk002 in the drug substance is managed not to exceed 0.1 mg/day by in-process control. Therefore, the safety for this impurity is considered to be assured.

3.(iii).A.(6).3) *In vitro* phototoxicity

In vitro neutral red uptake phototoxicity assay using Balb/c 3T3 mouse fibroblast cells was performed. Regardless of absence or presense of UV-A light (wave length, 315-400 nm), a concentration-related increase in cytotoxicity was observed in pazopanib-treated group and the cytotoxicity profiles were similar with and without UV-A light. Therefore, it was concluded that pazopanib shows no phototoxicity.

3.(iii).B Outline of the review by PMDA

PMDA concluded as follows:

Although pazopanib has no safety margin, based on the submitted data and the following review, pazopanib can be used clinically, considering the seriousness of the diseases for which pazopanib

is indicated. However, pazopanib needs to be used carefully in children because irreversible bone lesions were observed in the toxicity study in neonatal animals.

Effects on the liver
Proliferative changes (eosinophilic foci, adenomas) were observed in the liver in females in the 1000 mg/kg/day group in the 13-week oral dose toxicity study in mice [see "3.(iii).A.(2).1) Thirteen-week oral dose toxicity study in mice"]. PMDA asked the applicant to explain the mechanism of formation of these proliferative lesions and carcinogenic potential of pazopanib.

The applicant responded as follows:
In the 13-week oral dose toxicity study in mice, hepatic eosinophilic foci were found in 2 females and hepatic adenomas in 1 female in the 1000 mg/kg/day group, and hepatocellular hypertrophy was also found in this group. It has been reported that hepatomegaly or hepatic adenoma in mice is caused by prolonged liver enzyme induction (*Mutat Res.* 1991; 248: 271-90). It is also known that hepatic adenoma appears following hepatocellular foci (*toxicologic pathology*. 1st ed. Nakayama Shoten Co., Ltd.; 1994), and is more prevalent with increasing age in rodents (*Histopathology of Preclinical Toxicity Studies.* 2nd ed. Amsterdam, The Netherlands: Elsevier Press; 2000). Considering that $AUC_{0\text{-}24}$ for pazopanib in mice given 1000 mg/kg/day was lower in the 13-week oral dose toxicity study (932 μg·h/mL in males, 1607 μg·h/mL in females) than in the 14-day oral dose-finding study (2041 μg·h/mL in males, 2453 μg·h/mL in females) and that hepatocellular hypertrophy was observed in histopathology in the 13-week oral dose toxicity study in mice, long term treatment with pazopanib is likely to have induced liver enzymes. Therefore hepatic adenoma is considered to be a lesion associated with enzyme induction.

However, taking into account that no apparent induction of CYPs by pazopanib was found in rats or cynomolgus monkeys (except mice) [see "3.(ii).A.(5).2) Enzyme induction"], and that there were no pharmacokinetic findings suggesting CYP induction after multiple dose of pazopanib to foreign cancer patients [see "4.(ii)A.(3).4) Drug-drug interaction study with various CYP substrates"], pazopanib is unlikely to show carcinogenicity with this mechanism of action in humans.

Other possible causes of proliferative changes include reduction in the number of hepatocytes or outgrowth after necrosis, and initiation and progression induced by exposure to a carcinogen (*toxicologic pathology*. 1st ed. Nakayama Shoten Co., Ltd.; 1994). However, these mechanisms of action of pazopanib are unlikely to have caused the proliferative changes in the liver as well since there were no histopathological findings indicating hepatic necrosis in the toxicity studies of pazopanib in rodents, and pazopanib was tested negative in all genotoxicity studies.

PMDA accepted the above explanation.

4. Clinical data
4.(i) Summary of biopharmaceutical studies and associated analytical methods
4.(i).A Summary of the submitted data
Pazopanib hydrochloride (hereinafter referred to as pazopanib) tablets are supplied as 50, 100, 200, 400, and 500 mg tablets for clinical development formulation. Of these strengths, 200 and 400 mg tablets were used in the Japanese phase I study (Study VEG109693) and global phase III study (Study VEG110727), and 100 and 500 mg tablets were used in the foreign phase II study (Study VEG20002). Although 200 mg tablets for market formulation were not used in the clinical studies, the bioequivalency between 200 mg tablet for development formulation and 400 mg tablet for development formulation and between 200 mg tablet for development formulation and 200 mg tablet for market formulation was proven by dissolution test.

4.(i).A.(1) Assay

Pazopanib and its metabolites (M24 [mono-oxygenation], M26 [mono-oxygenation], M27 [demethylation] and M28 [demethylation]) in human plasma were quantified by LC-MS/MS, and the lower limit of quantification for pazopanib was 10 ng/mL (foreign clinical studies) or 100 ng/mL (Japanese clinical studies), and that for metabolites was 50 ng/mL.

4.(i).A.(2) Foreign phase I study (5.3.1.1.1/ref, 5.3.1.1.2/ref: Study VEG10004 [July 2007 to July 2008])

An open-label study was conducted in patients with solid tumors to investigate the PK of a single oral dose (Part A) and a single intravenous dose (Part B) of ^{14}C-labeled pazopanib.

a. Part A

The mass balance of pazopanib was investigated in 3 patients with solid tumors. In Cycle 1, a single oral dose of ^{14}C-labeled pazopanib was administered at 400 mg on Day 1, and pazopanib was orally administered at 800 mg once daily (QD) on Days 8 to 28. In Cycle 2, pazopanib was administered at 800 mg QD on Days 1 to 28. Plasma concentrations of radioactivity were evaluated in 2 subjects, because blood samples obtained from 1 subject for the first 48 hours were mistakingly frozen and the plasma could not be obtained.

The major proportion of radioactivity in plasma and blood was unchanged pazopanib at all time points (86%-95% of total plasma radioactivity, 79%-89% of total blood radioactivity), and each metabolite observed in plasma and blood accounted for <10% of total plasma radioactivity. In the 3 subjects, 96.9%, 95.3%, and 62.4% of the administered radioactivity was excreted in urine (3.48%, 3.10%, 1.32%) and in feces (93.4%, 92.2%, 61.1%) by 168 hours after administration. In feces, approximately 67% of the administered radioactivity was recovered as unchanged pazopanib, and approximately 6%, 2%, and 3% as M24, M26, and M8 (carboxylation), respectively. In the 2 subjects, the blood to plasma radioactivity ratio ranged from 0.63 to 0.93 and 0.59 to 0.83 at all time points.

Based on the above, the applicant explained as follows: pazopanib is mainly found as unchanged drug in blood, plasma and feces, the major excretion route of radioactivity is via feces, and the distribution of pazopanib into blood cells is low in humans.

b. Part B

The plasma pazopanib concentrations were determined in 7 patients with solid tumors. In Cycle 1, a single intravenous dose of pazopanib was administered at 5 mg on Day 1 and pazopanib was orally administered at 800 mg QD from Day 3 (4 of 7 subjects) or Day 5 (3 of 7 subjects) through Day 28. In Cycle 2, pazopanib was orally administered at 800 mg QD on Days 1 to 28. PK parameters were evaluated in 3 of 7 subjects, because 1 subject was withdrawn from pazopanib due to adverse events, and 3 subjects were excluded from the calculation of CL, V_{ss} and F because AUC extrapolated from time last to infinity (AUC_{extrap}) exceeded 30% of $AUC_{0-\infty}$.

Pazopanib $t_{1/2}$ (median) after intravenous administration was approximately 27.5 hours. Absolute bioavailability (BA) values were 13.5%, 21.4%, and 38.9% in each subject, CL values were 0.206, 0.246, and 0.347 L/h, and V_{ss} values were 11.1, 9.15, and 13.1 L, respectively.

Based on the above, the applicant explained as follows: (1) After being absorbed from the gastrointestinal tract, pazopanib is not extensively metabolized and effects of first-pass metabolism is minor, and (2) renal impairment is not expected to influence pazopanib exposure since only a minor proportion of radioactivity was excreted in urine.

4.(i).A.(3) Foreign phase I study (5.3.1.1.3/ref, 5.3.1.1.4/ref: Study VEG10005 [September 2006 to August 2007])

The plasma pazopanib concentrations were determined in 35 patients with solid tumors after a single oral dose of pazopanib at 800 mg in the fasted state, at least 1 hour before or 2 hours after a meal (Regimen A), after a high fat meal containing fat that offered approximately 50% of total calories (Regimen B), and after a low fat meal containing fat that offered approximately 5% of total calories (Regimen C). In another study, the plasma pazopanib concentrations were determined in 9 patients with solid tumors after oral doses of pazopanib at 400 mg (as a crushed tablet or a whole tablet) on Days 1 and 15. Each study was conducted as an open-label, cross-over study.

PK parameters for Regimen A, B, and C are shown in the following table. Geometric least square mean ratios of C_{max} and AUC_{0-24} for Regimen B to Regimen A (B/A) and Regimen C to Regimen A (C/A) were calculated. Geometric least square mean ratios [90% confidence interval, CI] of C_{max} and AUC_{0-t} were 2.34 [1.64, 3.35] and 2.08 [1.51, 2.87] for B/A, and 1.92 [1.24, 2.98] and 2.10 [1.51, 2.91] for C/A, respectively. The median t_{max} differences (h) [90% CI] for B/A and C/A were 3.00 [0.02, 6.00] and 0.06 [-1.00, 1.22], respectively. Pazopanib $t_{1/2}$ was not affected by food.

Based on the above, the applicant explained as follows: Pazopanib should be administered at least 1 hour before or 2 hours after a meal, because pazopanib exposure is increased by food compared with administration in the fasted state. There was no obvious difference in the change in pazopanib exposure with a low fat or high fat meal.

The applicant also explained as follows: This study was conducted in foreign subjects using 200 and 400 mg tablets for clinical development formulation. However, it is possible to discuss the effect of food on the PK of pazopanib tablets for market formulation based on the results of this study, because of their formulations, dissolution behavior, and comparison of the PK of pazopanib tablets between Japanese and foreign patients [see "4.(ii).B.(1) PK of pazopanib in Japanese and foreign patients"]. The PK of pazopanib tablets for market formulation will be affected by food as with pazopanib tablets for development formulation.

Summary of PK parameters after administration of pazopanib 800 mg in the fed and fasted states

Sequences	Treatment	n	C_{max} (μg/mL)	t_{max} (h)*1	AUC_{0-24} (μg·h/mL)	$t_{1/2}$ (h)	AUC_{0-t} (μg·h/mL)
AB/BA*2	Fasted*4	16	22.5 (40.8)*5	4.00 (2.0, 10.0)*5	367 (39.5)*5	30.4 (10.8)*6	735 (47.5)*5
	High-fat meal	12	48.1 (50.9)	6.04 (4.0, 24.0)	803 (53.2)	33.1 (8.4) *6	1844 (47.6)
AC/CA*3	Fasted*4	13	18.5 (80.3)*5	4.00 (2.0, 23.8)*5	292 (77.2)*5	29.4 (25.1)*7	609 (76.0)*5
	Low-fat meal	12	38.8 (74.6)	6.00 (3.0, 6.4)	566 (72.5)	28.4 (23.0)*8	1118 (64.2)

Geometric mean (coefficient of variation [CV%]), *1: Median (range), *2: High-fat treatment sequences, *3: Low-fat treatment sequences, *4: Administration of 800 mg orally once daily, at least 1 hour before or at least 2 hours after a meal, *5: n = 12, *6: n = 3, *7: n = 6, *8: n = 7

PK parameters after administration of a crushed tablet or a whole tablet are shown in the following table. Geometric least square mean ratios of C_{max} and AUC_{0-72} [90% CI] for administration of a whole tablet to administration of crushed tablet were 2.09 [1.33, 3.26] and 1.46 [1.08, 1.97], respectively. The applicant explained that the oral bioavailability and the rate of pazopanib oral absorption are increased after dosing of the crushed tablet, relative to dosing of the whole tablet, therefore, pazopanib tablets should not be crushed.

PK parameters of crushed tablet or whole tablet of pazopanib

	C_{max} (μg/mL)	t_{max} (h)*	AUC_{0-72} (μg·h/mL)
Whole tablet	10.5 (64.6)	4.05 (3.0, 6.0)	361 (72.5)
Crushed tablet	22.0 (26.4)	2.52 (2.0, 4.0)	651 (26.8)

Geometric mean (CV%), n = 8, *: Median (range)

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Effect of food

PMDA asked the applicant to explain the necessity of specifying the timing of pazopanib administration relative to a meal in the Dosage and Administration section of the package insert, taking into account that the PK of pazopanib is affected by food [see "4.(i).A.(3) Foreign phase I study"].

The applicant responded as follows:
As for the timing of pazopanib administration relative to a meal, a caution stating that pazopanib should not be administered from 1 hour before and until 2 hours after a meal is included in the Precautions for dosage and administration section. However, in order to ensure that pazopanib is administered properly, the timing of pazopanib administration relative to a meal will be specified in the Dosage and Administration section.

PMDA accepted the above explanation.

4.(i).B.(2) Effect of gastric pH

The solubility of pazopanib in buffer solution was 1.41 mg/mL at pH 1.0, 3.61×10^{-5} mg/mL at pH 7.0, and 2.38×10^{-4} mg/mL at pH 10.3. Pazopanib is almost insoluble in neutral to alkaline solutions. In the dissolution test of pazopanib tablets, pazopanib was hardly dissolved at pH 6.8 (below the detection limit). PPK analysis suggested that the PK of pazopanib may be altered in concomitant use with a drug affecting gastric pH [see "4.(ii)A.(5) Population pharmacokinetics (PPK) analysis"].

PMDA asked the applicant to explain the necessity of administering pazopanib carefully to patients with hypoacidity or patients in hypoacidic conditions due to treatment with a proton pump inhibitor, because the absorption of pazopanib could be decreased in this patient population.

The applicant responded as follows:
In addition to the results of PPK analysis, the results have been obtained from a drug-drug interaction study with ketoconazole in patients with solid tumors (Study VEG113971), which was ongoing at the time of regulatory submission. In this study, pazopanib was concomitantly administered with esomeprazole magnesium hydrate (esomeprazole), a proton pump inhibitor, and the PK of pazopanib was evaluated in hypoacidic patients. The study results are summarized below.

An open-label, cross-over study was conducted in 12 foreign patients with solid tumors to evaluate the effect of esomeprazole on the PK of pazopanib. In the monotherapy phase, pazopanib was administered orally at 800 mg QD for at least 7 days. Then in the combination therapy phase, pazopanib was administered at 800 mg QD in the morning and esomeprazole at 40 mg QD in the evening for 4 days, and the PK of pazopanib was evaluated on Day 5. PK parameters for pazopanib are shown in the following table. Geometric least square mean ratios [90% CI] of AUC_{0-24} and C_{max} for concomitant use with esomeprazole to pazopanib monotherapy were 0.60 [0.52, 0.70] and 0.58 [0.50, 0.67], respectively.

Pazopanib PK parameters after administration of pazopanib alone or concomitant use with esomeprazole

	C_{max} (μg/mL)	t_{max} (h)*	AUC_{0-24} (μg·h/mL)	C_{24} (μg/mL)
Pazopanib alone	48.9 [39.5, 60.6]	3.0 (1.9, 7.8)	848 [660, 1090]	27.2 [20.4, 36.4]
Concomitant use with esomeprazole	28.4 [23.8, 33.9]	3.9 (1.0, 24.8)	512 [418, 627]	17.3 [12.6, 23.7]

Geometric mean [95%CI], n = 12, *: Median (range)

Based on the above, the applicant explained as follows:
A caution stating that concomitant use of pazopanib with an antacid should be avoided will be added, because pazopanib exposure is likely to be decreased in patients with hypoacidity due to an antacid.

PMDA accepted the above explanation. However, when cautioning the effect of gastric pH on the PK of pazopanib, PMDA considers it necessary to provide appropriate information, taking into account that hypoacidity is generally more prevalent in the Japanese elderly than in Westerners, in addition to the results of Study VEG113971.

4.(ii) Summary of clinical pharmacology data

4.(ii).A Summary of the submitted data

The PK of pazopanib was evaluated in healthy adult subjects and cancer patients by pazopanib monotherapy, concomitant use with lapatinib tosilate hydrate (lapatinib), concomitant use with paclitaxel, and concomitant use with a CYP3A4 inhibitor or inducer.

4.(ii).A.(1) Healthy adult subjects

Foreign phase I study (5.3.3.1.1/ref: Study MD1103367 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A single-blind, parallel group, placebo-controlled, randomized study was conducted in 9 healthy adult subjects aged ≥55 years to evaluate the PK of pazopanib by 14-day multiple oral dose of placebo or pazopanib 100 mg QD. However, the study was terminated prematurely, because pazopanib-related adverse events were reported by 5 of 6 subjects in the pazopanib group and 3 of them had elevations in plasma alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN) range. There were no deaths or serious adverse events.

PK parameters for pazopanib obtained before study termination are shown in the following table.

PK parameter of pazopanib

Subject ID	Day	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)
1101	1	1.02	4	18.9	27.8
1102	1	8.98	3	137.8	18.6
1104	1	6.19	4	111.5	47.8
1105	1	0.87	2	11.0	17.4
1106	1	8.44	4	134.1	25.2
	14	9.63	1	190.4	-
1108	1	0.97	8	17.2	27.0

Individual values

4.(ii).A.(2) Cancer patients

4.(ii).A.(2).1) Japanese Phase I study (5.3.5.2.2: Study VEG109693 [September 2007 to August 2010])

An open-label study was conducted in patients with solid tumors to evaluate the PK of pazopanib, its metabolites, and lapatinib by administration of pazopanib alone or pazopanib in combination with lapatinib. The study consisted of Part A and Part B (dose escalation phase, PK phase).

a. Part A

Pazopanib was orally administered to 13 patients with solid tumors at 400 to 1000 mg QD for 22 days and the plasma concentrations of pazopanib and its metabolites (M24, M26, M27, M28) were determined [the table below]. The plasma concentrations of pazopanib and its metabolites showed large inter-individual variations. The percentage of each metabolite to unchanged pazopanib was ≤5%. The applicant explained that there was no dose-proportionality between the dose of pazopanib and C_{max} or AUC_{0-24} values on Day 1, which resulted from the saturation of gastrointestinal absorption because of the low solubility of pazopanib.

PK parameters of pazopanib in monotherapy

Parameter	n	Day	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{0-24} (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	C_{24} (μg/mL)
400/800 mg*2	3	Day 1	25.1 (34.0)	4.00 (3.00, 23.7)	402 (17.7)	1224 (10.8)	28.4 (35.9)	14.8 (12.7)
		Day 22	55.8 (35.2)	2.50 (2.00, 3.00)	962 (46.3)	-	40.1 (67.2)	34.6 (47.2)
800 mg	7	Day 1	22.9 (69.5)	2.98 (1.97, 5.95)	325 (76.7)	864 (95.2)	42.5 (31.6)	9.1 (90.1)
		Day 22	40.6 (47.7)	2.52 (1.92, 3.97)	677 (45.5)	-	37.8 (47.2)	22.0(48.4)
1000 mg	3	Day 1	21.3 (118.1)	3.00 (2.97, 3.00)	305 (128.6)	714 (148)	33.0 (23.8)	8.5 (139.6)
		Day 22	53.9 (55.4)	4.00 (3.00, 4.05)	759 (63.8)	-	21.4 (60.7)	21.1 (80.5)

Geometric mean (CV%), *1: Median (range), *2: 400 mg on Day 1 and 800 mg from Day 2 onward

b. Part B (dose escalation phase and PK phase)

In the dose escalation phase, the plasma concentrations of pazopanib and lapatinib were determined in 10 patients with solid tumors treated with pazopanib 400 or 800 mg in combination with lapatinib 1000 or 1500 mg [the table below]. The plasma concentrations of pazopanib and lapatinib showed large inter-individual variations. There was neither dose-relationship between the dose of pazopanib or lapatinib and C_{max} or AUC_{0-24} on both Day 1 and Day 22, nor dose-dependent effect of pazopanib or lapatinib on the PK of the drugs used concomitantly.

PK parameters of pazopanib (P) in combination with lapatinib (L)

Parameter	Day	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{0-24} (μg·h/mL)	$t_{1/2}$ (h)	C_{24} (μg/mL)
P400 mg + L1000 mg	Day 1	4	46.4 (10.1)	5.03 (3.03, 8.00)	755 (15.0)	30.1 (21.5)	26.8 (17.9)
	Day 22		57.9 (18.6)	4.05 (3.98, 8.00)	988 (33.2)	35.7 (26.2)	34.8 (27.6)
P800 mg + L1000 mg	Day 1	3	48.9 (51.1)	6.00 (3.98, 7.98)	853 (53.8)	33.7 (48.3)	31.0 (37.5)
	Day 22		55.6 (7.3)	3.00 (0.48, 6.15)	1141 (18.4)	66.7 (143.3)	41.9 (28.5)
P400 mg + L1500 mg	Day 1	3	31.7 (68.6)	4.00 (2.95, 4.03)	524 (66.6)	29.3 (24.8)	17.6 (61.2)
	Day 22		51.7 (69.8)	3.95 (3.00, 7.98)	1004 (65.6)	41.2 (30.4)	35.2 (65.2)

Geometric mean (CV%), *: Median (range)

In the PK phase, the plasma concentrations of pazopanib, its metabolites (M24, M26, M27)

and lapatinib were determined in 7 patients with solid tumors treated with pazopanib alone at 600 mg or lapatinib alone at 1250 mg from Day 1 to Day 15, and pazopanib 600 mg in combination with lapatinib 1250 mg from Day 16 to Day 37 [the table below]. The plasma concentrations of pazopanib and its metabolites showed large inter-individual variations. Geometric least square mean ratios [90% CI] of C_{max} and AUC_{0-24} for pazopanib plus lapatinib to pazopanib alone were 0.684 [0.270, 1.732] and 0.766 [0.327, 1.793], respectively.

PK parameters of pazopanib in monotherapy or combination with lapatinib

Parameter	Day	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{0-24} (μg·h/mL)	$t_{1/2}$ (h)	C_{24} (μg/mL)
Pazopanib monotherapy	Day 15	3	79.6 (10.3)	3.00 (3.00, 3.98)	1331 (13.8)	42.2 (62.9)	45.1 (4.2)
Combination with lapatinib	Day 37	6	63.5 (40.6)	3.00 (2.95, 5.93)	1189 (37.1)	51.9 (69.8)	43.0 (38.4)

Geometric mean (CV%), *: Median (range)

4.(ii).A.(2).2) Foreign phase I study (5.3.5.2.3/ref: Study VEG10003 [December 2002 to September 2006])

An open-label study was conducted in 63 patients with solid tumors to evaluate the PK of pazopanib when administered orally at 50 to 2000 mg QD, 300 or 400 mg BID, and 50 or 100 mg 3 times a week (TIW). In the dose range evaluated, C_{max} and AUC_{0-24} of pazopanib on Day 1 approximately elevated with increasing dose. The highest C_{max} and AUC_{0-24} values were observed in the 2000 mg group, but C_{max} and AUC_{0-24} values increased at a lower rate than the dose increase. The median t_{max} ranged from 2.0 to 4.0 hours and the mean $t_{1/2}$ ranged from 18.1 to 52.3 hours. At all dose levels studied, pazopanib AUC_{0-24} values on Day 22 were higher than those on Day 1, indicating accumulation of pazopanib in the plasma after multiple administration. Multiple QD administration of pazopanib at ≥800 mg did not result in marked increase in systemic exposure.

4.(ii).A.(2).3) Foreign phase II study (5.3.5.2.1: Study VEG20002 [October 2005 to Ongoing (Data Cut-off Date: [redacted], 20[redacted])])

An open-label study was conducted in 142 patients with soft tissue sarcoma by administering multiple oral dose of pazopanib 800 mg QD. The plasma pazopanib concentrations before treatment (arithmetic mean) were similar regardless of duration of treatment, as they were 37.1, 36.1, and 36.0 μg/mL on Days 29, 57, and 85, respectively.

4.(ii).A.(2).4) Foreign phase II study (5.3.3.2.1/ref: Study VEG20006 [January 2005 to December 2006])

An open-label study was conducted in 21 patients with multiple myeloma (15 patients included in PK analysis) by administering multiple oral dose of pazopanib 800 mg QD. The geometric mean AUC_{0-24}, C_{max}, and C_{24} of pazopanib were 487 μg·h/mL, 27.5 μg/mL, and 17.1 μg/mL, respectively. Clinical efficacy was not seen in patients with multiple myeloma in Study VEG20006, although the C_{24} of pazopanib was higher than the plasma concentration (15 μg/mL) associated with clinical efficacy shown in Study VEG10003.

4.(ii).A.(3) Drug-drug interaction studies

4.(ii).A.(3).1) Drug-drug interaction study with ketoconazole (5.3.3.4.1/ref: Study VEG113971 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, cross-over study was conducted in 21 foreign patients with solid tumors to evaluate the effect of ketoconazole (a potent CYP3A4 and P-gp inhibitor) on the PK of pazopanib. In the monotherapy phase, pazopanib was administered orally at 400 mg QD for at least 7 days, and then in the combination therapy phase, pazopanib at 400 mg QD and ketoconazole at 400 mg QD were administered for 5 days. PK parameters are shown in the following table. Geometric least square mean ratios [90% CI] of C_{max} and AUC_{0-24} for concomitant use with ketoconazole to pazopanib monotherapy were 1.45 [1.14, 1.86] and 1.66 [1.39, 1.99], respectively.

Based on the above, the applicant explained that since pazopanib exposure is considered to be elevated at concomitant use with ketoconazole, concomitant use with potent CYP3A4 and P-gp inhibitors (ketoconazole, ritonavir, clarithromycin) should be avoided.

PK parameters of pazopanib in monotherapy or combination with ketoconazole

	n	C_{max} (μg/mL)	t_{max} (h)*	AUC_{0-24} (μg·h/mL)	C_{24} (μg/mL)
Pazopanib monotherapy	21	40.7 [32.8, 50.6]	3.98 (2.0, 24.0)	786 [632, 976]	26.9 [21.5, 33.6]
Combination with ketoconazole	16	59.2 [45.1, 77.6]	3.48 (2.0, 23.9)	1300 [1030, 1620]	48.7 [36.5, 65.0]

Geometric mean [95%CI], *: Median (range)

4.(ii).A.(3).2) Drug-drug interaction study with lapatinib (5.3.3.4.2/ref: Study VEG10006 [September 2004 to August 2007])

An open-label study was conducted in 75 foreign patients with solid tumors to administer pazopanib in combination with lapatinib. The study consisted of the dose-escalation phase and the extension phase.

In the dose-escalation phase, pazopanib 200 to 800 mg and lapatinib 750 to 1500 mg QD were concomitantly administered for 22 days. The optimal regimen could not be identified in the dose-escalation phase. In the expansion phase, in order to further evaluate the safety, tolerability, and pharmacokinetic drug interactions of pazopanib in combination with lapatinib, pazopanib alone 400 or 800 mg, or lapatinib alone 1000 or 1500 mg was administered QD for the first 15 days, and then concomitant use of pazopanib 400 mg and lapatinib 1000 mg, or pazopanib 800 mg and lapatinib 1500 mg were administered from Day 16 to Day 37. PK parameters for pazopanib and lapatinib are shown in the following table. When pazopanib 400 mg was concomitantly administered with lapatinib 1000 mg, lapatinib showed no apparent effect on the PK of pazopanib. On the other hand, when pazopanib 800 mg was concomitantly administered with lapatinib 1500 mg, pazopanib C_{max} and AUC_{0-24} increased by approximately 50% and 60%, respectively, compared with administration of pazopanib alone. Pazopanib had no apparent effect on the PK of lapatinib.

Based on the above, the applicant explained that pazopanib exposure may be elevated in concomitant use with lapatinib, since lapatinib is a substrate and weak inhibitor of CYP3A4, P-gp, and BCRP (see "Review Report of Tykerb Tablets 250 mg, dated February 9, 2009").

PK parameters of pazopanib

Study day	n	C_{max} (μg/mL)	t_{max} (h)*	AUC_{0-24} (μg·h/mL)	AUC_{0-t} (μg·h/mL)
Day 15 Pazopanib 400 mg	9	34.9 [22.4, 54.3]	4.00 (1.50, 7.80)	614 [382, 986]	616 [383, 990]
Day 37 Pazopanib 400 mg + lapatinib 1000 mg	7	37.7 [25.4, 55.9]	3.00 (1.00, 8.00)	616 [379, 1000]	719 [472, 1093]
Day 15 Pazopanib 800 mg	5	34.4 [19.4, 61.1]	3.96 (1.6, 4.2)	567 [276, 1160]	615 [345, 1100]
Day 37 Pazopanib 800 mg + lapatinib 1500 mg	6	52.0 [38.1, 71.0]	3.58 (1.5, 6.8)	975 [736, 1290]	976 [737, 1290]

Geometric mean [95% CI], *: Median (range)

PK parameters of lapatinib

Study day	n	C_{max} (μg/mL)	t_{max} (h)*1	AUC_{0-24} (μg·h/mL)	AUC_{0-t} (μg·h/mL)
Day 15 Lapatinib 1000 mg	4	1.60 [0.610, 4.19]	3.39 (0.4, 6.4)	19.5 [7.13, 53.5]	19.5 [7.14, 53.4]
Day 37 Pazopanib 400 mg + lapatinib 1000 mg	4	1.72 [0.609, 4.85]	3.78 (1.1, 6.5)	22.6 [8.80, 58.3]	22.7 [8.82, 58.2]
Day 15 Lapatinib 1500 mg	4	2.19 [0.893, 5.38]	5.53 (2.4, 8.6)	26.9*2 [9.82, 73.7]	33.9 [13.7, 84.1]
Day 37 Pazopanib 800 mg + lapatinib 1500 mg	4	1.51 [0.713, 3.19]	5.85 (1.0, 10.7)	21.4*2 [4.93, 92.6]	23.6 [10.3, 54.2]

Geometric mean [95% CI], *1: Median (range), *2: n = 3

4.(ii).A.(3).3) Drug-drug interaction study with lapatinib and CYP enzyme inducing anticonvulsants (5.3.3.4.5/ref: Study VEG102857 [December 2006 to December 2009])

An open-label study of pazopanib in combination with lapatinib was conducted in 34 foreign patients with relapsed malignant glioma receiving enzyme inducing anticonvulsants to investigate the effect of CYP inducers on the PK of pazopanib. When pazopanib 800 mg and lapatinib 1500 mg were orally administered QD, the geometric means of AUC_{0-24}, C_{max}, and C_{24} of pazopanib were 449 μg·h/mL, 33.6 μg/mL, and 8.74 μg/mL, respectively. Administration of enzyme inducing anticonvulsants resulted in decreases in these parameters by approximately 54%, 35%, and 74%, respectively, compared with the results from Study VEG10006, in which pazopanib was concomitantly administered with lapatinib [see "4.(ii).A.(3).2) Drug-drug interaction study with lapatinib"].

Based on the above, the applicant explained that pazopanib exposure may be reduced in combination with a potent CYP3A4 inducer.

4.(ii).A.(3).4) Drug-drug interaction study with various CYP substrates (5.3.3.4.3/ref: Study VEG10007 [July 2006 to February 2008])

An open-label study was conducted in 24 foreign patients with solid tumors to investigate the effect of pazopanib on the PK of various CYP substrates. Midazolam 3 mg (CYP3A4 substrate) was administered orally on Days 1 and 23, a mixed solution of caffeine 200 mg (CYP1A2 substrate), omeprazole 40 mg (CYP2C19 substrate), dextromethorphan hydrobromide hydrate

(dextromethorphan) 30 mg (CYP2D6 substrate), and potassium warfarin (warfarin) 10 mg (CYP2C9 substrate) was administered orally on Days 2 and 24, and pazopanib was administered orally at 800 mg QD from Day 6. The applicant explained as follows: these CYP substrates are unlikely to cause pharmacokinetic drug interactions with each other, because it has been reported that midazolam, caffeine, omeprazole, and dextromethorphan do not interact with each other pharmacokinetically or pharmacodynamically when administered at the same time (*Clin Pharmacol Ther*. 2000; 68: 375-83), and there is no evidence that warfarin inhibits or induces CYPs other than CYP2C9.

For each substrate, geometric least square mean ratios of PK parameters for pazopanib combination therapy to pazopanib monotherapy are shown in the following table. Pazopanib had no apparent effect on the PK of CYP1A2 and 2C9 substrates. The applicant explained as follows: concomitant use with pazopanib resulted in an increase of approximately 30% in the AUC and C_{max} of midazolam and increases of 33% to 64% in the ratio of dextromethorphan to 1-dextrorphan concentrations in the urine, which indicates that pazopanib is a weak inhibitor of CYP3A4 and 2D6. Omeprazole exposure tended to decrease in combination with pazopanib, but this is an incidental finding and pazopanib has no apparent effect on CYP2C19 since the exposure of its metabolite, 5-hydroxy omeprazole did not tend to increase.

PK parameters of various substrates in pazopanib monotherapy or in concomitant use with pazopanib

		n	Geometric least squares mean* [90% CI]
Midazolam (CYP3A4 substrate)			
C_{max} (ng/mL)		21	1.29 [1.12, 1.49]
AUC_{0-t} (ng·h/mL)		21	1.35 [1.18, 1.54]
$AUC_{0-\infty}$ (ng·h/mL)		14	1.32 [1.11, 1.57]
S-Warfarin (CYP2C9 substrate)			
C_{max} (ng/mL)		19	1.03 [0.88, 1.20]
AUC_{0-t} (ng·h/mL)		19	0.93 [0.84, 1.03]
$AUC_{0-\infty}$ (ng·h/mL)		9	0.82 [0.64, 1.06]
Omeprazole (CYP2C19 substrate)			
C_{max} (ng/mL)		20	0.84 [0.59, 1.21]
AUC_{0-t} (ng·h/mL)		19	0.81 [0.59, 1.12]
$AUC_{0-\infty}$ (ng·h/mL)		9	0.65 [0.50, 0.84]
Plasma concentration ratio at 2 hours for 5-hydroxy omeprazole to omeprazole		12	0.92 [0.61, 1.37]
Caffeine (CYP1A2 substrate)			
C_{max} (ng/mL)		20	0.98 [0.76, 1.26]
AUC_{0-10} (ng·h/mL)		20	1.00 [0.77, 1.30]
Plasma concentration ratio at 3 hours for paraxanthine to caffeine		20	0.97 [0.82, 1.16]
AUC_{0-10} ratio for paraxanthine to caffeine		19	0.84 [0.71, 0.99]
Dextromethorphan (CYP2D6 substrate)			
1-dextrorphan urinary concentration ratio to dextromethorphan	Concentration ratio at 0-4 hours	16	1.33 [0.99, 1.77]
	Concentration ratio at 4-8 hours	15	1.64 [1.16, 2.32]
	Concentration ratio at 8-10 hours	17	1.62 [1.13, 2.34]
	Concentration ratio at 10-24 hours	17	1.45 [1.02, 2.07]

*: Geometric least squares mean ratios of PK parameters of each substrate for pazopanib combination therapy to pazopanib monotherapy

4.(ii).A.(3).5) Drug-drug interaction study with paclitaxel (5.3.3.4.4/ref: Study VEG105427 [December 2004 to May 2008])

An open-label study was conducted in 26 foreign patients with solid tumors to investigate the effect of pazopanib on the PK of paclitaxel. Paclitaxel was administered intravenously at 15 to 80 mg/m^2 on Days 1, 8, and 15, and pazopanib was administered orally at 400 or 800 mg QD from Day 2. PK parameters for paclitaxel when concomitantly administering paclitaxel 80 mg/m^2 and pazopanib 800 mg are shown in the following table. Concomitant use with pazopanib increased the $AUC_{0-\infty}$ and C_{max} of paclitaxel (Day 15) by approximately 26% and 36%, respectively, compared with paclitaxel alone. The applicant explained that paclitaxel exposure is elevated in concomitant use with pazopanib, because geometric least square mean ratios of paclitaxel C_{max} and CL [90% CI] for concomitant use with pazopanib (Day 15) to paclitaxel alone (Day 1) were 1.31 [1.03, 1.67] and 0.86 [0.72, 1.02], respectively.

PK parameter of paclitaxel

Study day	n	C_{max} (μg/mL)	AUC_{0-6} (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)
Day1 (Paclitaxel alone)	16	2.38 (25)	2.86 (22)	3.88 (23)	10.3 (16)
Day8 (Paclitaxel with pazopanib)	14	2.73 (39)	4.02 (35)	-	-
Day15 (Paclitaxel with pazopanib)	12	3.23 (39)	3.74 (38)	4.89 (41)	11.1 (12)

Geometric mean (CV%)

4.(ii).A.(4) Pharmacodynamic Studies

The applicant explained that the target plasma concentration in clinical use is 15 to 20 μg/mL, based on the results of the non-clinical study on the inhibition of phosphorylation of vascular endothelial growth factor receptor (VEGFR)-2 [see "3.(i).A.(1).2).i) Inhibition of phosphorylation"] and the following review.

4.(ii).A.(4).1) Foreign phase II study (5.3.4.2.1/ref: Study VEG102616 [October 2005 to March 2008])

A phase II study of pazopanib using an open-label, placebo-controlled, randomized discontinuation design was conducted in 225 patients with clear-cell renal cell carcinoma to investigate the PK and pharmacodynamics of multiple oral dose of pazopanib 800 mg QD. The mean C_{24} values of pazopanib at Weeks 4, 8 and 12 were 28.8, 29.8, and 30.7 ng/mL, respectively. The analysis using an E_{max} model showed the relationship between the C_{24} of pazopanib measured at Week 4 and the percent change from baseline in the plasma soluble VEGFR (sVEGFR)-2 nadir. Plasma sVEGFR-2 concentration decreased with increasing plasma pazopanib concentration, and EC_{50} was 21.3 μg/mL. The applicant explained that the relationship between the reduction of plasma sVEGFR-2 concentration and the efficacy of pazopanib was not investigated, because the correlation between pazopanib exposure and percent change in the plasma sVEGFR-2 concentration was weak ($r^2 = 0.27$).

The applicant explained as follows: in Caucasians, there was a statistically significant relationship between *UGT1A1* genotype (repeating numbers of TA repetitive sequences) and the highest total bilirubin value during the treatment period. This suggests that Caucasian patients with *UGT1A1* gene with TA7/TA7 genotype (*UGT1A1*28/*28*) are more likely to develop pazopanib-induced hyperbilirubinaemia, compared with those without this genotype. However, this effect could not be evaluated in other races because of the small number of cases.

4.(ii).A.(4).2) Relationship between exposure and changes in blood pressure or efficacy

In Study VEG10003 [see "4.(ii).A.(2).2) Foreign phase I study"] in foreign patients with solid tumors, the relationship between pazopanib exposure and changes in blood pressure or efficacy was evaluated. The analysis using a logistic regression model indicated that the C_{24} of pazopanib

at which a 50% probability of hypertension* to be observed is approximately 15 μg/mL. In this study, the efficacy of pazopanib was also evaluated in 10 patients with renal cell carcinoma. The C_{24} of pazopanib was ≥15 μg/mL in 5 of 6 patients with partial response (PR) or stable disease (SD). On the other hand, C_{24} was <15 μg/mL in 4 patients with progressive disease (PD).

*: ≥15 mmHg rise from baseline in mean arterial blood pressure on at least 3 separate occasions, or ; initiation or dose escalation of anti-hypertensive medications; or both

In Study VEG20002 in foreign patients with soft tissue sarcoma, there was no clear relationship between the C_{24} of pazopanib and progression-free survival (84 patients included in PK analysis).

4.(ii).A.(4).3 Relationship between exposure and changes in QT/QTc Interval (5.3.4.2.2/ref: Study VEG111485 [20 to 20])

A placebo and moxifloxacin-controlled, double-blind, randomized study was conducted in 96 foreign patients with solid tumors to evaluate the effect of pazopanib on cardiac conduction system (QT/QTc interval). The analysis using a mixed effect model showed no correlation between the mean change from baseline in QTcF (time matched placebo corrected) and the plasma concentrations of pazopanib and its metabolites (M24, M26, M27). The applicant explained that pazopanib does not cause clinically significant QTc interval prolongation because the mean change in QT interval individually corrected for heart rate (QTci) was small after pazopanib administration in the post-hoc analysis, and there were no abnormal clinical findings in patients with QTc outliers.

4.(ii).A.(4).4 Relationship between exposure and changes in liver function values

The relationship between pazopanib exposure and changes in liver function values (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin) was evaluated using data from a total of 344 foreign cancer patients enrolled in the clinical studies (VEG10003, VEG10007, VEG20006, VEG105192, VEG102616). The analysis using a logistic regression model indicated a correlation between the steady state C_{24} of pazopanib and the probability of observing ALT ≥3 times upper limit of normal. The proportion of subjects who experienced an ALT ≥3 times upper limit of normal was approximately 26% at maximum in the range of plasma pazopanib concentrations observed. On the other hand, there was no clear relationship between the C_{24} of pazopanib and the maximum value of AST, ALP, or bilirubin.

4.(ii).A.(5) Population pharmacokinetics (PPK) analysis

The PPK analysis was performed on data from healthy adult subjects and cancer patients (408 in total) enrolled in the foreign phase I studies (Study VEG10003, Study VEG10005 , Study VEG10006 , Study VEG10007, Study MD1103367), foreign phase II studies (Study VEG102616, Study VEG20006), and foreign phase III study (Study VEG105192) using NONMEM version 6.0 (GloboMax LLC). Subject characteristics included 258 males and 150 females; 325 Caucasians, 67 Asians, 10 blacks, and 6 others; aged 23 to 81 years old; body weight, 38.7 to 147 kg; and baseline creatinine clearance, 30.8 to 150 mL/min. The PK of pazopanib was described as 1-compartment model with first order absorption.

The applicant explained the results of this PPK analysis as follows:

- The CL, V/F, and F of pazopanib estimated in the final model were similar to those in Study VEG10004 [see “4.(i).A.(2) Foreign phase I study”].

- The relative BA was estimated to be 40% higher at 400 mg than at 800 mg.

- The BA of pazopanib after administration after meal was estimated to be 2.6-fold higher than that after administration in the fasted state, which was similar to the results of Study VEG10005 [see “4.(i).A.(3) Foreign phase I study”].

- The BA of pazopanib is likely to be elevated in concomitant use with drugs that increase gastric pH. This result was contradictory to that from the combination therapy study with esomeprazole [see "4.(i).B.(2) Effect of gastric pH"]. This discrepancy was probably because various drugs that increase gastric pH, such as H_2 receptor inhibitors and proton pump inhibitors, were used and the timing of pazopanib and antacid administration was not specified in the protocol in the clinical studies from which data were included in the PPK analysis.

- The CL of pazopanib was estimated to be decreased by 36% in concomitant use with lapatinib, which was similar to the result from Study VEG10006 [see "4.(ii).A.(3).2) Drug-drug interaction study with lapatinib"].

- The CL of pazopanib in patients with ECOG 1 was higher by approximately 18% than in patients with ECOG 0.

- Age, body weight, gender, race, and creatinine clearance were not significant covariates in the estimation of PK parameters for pazopanib.

- Because of a small number of subjects in whom pazopanib was concomitantly administered with a CYP3A4 inhibitor or inducer (4 subjects, 2 subjects, respectively), data were not sufficient to evaluate the effect of drugs with these actions on the PK of pazopanib.

4.(ii).A.(6) Foreign phase I study in patients with hepatic impairment (5.3.3.3.1/ref: Study NCI-8063 [VEG110827] [[redacted] to [redacted]])

The effect of hepatic impairment on the PK of pazopanib was evaluated in 98 patients with solid tumors and hepatic impairment (69 patients included in PK analysis). Pazopanib was administered orally for 21 days at 800 mg QD in patients with normal hepatic function, at 400 and 800 mg QD in patients with mild hepatic impairment (defined as either bilirubin within normal range and ALT > upper limit of normal (ULN), or as an elevation of bilirubin up to 1.5 times ULN regardless of the ALT value), at 200 and 400 mg QD in patients with moderate hepatic impairment (defined as an elevation of bilirubin 1.5 to 3 times ULN regardless of the ALT value), and at 100 and 200 mg QD in patients with severe hepatic impairment (defined as an elevation of bilirubin >3 times ULN regardless of the ALT value). The maximum tolerated dose of pazopanib in patients with moderate hepatic impairment was 200 mg QD.

PK parameters at the maximum tolerated dose in each group are shown in the following table. The steady-state C_{max} and AUC_{0-24} in patients with mild hepatic impairment after oral administration of pazopanib 800 mg QD were similar to those in patients with normal hepatic function. The steady-state C_{max} in patients with moderate and severe hepatic impairment after oral administration of pazopanib 200 mg QD was approximately 44% and 18%, respectively, of those in patients with normal hepatic function after oral administration of pazopanib 800 mg QD. The steady-state AUC_{0-24} in patients with moderate and severe hepatic impairment after oral administration of pazopanib 200 mg QD was approximately 37% and 15%, respectively, of those in patients with normal hepatic function after oral administration of pazopanib 800 mg QD.

Based on the above, the applicant considered that the starting dose of pazopanib needs to be reduced to 200 mg in patients with moderate hepatic impairment. However, at this dose, the C_{24} of pazopanib does not reach 17.5 μg/mL, the concentration required to inhibit VEGFR-2 activity [see "3.(i).A.(1).2).i) Inhibition of phosphorylation"], and it is possible that clinical efficacy of pazopanib cannot be achieved. Therefore, careful administration will be needed with close monitoring on the patient's condition. In addition, the applicant explained that administration of pazopanib is not recommended in patients with severe hepatic impairment, because at 200 mg QD, the C_{24} of pazopanib does not reach the concentration required to inhibit

VEGFR-2 activity.

PK parameter of pazopanib in patients with normal hepatic function or hepatic impairment

Severity	Dose (mg)	n	C_{max} (μg/mL)	AUC_{0-24} (μg·h/mL)	C_{24} (μg/mL)
Normal	800	18	52.0 (17.1, 85.7)	888.2 (345.5, 1482)	29.8 (10.3, 75.0)
Mild		12[*1]	33.5 (11.3, 104.2)	774.2 (214.7, 2034.4)	24.0 (8.3, 74.6)
Moderate	200	11[*2]	22.2 (4.2, 32.9)	256.8 (65.7, 487.7)	16.2 (3.1, 24.2)
Severe		14[*3]	9.4 (2.4, 24.3)	130.6 (46.9, 473.2)	5.7 (1.5, 18.4)

Median (range), *1: 1 subject (300 mg QD) and 5 subjects (400 mg QD) were excluded, *2: 3 subjects (400 mg QD) were excluded, *3: 5 subjects (100 mg QD) were excluded

4.(ii).A.(7) Effect of renal impairment on the PK of pazopanib

Renal impairment is unlikely to affect the PK of pazopanib, because the recovery of radioactivity in urine was approximately 2.6% when ^{14}C-labeled pazopanib was administered orally [see "4.(i).A.(2) Foreign phase I study"], and the results of PPK analysis indicate that creatinine clearance does not affect the CL of pazopanib [see "4.(ii).A.(5) Population pharmacokinetics (PPK) analysis"]. Therefore, dose adjustment is not necessary in patients with renal impairment. No clinical pharmacology study of pazopanib was conducted in patients with renal impairment.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) PK of pazopanib in Japanese and foreign patients

The applicant explained the ethnic differences in the PK of pazopanib as follows:

The difference in PK of pazopanib between Japanese and foreign patients was evaluated, based on PK data from the Japanese clinical study conducted in patients with solid tumors (Study VEG109693) and foreign clinical studies (Study VEG10003, Study VEG10005, Study VEG10006, Study VEG10007, Study VEG20006, Study VEG105192, Study VEG102616).

In PK parameters (C_{max}, AUC_{0-24}, $t_{1/2}$, t_{max}) for pazopanib 800 mg after a single oral dose (Study VEG109693, Study VEG10003, Study VEG10005) and multiple oral dose QD (Study VEG109693, Study VEG10003, Study VEG10006, Study VEG10007, Study VEG20006) [see "4.(ii).A.(2) Cancer patients"], there were no clear differences between Japanese and foreign patients although there were large inter-individual variations. There seems to be no clear difference in the PK of pazopanib between Japanese and foreign populations, because the distribution of C_{max} and AUC_{0-24} individual values for pazopanib after single and multiple dose in Japanese patients generally overlaps with that of foreign patients, although some Japanese patients showed high outliers outside the range of the whole foreign patient values. Pazopanib exposure was high in some subjects, possibly because of individual variations in gastric pH and gastric emptying rate, but the definite reason is unknown.

PMDA considers as follows:

There has been no tendency to suggest any apparent difference in the PK of pazopanib between Japanese and foreign populations, although it is difficult to discuss potential ethnic differences in the PK of pazopanib, since there were large individual variations regardless of ethnicity, and the sample size for Japanese PK data was small (n = 7). As only limited data are available so far for the evaluation of ethnic differences in the PK of pazopanib, it is necessary to continuously collect evaluable information for this matter, and appropriately provide information to the medical practice when new findings become available.

4.(ii).B.(2) Pharmacokinetic drug interactions

The applicant explained as follows:

Pazopanib treatment in combination with strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, etc.) should be avoided. When pazopanib has to be concomitantly administered

with a strong CYP3A4 inhibitor, a dose reduction of pazopanib to 400 mg is necessary.

PMDA asked the applicant to explain the clinical pharmacology rationale for the dose adjustment of pazopanib in concomitant use with a CYP3A4 inhibitor.

The applicant responded as follows:
A dose reduction to 400 mg of pazopanib for concomitant use with a strong CYP3A4 inhibitor was specified for the following reasons.

- In the drug-drug interaction study with ketoconazole (Study VEG113971), concomitant use with ketoconazole resulted in an approximately 2-fold increase in C_{max} and AUC_{0-24} for pazopanib compared with pazopanib 400 mg QD alone; and the geometric mean C_{24} for concomitant use of pazopanib with ketoconazole was higher than 17.5 μg/mL, the concentration required to inhibit VEGFR-2 activity [see "3.(i).A.(1).2).i) Inhibition of phosphorylation"] [see "4.(ii).A.(3).1) Drug-drug interaction study with ketoconazole"].

- Pazopanib 800 mg QD was shown to be well tolerated in foreign and Japanese clinical studies.

PMDA considers as follows:
The relationship between the C_{24} of pazopanib and its efficacy has not been elucidated in patients with soft tissue sarcoma [see "4.(ii).A.(4).2) Relationship between exposure and changes in blood pressure or efficacy"]. Therefore, the efficacy of concomitant use of pazopanib with ketoconazole cannot be assured by the finding that the C_{24} of concomitant use of pazopanib 400 mg with ketoconazole was higher than the concentration required to inhibit VEGFR-2 activity (Study VEG113971). Therefore, the optimal dose of pazopanib in combination with a strong CYP3A4 inhibitor is unknown.

When pazopanib is concomitantly administered with a strong CYP3A4 inhibitor, it is possible that the dose reduction for pazopanib is needed because of the likelihood of increase in pazopanib exposure. However, since an appropriate range of dose reduction for pazopanib is unknown at present, combination with strong CYP3A4 inhibitors should be avoided, and it is preferable to consider use of an alternate concomitant medication. When concomitant use of pazopanib with a strong CYP3A4 inhibitor is unavoidable, a dose reduction of pazopanib should be considered and the patient's condition should be monitored closely particularly for incidence of adverse events.

The above information needs to be appropriately provided via the package insert etc.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

Clinical data from a total of 3 studies (i.e., 1 Japanese phase I study, 1 foreign phase II study, 1 global phase III study) were submitted as pivotal data for the evaluation of efficacy and safety. In addition, data from a total of 13 foreign clinical studies (i.e., 9 phase I studies, 1 phase I/II study, 2 phase II studies, 1 phase IV study) were submitted as reference data.

List of individual clinical studies regarding efficacy and safety

Data category	Region	Study number	Phase	Study population	No. of enrollment	Dosage regimen[*1]	Major endpoints
Evaluation	Japan	VEG109693	I	Solid tumors	Part A: 13, Part B: 17	Part A (pazopanib alone) • Single 400 mg[*2], then 800 mg QD • Single 800 mg[*2], then 800 mg QD • Single 1000 mg[*2], then 1000 mg QD Part B (with lapatinib) • Pazopanib 400 mg + lapatinib 1000 mg QD • Pazopanib 800 mg + lapatinib 1000 mg QD • Pazopanib 400 mg + lapatinib 1500 mg QD • Pazopanib 600 mg or lapatinib 1250 mg QD for 15 days, then pazopanib 600 mg + lapatinib 1250 mg QD	Safety, tolerability, PK
	Foreign	VEG20002	II	Relapsed or refractory soft tissue sarcoma	142	Pazopanib 800 mg QD	Efficacy, safety
	Global	VEG110727	III	Metastatic soft tissue sarcoma whose disease has progressed following prior chemotherapy	369 a. 246 b. 123	a. Pazopanib 800 mg QD b. Placebo QD	Efficacy, safety
References	Foreign	VEG10003	I	Solid tumors	63	• Pazopanib 50, 100, 200, 400, 600, 800, 1000, 1400 or 2000 mg QD • Pazopanib 300 or 400 mg BID • Pazopanib 50 or 100 mg TIW	Safety, tolerability, PK/PD
		VEG10004	I	Solid tumors	Part A: 3, Part B: 7	Part A • Single 400 mg pazopanib (^{14}C-labeled), then 800 mg QD • Pazopanib 800 mg QD Part B • Single IV pazopanib 5 mg, then 800 mg QD • Pazopanib 800mg QD	PK, safety
		VEG10005	I	Solid tumors	Part 1: 44 a. 6 b. 29 c. 9 Part 2: 26	Part 1: a. Single pazopanib 400 mg (after high-fat meal) b. Pazopanib 800 mg QD (Fasted, after high-, low-fat meal) c. Single pazopanib 400 mg (crashed or whole tablets) Part2: • Pazopanib 800 mg QD	PK , Safety, tolerability
		MD1103367	I	Healthy adult subjects (elderly)	9 a. 6 b. 3	a. Pazopanib 100 mg QD, b. Placebo QD	Safety, tolerability, PK
		VEG20006	II	Multiple myeloma	21	Pazopanib 800 mg QD	Safety, tolerability, PK
		NCI-8063 (VEG110827)	I	Solid tumors or lymphoma, and hepatic impairment	98	Pazopanib 50, 100, 200, 400 or 800 mg QD	Safety, PK/PD

		VEG113971	IV	Solid tumors	Group A: 21, Group B: 13	Group A: • Pazopanib 400 mg QD • Pazopanib 400 mg + ketoconazole 400 mg QD Group B • Pazopanib 400 mg QD • Pazopanib 400 mg + esomeprazole 40 mg QD	PK, safety
		VEG10006	I	Solid tumors	75	• Pazopanib 200-800 mg + lapatinib 750-1500 mg QD for 22 days • Pazopanib 400 or 800 mg or lapatinib 1000 or1500 mg QD for the first 15 days, pazopanib 400 mg + lapatinib 1000 mg or pazopanib 800 mg + lapatinib 1500 mg QD from Day 16 to Day 37	Safety, tolerability, PK
		VEG10007	I	Solid tumors	24	Single midazolam 3 mg on Days 1 and 23, single warfarin 10 mg, omeprazole 40 mg, caffeine 200 mg + dextromethorphan 30 mg on Days 2 and 24, then pazopanib 800 mg QD from Day 6 to Day 28	PK , Safety, tolerability
		VEG105427	I	Cancer	26	Paclitaxel 15-80 mg/m^2 IV on Days 1, 8, 15 Pazopanib 400 or 800 mg QD from Day 2	Safety, tolerability, PK
		VEG102857	I/II	Malignant glioma	Phase I: 34, Phase II: 41	Phase I: • Pazopanib 200 or 800 mg + lapatinib 1500 mg QD • Pazopanib 800 mg QD + lapatinib 500-1000 mg BID • Pazopanib 600 mg + lapatinib 1000 mg BID Phase II: • Pazopanib 400 mg + lapatinib 1000 mg QD	Safety, tolerability, PK
		VEG102616	II	Renal cell carcinoma	225	Pazopanib 800 mg QD	Safety, tolerability, PK/PD
		VEG111485	I	Solid tumors	96	Single moxifloxacin 400 mg or placebo on Day 1, pazopanib 800 mg or placebo from Day 2 to Day 8, then pazopanib 1600 mg or placebo on Day 9	Safety

QD: Once daily, BID: Twice daily, TIW: 3 times a week, *1: Pazopanib was orally administered. *2: Blood sampling for PK was performed up to 96 hours after administration.

The outline of individual clinical studies is provided below.
Major adverse events other than deaths reported in each clinical study are described under “4.(iv) Adverse events observed in clinical studies,” and PK data under “4.(i) Summary of biopharmaceutic studies and associated analytical methods” and “4.(ii) Summary of clinical pharmacology data.”

Evaluation data

(1) Japanese phase I study (5.3.5.2.2: Study VEG109693 [September 2007 to ongoing (Data Cut-off Date: October 29, 2010)])

An open-label study was conducted at 2 medical institutions in Japan to evaluate the safety, tolerability, and PK of pazopanib in patients with solid tumors who have not responded to standard therapy (target sample size: Part A, 6 subjects in Original cohort and 3 subjects each in Additional cohorts [6 in total]; Part B, 3 subjects each in Dose escalation cohort and 6 subjects in PK cohort).

Regarding Part A (pazopanib alone), in the Original cohort, a single oral dose of pazopanib was administered at 800 mg, and after blood sampling for PK, pazopanib was administered orally at 800 mg QD (P800 mg group). In the Additional cohort, a single oral dose of pazopanib was administered at 400 mg, and after blood sampling for PK, pazopanib was administered orally at 800 mg QD (P400/800 mg group), or a single oral dose of pazopanib at 1000 mg was administered, and after blood sampling for PK, pazopanib was administered orally at 1000 mg QD (P1000 mg group). Regarding Part B (concomitant use with lapatinib), in the Dose escalation cohort, pazopanib 400 mg QD and lapatinib 1000 mg QD (P400/L1000 group), pazopanib 800 mg QD and lapatinib 1000 mg QD (P800/L1000 group), or pazopanib 400 mg QD and lapatinib 1500 mg QD (P400/L1500 group) were administered orally, and in the PK cohort, pazopanib 600 mg QD or lapatinib 1250 mg QD was administered orally for 15 days, and then pazopanib 600 mg QD and lapatinib 1250 mg QD were administered orally (P600/L1250 group).

All subjects enrolled in this study (i.e., 13 subjects) in Part A (3 subjects in P400/800 mg group, 7 subjects in P800 mg group, 3 subjects in P1000 mg group) and 17 subjects in Part B (4 subjects in P400/L1000 group, 3 subjects in P800/L1000 group, 3 subjects in P400/L1500 group, 7 subjects in P600/L1250 group) were treated with pazopanib, and evaluated for safety and pharmacokinetics.

As for safety, 1 subject (P800/L1000 group) died 47 days after the last dose in Part B. The cause of death was considered to be disease progression, and not related to pazopanib. There were no deaths in Part A.

(2) Foreign phase II study (5.3.5.2.1: Study VEG20002 [October 2005 to Ongoing (Data Cut-off Date: [redacted], 20[redacted])])

An open-label study was conducted at 15 medical institutions overseas to evaluate the efficacy and safety of pazopanib in patients with relapsed or refractory soft tissue sarcoma (target sample size; 37 subject [17 subjects for Stage 1, 20 subjects for Stage 2] each in leiomyosarcoma, adipocytic sarcoma, synovial sarcoma, and other soft tissue sarcoma, 148 subjects in total).

For efficacy analysis, 138 subjects were included in the intent-to-treat (ITT) population. All of 142 enrolled into the study were included in the safety analysis.

Simon's two-stage optimal design was used for efficacy analysis [see "4.(iii).B.(5).1) Patient populations and tumor histology"]. The percentage of subjects who achieved at least SD at Week 12 (progression free rate [PF rate]) by the tumor histology of soft tissue sarcoma was 5 of 19 subjects (26%) for adipocytic sarcoma, 17 of 41 subjects (41%) for leiomyosarcoma, 18 of 37 subjects (49%) for synovial sarcoma, and 17 of 41 subjects (41%) for other soft tissue sarcoma (other than adipocytic sarcoma, leiomyosarcoma or synovial sarcoma).

As for safety, there were 19 deaths between the first day of study treatment and 28 days after the last dose. Of them, 14 deaths were due to disease progression, and other causes of death were somnolence, depression, disseminated intravascular coagulation (DIC), peritonitis/small intestinal perforation/peritoneal infection, and pneumonia (1 subject each). Of these events, DIC

and peritonitis/small intestinal perforation/peritoneal infection were considered to be related to pazopanib, and for somnolence the causal relationship to pazopanib was decided to be unevaluable by the investigator.

(3) Global phase III study (5.3.5.1.1: Study VEG110727 [October 2008 to Ongoing (Data Cut-off Date: November 22, 2010)])

A randomized, placebo-controlled, double blind, parallel group phase III study was conducted at 72 medical institutions in 13 countries including Japan to evaluate the efficacy and safety of pazopanib in subjects with metastatic soft tissue sarcoma which has progressed during or following anthracycline therapy or, during or following standard chemotherapy available in each medical institution (target sample size of 360 subjects*) [see "4.(iii).B.(5).1) Patient populations and tumor histology" for the eligible histology subtypes].

*: The target sample size was 255 subjects in the first version of protocol ([redacted], 20[redacted]), but when subject enrolment proceeded faster than expected, in order to increase the power for overall survival (OS), reevaluation of the target sample size was allowed. Since the number of emrolled subjects exceeded the expected number (10 subjects/month) within the first 6 months, the enrolled subjects were estimated to be 17 subjects/month. Therefore, the target sample size was changed to 360 subjects under blind conditions.

Placebo or pazopanib was administered orally at 800 mg QD, and subjects continued on treatment until disease progression, death, the occurrence of an unacceptable adverse event, or withdrawal of consent.

A total of 369 subjects (246 subjects in pazopanib group, 123 subjects in placebo group) were enrolled and randomized in this study, and all of them were included in the ITT population for efficacy analysis. Of the ITT population, 363 subjects (240 subjects in pazopanib group, 123 subjects in placebo group) who received at least one dose of the study drug were included in the safety analysis.

As for efficacy, independent reviewer-assessed (radiology review by independent radiologists under blind conditions) progression-free survival (PFS) was the primary endpoint, and OS was the principal secondary endpoint.

In this study, subjects withdrawn for a reason other than disease progression or death were also followed until disease progression or initiation of new antineoplastic therapy. In the protocol, subjects withdrawn from study treatment before PD were to be censored at withdrawal and the date of censor is defined as the last day of adequate disease assessment, for the primary analysis. However, considering the effect of possible imbalance in censoring between the two groups on the results of primary analysis, the Statistical Analysis Plan (prepared on [redacted], 20[redacted]) specified that the primary analysis of PFS should be based on the period until PD or death is confirmed during the follow-up period (i.e., not to be censored at withdrawal from study treatment).

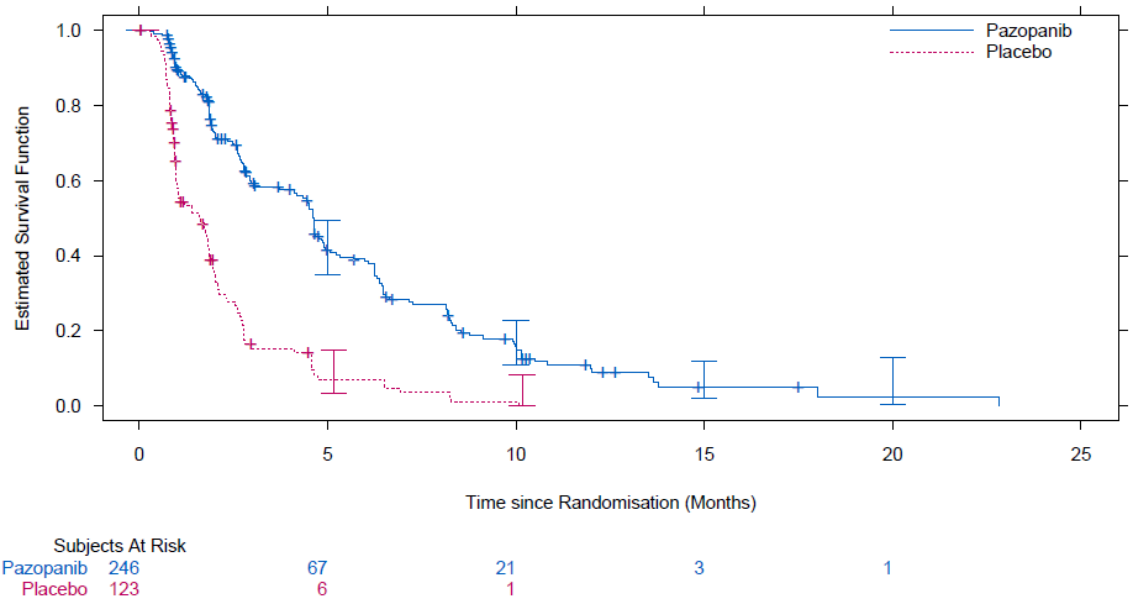
The interim analysis of OS at the time of final analysis of PFS was planned and a Lan and DeMets α-spending function with O'Brien-Fleming was introduced. Subjects in the placebo group were not to be crossed-over to the pazopanib group after PD.

As for independent reviewer-assessed PFS, which was the primary endpoint, the results of the primary analysis planned in the Statistical Analysis Plan are shown in the following table and figure. A statistically significant improvement in PFS was observed in the pazopanib group. In the primary analysis specified in the protocol, the hazard ratio [95% CI] for PFS in the pazopanib group relative to the placebo group was 0.33 [0.24, 0.46].

Results of PFS final analysis
(Independent radiologist assessment, ITT population, cut-off date: Nov. 22, 2010)

	Pazopanib	Placebo
Number of Subjects	246	123
Progressed or died (regardless of the cause) *1	163 (66%)	106 (86%)
Median [95% CI] (months)	4.6 [4.1, 4.9]	1.6 [1.0, 1.9]
Hazard ratio [95% CI]*2	0.35 [0.26, 0.48]	
P-value (two-sided test)*3	<0.001	

*1: Includes 6 subjects in the placebo group and 15 subjects in the pazopanib group who died during adequate follow-up period without documentation of progression
*2: Hazard ratio is estimated using the Pike estimator and adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease.
*3: Stratified log-rank test



Kaplan-Meier curve for PFS
(Independent radiologist assessment, ITT population, cut-off date: Nov. 22, 2010)

As for safety, there were 39 deaths (26 subjects in pazopanib group, 13 subjects in placebo group) between the first day of study treatment and 28 days after the last dose. Of them, 34 deaths (22 subjects in pazopanib group, 12 subjects in placebo group) were due to disease progression, and other causes of deaths were pneumonia, lung disorder, multi-organ failure, and unknown (1 subject each) in the pazopanib group, and sepsis (1 subject) in the placebo group. The causal relationship to pazopanib was not ruled out for the case of multi-organ failure.

Reference data

(1) Foreign phase I study (5.3.5.2.3: Study VEG10003 [December 2002 to September 2006])

An open-label study was conducted at 2 medical institutions overseas to investigate the safety, tolerability, and PK of pazopanib in patients with solid tumors (target sample size; ≥2 subjects per group, 30-65 in total).
Sixty-three subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.
As for safety, there were no deaths during the study period (from the first dose of pazopanib until 21 days after the last dose).

(2) Foreign phase I study (5.3.1.1.1, 5.3.1.1.2: Study VEG10004 [July 2007 to July 2008])
An open-label study was conducted at 2 medical institutions overseas to investigate the PK and safety of pazopanib in patients with solid tumors (target sample size of 10 subjects).

Ten subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were no deaths during the study period (from the first dose of pazopanib until 14 days after the last dose).

(3) Foreign phase I study (5.3.1.1.3, 5.3.1.1.4: Study VEG10005 [September 2006 to August 2007])
An open-label study was conducted at 2 medical institutions overseas to investigate the PK, safety, and tolerability of pazopanib in patients with solid tumors (target sample size; 36 subjects in Part 1, not specified for Part 2).

Sixty-nine subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were 3 deaths during the study period (from the first dose of pazopanib until 14 days after the last dose), due to disease progression (2 subjects) and road traffic accident (1 subject). Causal relationship to pazopanib was ruled out in all cases.

(4) Foreign phase I study (5.3.3.1.1: Study MD1103367 [[redacted] 20[redacted] to [redacted] 20[redacted]])
A single-blind study was conducted at a center overseas to investigate the safety, tolerability, and PK of pazopanib in healthy elderly subjects (target sample size of 9 subjects).

Nine subjects enrolled in this study who received at least one dose of the study drug were included in the safety analysis.

As for safety, there were no deaths during the study period (from the first dose of study drug until 7 days after the last dose).

(5) Foreign phase II study (5.3.3.2.1: Study VEG20006 [January 2005 to December 2006])
An open-label study was conducted at 4 medical institutions overseas to evaluate the safety, tolerability, and PK of pazopanib in patients with multiple myeloma (target sample size of 40 subjects).

Twenty-one subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were no deaths during the study period (from the first dose of pazopanib until 28 days after the last dose).

(6) Foreign phase I study (5.3.3.3.1: Study NCI-8063 (VEG110827) [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label study was conducted at 18 medical institutions overseas to investigate the safety, PK, and pharmacodynamics of pazopanib in patients with solid tumors or lymphoma, and hepatic impairment (target sample size of 132 subjects).

Ninety-seven subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were 40 deaths during the study period (within 30 days of the last dose of pazopanib). All deaths were due to disease progression.

*: In 10 of 40 deaths, the primary cause was considered to be disease progression, but renal failure and encephalopathy (2 subjects each), dyspnoea, administration of narcotics, gastric haemorrhage/gastroduodenal pseudoaneurysm/nausea/vomiting, ischaemia cerebrovascular/ hypertension/congenital anomaly of the central nervous system, fungemia/cellulitis, and hepatic failure (1 subject each) were also considered to be adverse events related to the cause of deaths. Causal relationship to pazopanib could not be ruled out for the events of gastric haemorrhage and ischaemia cerebrovascular.

(7) Foreign phase IV study (5.3.3.4.1, 5.3.3.4.6: Study VEG113971 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at 2 medical institutions overseas to investigate the PK and safety of pazopanib in patients with solid tumors (target sample size; 12 subjects in Arm A, 12 subjects in Arm B).

Of subjects enrolled in this study, 21 subjects in Arm A and 13 subjects in Arm B who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were no deaths during the study period (from the first dose of pazopanib until 28 days after the last dose).

(8) Foreign phase I study (5.3.3.4.2: Study VEG10006 [September 2004 to July 2007])

An open-label study was conducted at 1 medical institution overseas to investigate the safety, tolerability, and PK of pazopanib in patients with solid tumors (target sample size of 75 subjects).

Seventy-five subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were 4 deaths during the study period (from the first dose of pazopanib until 28 days after the last dose). The cause of 1 death, except 3 deaths* due to disease progression, was upper gastrointestinal haemorrhage, for which causal relationship to pazopanib could not be ruled out.

*: In 1 of these 3 deaths, the primary cause was considered to be disease progression, but vomiting, dehydration, and renal failure were also considered to be adverse events related to the cause of death. Causal relationship to pazopanib could not be ruled out for vomiting and dehydration.

(9) Foreign phase I study (5.3.3.4.3: Study VEG10007 [July 2006 to February 2008])

An open-label study was conducted at 1 medical institution overseas to investigate the PK, safety, and tolerability of pazopanib in patients with solid tumors (target sample size of 30 subjects).

Twenty-four subjects enrolled in this study who received at least one dose of study drug were included in the safety analysis.

As for safety, there were 5 deaths during the study period (from the first dose of study drug until 28 days after the last dose), 4 deaths were due to disease progression and 1 death due to pneumonia. Causal relationship to study drug was ruled out in all cases.

(10) Foreign phase I study (5.3.3.4.5: Study VEG105427 [December 2004 to May 2008])

An open-label study was conducted at 3 medical institutions overseas to investigate the safety, tolerability, and PK of pazopanib in cancer patients (target sample size of 33 subjects).

Twenty-six subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were 6 deaths during the study period (from the first dose of pazopanib until 28 days after the last dose). Except 5 deaths due to the primary disease, the cause of 1 death was gastrointestinal haemorrhaget, for which causal relationship to pazopanib could not be ruled out.

(11) Foreign phase I/II study (5.3.3.4.5: Study VEG102857 [December 2006 to December 2009])

An open-label study was conducted at 6 medical institutions overseas to evaluate the safety, tolerability, and PK of pazopanib in patients with relapsed malignant glioma (target sample size of 48 subjects).

Thirty-four subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were 20 deaths (11 subjects for phase I, 9 subjects for phase II) during the study period (from the first dose of pazopanib until 28 days after the last dose), 19 deaths were due to disease progression and 1 death due to streptococcal pneumonia. Causal relationship to pazopanib was ruled out in all cases.

(12) Foreign phase II study (5.3.4.2.1: Study VEG102616 [October 2005 to March 2008])

An open-label study was conducted at 1 medical institution overseas to investigate the safety, tolerability, and PK of pazopanib in patients with renal cell carcinoma (target sample size of 160-230 subjects).

Two-hundred and twenty-five (225) subjects enrolled in this study who received at least one dose of pazopanib were included in the safety analysis.

As for safety, there were a total of 22 deaths, 13 subjects during the study period (from the first dose of pazopanib until 28 days after the last dose) and 9 subjects more than 28 days after the last dose. Of them, 15 deaths were due to disease progression and others were due to dyspnoea (2 subjects), road traffic accident, euthanasia, bowel perforation, acute renal failure, and unknown cause (1 subject each). Causal relationship to pazopanib could not be ruled out for bowel perforation and dyspnoea (1 subject each).

(13) Foreign phase I study (5.3.4.2.2: Study VEG111485 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A double-blind study was conducted at 8 medical institutions overseas to investigate the safety of pazopanib in patients with solid tumors (target sample size of 80 subjects).

Ninety-six subjects enrolled in this study who received at least one dose of pazopanib/placebo were included in the safety analysis.

As for safety, there were 3 deaths (1 subject in pazopanib group, 2 subjects in placebo group) during the study period (from the first dose of pazopanib/placebo until 46 days after the last dose). The causes of death were disease progression in the pazopanib group and ear haemorrhage and arrhythmia (1 subject each) in the placebo group. Causal relationship to pazopanib could not be ruled out for arrhythmia* in the placebo group.

* The subject, who received placebo in this study, was enrolled in another study of pazopanib after the completion of Study VEG111485, and died of arrhythmia 1 day after the last dose of pazopanib. Causal relationship of the arrhythmia to pazopanib could not be ruled out.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Data for review

PMDA determined that the global phase III study (Study VEG110727), in which the efficacy and safety of pazopanib were investigated in patients with metastatic soft tissue sarcoma that had progressed following chemotherapy, is the most important study among the submitted data in evaluating the efficacy and safety of pazopanib, and concluded to review the results of the study as the main study.

4.(iii).B.(2) Efficacy

Based on the following review, PMDA concluded that the efficacy of pazopanib has been demonstrated in patients with metastatic soft tissue sarcoma, the study population of Study VEG110727.

4.(iii).B.(2).1) Selection of comparator

The applicant explained that placebo was chosen for the comparator arm for the following reasons when Study VEG110727 was designed.

- There was no established therapy for patients whose disease had progressed following prior therapy with doxorubicin hydrochloride (doxorubicin), the main study population of Study VEG110727.

- A "physician's choice" was considered as the comparator arm, however, this option would not permit a robust assessment of the safety profile of pazopanib, given there is the diversity of salvage chemotherapy performed at candidate medical institutions in patients with metastatic soft tissue sarcoma, who have a previous history of doxorubicin treatment, and the study can not remain blinded.

PMDA considers that placebo is an appropriate comparator in Study VEG110727, because when it was designed, the standard primary therapy in patients with metastatic soft tissue sarcoma, the study population of Study VEG110727, was doxorubicin, but there was no standard therapy for patients whose disease had progressed following doxorubicin therapy.

4.(iii).B.(2).2) Efficacy endpoints

PMDA asked the applicant to explain why PFS was chosen as the primary endpoint in Study VEG110727.

The applicant responded as follows:
Metastatic soft tissue sarcoma is generally resistant to chemotherapy and cannot be cured by chemotherapy alone. Chemotherapy in this setting is symptomatic or palliative, and the therapeutic purposes are disease control and improvement of clinical symptoms (*Practical guide for soft tissue sarcoma.* Nakayama Shoten Co., Ltd.; 2011, *Bone/Soft Tissue Sarcoma and Related Diseases, Vol. 20, Integrated handbook of orthopedics.* Nakayama Shoten Co., Ltd.; 2007). These descriptions indicate that the prolongation of PFS delays tumor growth and moving to the next therapy. Therefore, prolonged PFS has a clinical significance in patients with metastatic soft tissue sarcoma. Also, PFS is one of the direct indices that can measure tumor growth inhibition objectively and quantitatively, and PFS is not affected by subsequent therapies given after the study period. Thus, PFS was chosen as the primary endpoint. OS was used as the "principal secondary endpoint" because it is also an important endpoint.

PMDA considers the efficacy endpoints in Study VEG110727 as follows:
The purpose of treatment is life prolongation in patients with incurable soft tissue sarcoma. Considering the fact that there is no therapy proven to have a survival advantage in the study

population for Study VEG110727, OS is the best primary efficacy endpoint for pazopanib. However, when Study VEG110727 was designed, there were no treatment options shown to prolong OS or shown to have clear clinical significance in terms of time-to-event efficacy such as PFS prolongation, for doxorubicin-treated patients. Also, taking into account that a new drug in this disease area was needed to be introduced to clinical practice as soon as possible, selecting PFS, for which data can be obtained earlier than OS, as the primary efficacy endpoint is partially acceptable. Based on the above, PMDA concluded to evaluate the efficacy in Study VEG110727 focusing on the primary endpoint, PFS, and also taking the "principal secondary endpoint" OS into consideration.

4.(iii).B.(2).3) Results of efficacy evaluation

In Study VEG110727, PFS in the ITT population by independent assessment was selected as the primary endpoint. A statistically significant improvement was observed in the independent reviewer-assessed PFS in the pazopanib group compared with the placebo group [see "4.(iii).A Evaluation data (3) Global phase III study"]. The results of analysis of investigator-assessed PFS conducted as a sensitivity analysis are shown below. These were consistent with the results of independent reviewer-assessed PFS.

Final analysis of PFS
(Investigator assessment, ITT population, cut-off date: Nov. 22, 2010)

	Pazopanib	Placebo
Number of subjects	246	123
Progressed, or died (regardless of cause) *1	192 (78%)	117 (95%)
Median [95% CI] (months)	4.6 [4.3, 5.7]	1.5 [1.0, 1.9]
Hazard ratio [95% CI]*2	0.39 [0.30, 0.52]	
P-value (two-sided test)*3	<0.001	

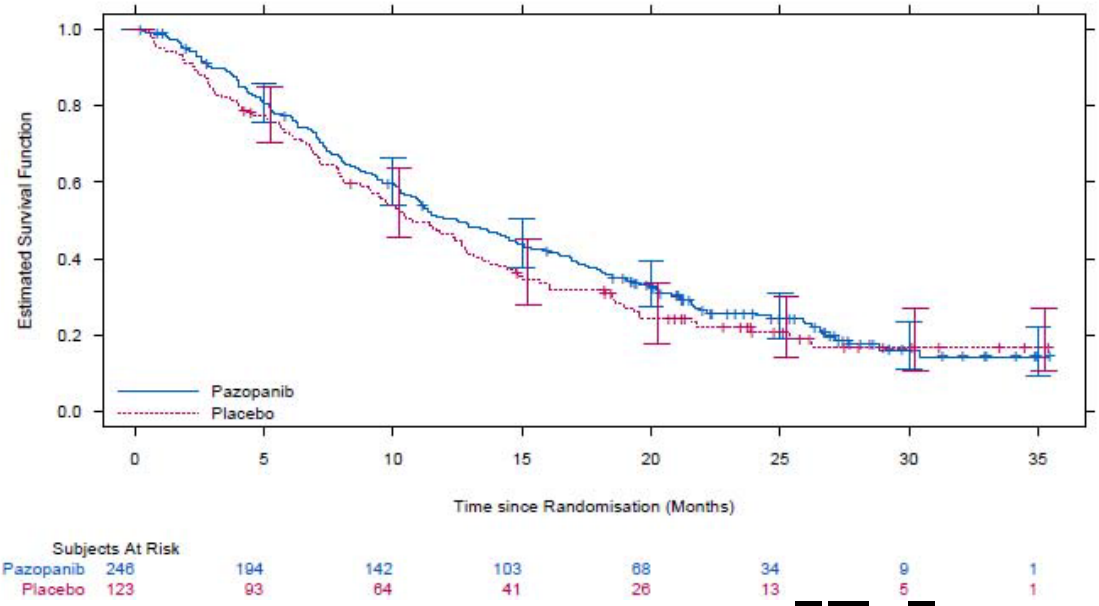
*1: Includes 4 subjects in the placebo group and 9 subjects in the pazopanib group who died during adequate follow-up period without documentation of progression
*2: Hazard ratio is estimated using the Pike estimator and adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease.
*3: Stratified log-rank test

At the time of final PFS analysis, the interim analysis of the principal secondary endpoint, OS, was conducted to show no statistically significant difference between the 2 groups (P = 0.156, stratified log-rank test, level of significance of 0.021). The results of final OS analysis, submitted after the application, are shown in the following table.

Final analysis of OS (ITT population, cut-off date: [redacted], 20[redacted])

	Pazopanib	Placebo
Number of subjects	246	123
Number of deaths	185 (75%)	95 (77%)
Median [95% CI] (months)	12.6 [10.9, 14.9]	10.7 [9.0, 13.1]
Hazard ratio [95% CI]*1	0.87 [0.67, 1.12]	
P-value (two-sided test)*2	0.256	

*1: Hazard ratio is estimated using the Pike estimator and adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease.
*2: Stratified log-rank test (0.044 significance level)



Kaplan-Meier curve of OS (ITT population, cut-off date: [redacted], 20[redacted])

PMDA asked the applicant to explain why there was no statistically significant difference in OS.

The applicant responded as follows:
When Study VEG110727 was designed, based on the sample size calculated from the hazard ratio and power for the primary endpoint, PFS, the hazard ratio detected with power of 80% was estimated at 0.67 for OS (4-month prolongation in median OS from 8 to 12 months). Therefore the hypothesis for OS was defined considering the feasibility of the study aiming to evaluate PFS, and the clinical benefit of pazopanib could have been overestimated.

Insufficient power is one of the causes for the lack of statistical significance in OS, because the effect of the study drug on OS may be diluted even when post-treatment anti-cancer therapies are similar between the groups, in the study population whose postprogression survival time is relatively long (*J Natl Cancer Inst* 2009; 101: 1642-9).

In Study VEG110727, there were no marked differences in the type of follow-up anti-cancer therapy after discontinuation of study treatment, although there was an imbalance in the percentage of subjects who received some follow-up anti-cancer therapy after disease progression, including surgery and radiotherapy, between the pazopanib group (149 of 246 subjects, 61%) and the placebo group (92 of 123 subjects, 75%). There were no large differences between the placebo group and pazopanib group in the subgroup analyses of OS by the number of prior systemic regimens, prior treatment agents, and the lesion site and the primary lesion.

PMDA considers the results of efficacy in Study VEG110727 as follows:
The clinical efficacy of pazopanib can be expected in patients with metastatic soft tissue sarcoma in terms of the primary endpoint, PFS, because the prolongation of PFS was shown consistently in the primary analysis as well as in the sensitivity analysis. On the other hand, the benefit of pazopanib to prolong OS could not be confirmed in this study, considering that the evaluation of OS was not the primary objective of Study VEG110727, and the rationale for setting the hypothesis for OS was weak. However, it was confirmed that at least pazopanib did not show any tendency toward shortening OS compared with placebo.

4.(iii).B.(2).4) Efficacy by tumor histology

PMDA asked the applicant to explain the efficacy of pazopanib by tumor histology.

The applicant responded as follows:

Patients with metastatic soft tissue sarcoma (STS) enrolled in Study VEG110727 were stratified by the major histology subgroups, leiomyosarcoma, synovial sarcoma, and other STS than leiomyosarcoma and synovial sarcoma (hereinafter referred to as "other STS") for the analysis. The results are shown in the following table. In the subgroup analysis by tumor histology, a statistically significant improvement in PFS was observed in the pazopanib group compared with the placebo group.

Summary of PFS by STS histology subgroups
(Independent radiologist assessment, ITT population, cut-off date: Nov. 22, 2010)

Histology subgroup	Pazopanib		Placebo		Hazard ratio [95% CI]*1	*P*-value (two-sided test)*2
	N	Median [95% CI] (months)	N	Median [95% CI] (months)		
Leiomyo-sarcoma	109	4.6 [3.1, 5.3]	49	1.9 [1.7, 2.1]	0.37 [0.23, 0.60]	<0.001
Synovial sarcoma	25	4.1 [2.0, 6.2]	13	1.0 [0.9, 2.0]	0.43 [0.19, 0.98]	0.005
Other STS	112	4.6 [3.0, 6.2]	61	1.0 [0.9, 1.8]	0.39 [0.25, 0.60]	<0.001

*1: Hazard ratios are estimated using the Pike estimator and adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease.
*2: Stratified log-rank test

The results of subgroup analysis of OS by tumor histology in Study VEG110727 are shown in the following table. In the subgroup of synovial sarcoma, OS was longer in placebo-treated subjects, while OS tended to be longer in pazopanib-treated subjects in the leiomyosarcoma and other STS subgroups. Although the reason for longer OS in placebo-treated patients with synovial sarcoma is unknown, some imbalances might have arisen between pazopanib group and placebo group, since the number of subjects in the subgroup of synovial sarcom was very small.

OS by histology subgroups (ITT population, cut-off date: [redacted], 20[redacted])

Histology subgroup	Pazopanib		Placebo		Hazard ratio [95% CI]*1
	N	Median [95% CI] (months)	N	Median [95% CI] (months)	
Leiomyosarcoma	109	16.7 (12.6, 19.0)	49	14.1 (11.8, 18.5)	0.84 (0.56, 1.26)
Synovial sarcoma	25	8.7 (5.7, 14.6)	13	21.6 (6.6, 25.4)	1.62 (0.79, 3.33)
Other STS	112	10.3 (8.0, 13.6)	61	9.5 (7.1, 10.7)	0.84 (0.59, 1.21)

*1: Hazard ratios are estimated using the Pike estimator and adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease.

Best response and overall response rate by tumor histology subgroups in Study VEG110727 are shown in the following table. There was no complete response (CR) in any subgroup, but PR was achieved only in the pazopanib group. A larger percentage of subjects in the pazopanib group experienced a best response of SD as compared with subjects in the placebo group.

Best confirmed response and response rate by STS histology subgroups (RECIST, independent radiologist assessment, cut-off date: Nov. 22, 2010)

		N	Best response, n (%)					No. of response cases (Response rate[*2] [%] [95% CI])
			CR	PR	SD[*1]	PD	NE	
Overall	Pazopanib	246	0	11 (4)	134 (54)	66 (27)	35 (14)	11 (4 [2.3, 7.9])
	Placebo	123	0	0	33 (27)	76 (62)	14 (11)	0 (0 [0.0, 3.0])
Leiomyo-sarcoma	Pazopanib	109	0	5 (5)	63 (58)	30 (28)	11 (10)	5 (5 [1.5, 10.4])
	Placebo	49	0	0	16 (33)	27 (55)	6 (12)	0 (0 [0.0, 7.3])
Synovial sarcoma	Pazopanib	25	0	1 (4)	11 (44)	6 (24)	7 (28)	1 (4 [0.1, 20.4])
	Placebo	13	0	0	2 (15)	11 (85)	0	0 (0 [0.0, 24.7])
Other STS	Pazopanib	112	0	5 (4)	60 (54)	30 (27)	17 (15)	5 (4 [1.5, 10.1])
	Placebo	61	0	0	15 (25)	38 (62)	8 (13)	0 (0 [0.0, 5.9])

NE: Not evaluable
*1: In order to qualify as a best response of SD, a response of SD has to be observed for ≥8 weeks.
*2: CR + PR

PFS could not be evaluated for each histology subtype in the other STS group, because the percentage of patients with each histology subtype was <10% of the entire population (246 subjects). Independent reviewer-assessed best response in the pazopanib group is shown in the following table. Best response was seen in 65 of 112 subjects (58%), PR in 5 of 112 subjects (4%), and SD in 60 of 112 subjects (54%). Some tumor shrinkage in the target lesion from baseline was observed in 52 of 112 subjects (46%). The applicant considered that these results suggest that pazopanib is effective against soft tissue sarcoma regardless of histology subtype.

Number of subjects with "other STS" histology and the efficacy (Independent radiologist assessment, cut-off date: Nov. 22, 2010)

Histology subtype	N (%)	Best response (n)		Tumour shrinkage (n)[*1]
		PR	SD	
Other STS	112 (46)	5	60	52
Fibroblastic				
Myxofibrosarcoma	8 (3)	0	4	5
Solitary fibrous tumour	8 (3)	0	6	4
Sclerosing epithelioid fibrosarcoma	3 (1)	0	2	1
Adult fibrosarcoma	2 (<1)	0	1	0
Low grade fibro myxoid sarcoma/hyalinizing spindle cell tumour[*2]	1 (<1)	1	0	1
So-called fibrohistiocytic tumours				
Pleomorphic malignant fibrous histiocytoma (MFH)	20 (8)	1	9	9
Giant cell MFH	1 (<1)	0	0	0
Inflammatory MFH	0	-	-	-
Malignant glomus tumors	0	-	-	-
Rhabdomyosarcoma				
Alveolar/pleomorphic rhabdomyosarcoma	0	-	-	-
Vascular tumours				
Epithelioid haemangioendothelioma/angiosarcoma	4 (2)	1	3	2
Tumours of uncertain differentiation				
Epithelioid sarcoma	7 (3)	0	3	3
Alveolar soft part sarcoma	6 (2)	0	5	5
Desmoplastic small round cell tumour	3 (1)	0	3	3
Clear cell sarcoma	1 (<1)	0	1	1
Extra-renal rhabdoid tumour	1 (<1)	0	0	0
Neoplasms with perivascular epithelioid cell differentiation (PEComa)	1 (<1)	0	0	1
Malignant mesenchymoma	0	-	-	-
Intimal sarcoma	0	-	-	-
Adipocytic sarcoma[*3]				
Dedifferentiated liposarcoma	1 (<1)	0	1	0
Malignant peripheral nerve sheath tumour (MPNST)	8 (3)	1	3	4
Undifferentiated sarcoma NOS	15 (6)	0	10	6
Others	22 (9)	1	9	7
Synovial sarcoma[*4]	2 (<1)	0	1	0
Leiomyosarcoma[*4]	2 (<1)	0	2	2
Malignant granular cell sarcoma[*4]	1 (<1)	0	1	1
Sarcoma NOS[*4]	1 (<1)	0	1	1
Endometrial stromal sarcoma[*4]	1 (<1)	0	0	0
MPNST[*4]	1 (<1)	0	0	0
Myofibroblastic sarcoma[*4]	2 (<1)	0	0	0
Spindle cell sarcoma NOS[*5]	7 (3)	0	2	2
Pleomorhphic myogenic sarcoma NOS[*5]	2 (<1)	1	0	1
Unclassified STS with chondro-osseous differentiation	1 (<1)	0	1	0
Undifferentiated stromal sarcoma	1 (<1)	0	1	0
Undifferentiated epithelioid sarcoma	1 (<1)	0	0	0

*1: Subjects with tumor shrinkage in the target lesion compared to the baseline in terms of the sum of the longest diameter of the target lesions (*Response Evaluation Criteria in Solid Tumors ver.1.0*)

*2: Hyalinizing spindle cell tumour is not specified in the inclusion criteria or exclusion criteria in the protocol.

*3: Adipocytic sarcoma was an ineligible type in VEG110727 study.

*4: Reclassified subtype: Subtypes initially classified as "others" were reclassified following retrospective central re-examination by pathologists. To facilitate this process, additional tumour tissue obtained after the initial pathology diagnosis, or additional diagnostic information, such as immunohistochemical staining or FISH testing, was used where available.

*5: Not otherwise specified

PMDA confirmed the following points from the results of Study VEG110727.

- No conclusion can be drawn for the efficacy of pazopanib by histology subtype because the number of subjects with each subtype was limited. In the subgroup analysis by tumor histology, however, PFS was prolonged in the pazopanib group compared with the placebo group, as with the entire population.

- In the subgroup with synovial sarcoma, OS was longer in placebo-treated subjects than in pazopanib-treated subjects. However, it is difficult to evaluate the effect of pazopanib on OS in this subgroup, because the prolongation of OS cannot be evaluated definitively in this study and the number of subjects in this subgroup was small.

- Best response of PR or some tumour shrinkage was seen in many histology subtypes classified under "other STS".

4.(iii).B.(2).5) Efficacy in Japanese patients

PFS and OS in Japanese subjects in Study VEG110727 are shown in the following table.

PFS analysis in Japanese subgroup
(Independent radiologist assessment, ITT population, cut-off date: Nov. 22, 2010)

	Pazopanib	Placebo
Number of subjects	31	16
Progressed, or died (regardless of the cause)*1	26 (84%)	15 (94%)
Median [95% CI] (months)	5.7 [2.0, 6.5]	1.6 [0.9, 2.7]
Hazard ratio [95% CI]*2	0.41 [0.19, 0.90]	
P-value (two-sided test)*3	0.002	

*1: Includes 1 subject in the pazopanib group who died during adequate follow-up period without documentation of progression
*2: Hazard ratio is estimated using the Pike estimator and adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease.
*3: Stratified log-rank test

OS analysis in Japanese subgroup (ITT population, cut-off date: [redacted], 20[redacted])

	Pazopanib	Placebo
Number of subjects	31	16
Number of deaths	21 (68%)	11 (69%)
Median [95% CI] (months)	15.4 [7.9, 28.8]	14.9 [6.8, NC]
Hazard ratio [95% CI]*1	0.87 [0.41, 1.83]	
P-value (two-sided test)*2	0.687	

NC: Not calculated
*1: Hazard ratio is estimated using the Pike estimator and adjusted for WHO performance status and number of prior lines of systemic treatment for advanced disease.
*2: Stratified log-rank test

PMDA confirmed that PFS and OS in Japanese subjects with metastatic soft tissue sarcoma were not substantially different from those in the entire population in Study VEG110727, although the number of Japanese subjects was small. PMDA considers that the efficacy of pazopanib can be expected in Japanese patients as well.

4.(iii).B.(3) Safety [see 4.(iv) "Adverse events observed in clinical studies" for adverse events]

Based on the following review, PMDA determined that adverse events requiring close monitoring are hepatic function disorder, hypertension, cardiovascular events (including venous

thromboembolic events), haemorrhagic events, pneumothorax, thyroid function abnormal, gastrointestinal perforations and gastrointestinal fistula, proteinuria and nephrotic syndrome, skin disorder, hair colour changes and skin hypopigmentation, and wound healing delayed. PMDA considers that occurrence of these adverse events should be monitored closely when using pazopanib.

However, PMDA concluded that pazopanib is tolerable in Japanese patients with soft tissue sarcoma, as long as it is prescribed by physicians who have adequate knowledge and experience in cancer chemotherapy and administered under appropriate supervision, including adverse event monitoring and control, and dose adjustment, such as dose interruption, reduction, or treatment discontinuation. However, safety information obtained in Japan is limited. It is necessary to continue to collect relevant information after the market launch and promptly and appropriately provide the new safety information to the medical practice.

After the regulatory submission, the applicant reported to PMDA that the precautions for use of pazopanib in the US and Europe, which were set at the time of approval with the indication for renal cell cancer, were changed and added with some statement. The additions and changes were based on the review result of pazopanib indicated for soft tissue sarcoma. PMDA has asked the applicant to provide the details.

4.(iii).B.(3).1) Safety profile of pazopanib and difference in safety between Japan and other countries

The safety profile of pazopanib obtained in Study VEG110727 is summarized in the following table.

Summary of safety (Study VEG110727)

	Number of subjects (%)	
	Pazopanib (N = 240)	Placebo (N = 123)
All adverse events	237 (99)	110 (89)
All serious adverse events	99 (41)	29 (24)
Death	134 (56)	78 (63)
Adverse events leading to discontinuation of study treatment or early withdrawal from study	48 (20)*	6 (5)
Adverse events leading to dose reduction	77 (32)	1 (<1)
Adverse events leading to dose interruption	120 (50)	12 (10)
Adverse events of ≥ Grade 3	149 (62)	34 (28)

*: Reasons of treatment discontinuation determined by investigator are as follows: Toxicity or toxicic deaths related to the study drug (28 subjects), Adverse events not related to the study drug (3 subjects), Deaths due to concurrent disease (not due to malignant disease nor toxicity) (3 subjects), Progression of disease/relapse/clinical progression/deaths due to PD (12 subjects), Subject's refusal/subject's decision (1 subject), and Other (1 subject).

In Study VEG110727, adverse events reported by ≥10% of subjects in either group are described under "4.(iv) Adverse events observed in clinical studies." Adverse events reported by ≥10% more frequently in the pazopanib group than in the placebo group were fatigue (65%), diarrhoea (59%), nausea (56%), weight decreased (48%), hypertension (42%), decreased appetite (40%), hair colour changes (39%), vomiting (33%), dysgeusia (28%), gastrointestinal pain (23%), headache (23%), myalgia (23%), ear, nose and throat examination abnormal (12%), alopecia (12%), skin disorder (11%), and skin hypopigmentation (11%). Serious adverse events reported by ≥3% of subjects in the pazopanib group were dyspnoea (4%), ALT increased (4%), AST increased (3%), γ-glutamyl transpeptidase (γ-GTP) increased (3%), haemoglobin decreased (3%), pneumothorax (3%), and embolism (3%). Adverse events leading to discontinuation of study

treatment reported in ≥1% (3 subjects) in the pazopanib group were ALT increased (2%), dyspnoea (2%), left ventricular dysfunction (2%), fatigue (1%), hypertension (1%), and vomiting (1%).

PMDA asked the applicant to explain the difference in the safety profile of pazopanib in Japanese and foreign subjects in Study VEG110727.

The applicant responded as follows:
Adverse events reported by ≥10% of subjects in either Japanese or foreign population in Study VEG110727 are shown in the following table.

Adverse events (Study VEG110727)

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)*							
	Japanese subjects				Foreign subjects			
	Pazopanib (N = 31)		Placebo (N = 16)		Pazopanib (N = 209)		Placebo (N = 107)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	31 (100)	19 (61)	12 (75)	2 (13)	206 (99)	130 (62)	98 (92)	32 (30)
Gastrointestinal disorders								
Nausea	18 (58)	0	5 (31)	0	117 (56)	8 (4)	22 (21)	2 (2)
Diarrhoea	17 (55)	2 (6)	4 (25)	0	124 (59)	9 (4)	15 (14)	1 (<1)
Vomiting	11 (35)	0	3 (19)	0	69 (33)	8 (4)	11 (10)	1 (<1)
Constipation	9 (29)	0	2 (13)	0	29 (14)	1 (<1)	19 (18)	3 (3)
Gastrointestinal pain	6 (19)	0	0	0	49 (23)	6 (3)	11 (10)	5 (5)
Stomatitis	5 (16)	0	0	0	22 (11)	1 (<1)	4 (4)	0
Dyspepsia	3 (10)	0	0	0	14 (7)	0	2 (2)	0
Skin and subcutaneous tissue disorders								
Exfoliative rash	11 (35)	0	2 (13)	0	33 (16)	1 (<1)	9 (8)	0
Pruritus	5 (16)	0	1 (6)	0	5 (2)	0	2 (2)	0
Hair colour changes	18 (58)	0	0	0	75 (36)	0	3 (3)	0
Skin disorder	9 (29)	1 (3)	0	0	18 (9)	3 (1)	1 (<1)	0
Alopecia	7 (23)	0	0	0	21 (10)	0	1 (<1)	0
Skin hypopigmentation	5 (16)	0	0	0	22 (11)	0	0	0
Hair growth abnormal	3 (10)	0	0	0	0	0	0	0
General disorders and administration site conditions								
Fatigue	18 (58)	1 (3)	5 (31)	0	139 (67)	32 (15)	54 (50)	6 (6)
Oedema peripheral	5 (16)	2 (6)	2 (13)	0	28 (13)	3 (1)	9 (8)	2 (2)
Chest pain	6 (19)	1 (3)	1 (6)	0	19 (9)	3 (1)	6 (6)	0
Pyrexia	3 (10)	0	1 (6)	0	22 (11)	0	11 (10)	1 (<1)
Investigations								
Weight decreased	20 (65)	1 (3)	3 (19)	0	96 (46)	8 (4)	15 (14)	0
Weight increased	0	0	2 (13)	0	11 (5)	1 (<1)	6 (6)	0
Ear, nose and throat examination abnormal	3 (10)	0	0	0	26 (12)	4 (2)	3 (3)	0
Metabolism and nutrition disorders								

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)*							
	Japanese subjects				Foreign subjects			
	Pazopanib (N = 31)		Placebo (N = 16)		Pazopanib (N = 209)		Placebo (N = 107)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Decreased appetite	18 (58)	2 (6)	6 (38)	0	79 (38)	12 (6)	17 (16)	0
Nervous system disorders								
Dysgeusia	13 (42)	0	1 (6)	0	53 (25)	0	3 (3)	0
Headache	7 (23)	0	0	0	49 (23)	2 (<1)	10 (9)	0
Peripheral sensory neuropathy	4 (13)	0	0	0	18 (9)	1 (<1)	10 (9)	1 (<1)
Somnolence	3 (10)	0	0	0	5 (2)	0	0	0
Dizziness	0	0	1 (6)	0	27 (13)	2 (<1)	4 (4)	0
Infections and infestations								
Nasopharyngitis	6 (19)	0	4 (25)	0	6 (3)	0	3 (3)	0
Vascular disorders								
Hypertension	16 (52)	5 (16)	3 (19)	0	85 (41)	11 (5)	4 (4)	0
Respiratory, thoracic and mediastinal disorders								
Cough	6 (19)	0	2 (13)	1 (6)	35 (17)	1 (<1)	13 (12)	0
Dysphonia	3 (10)	0	1 (6)	0	15 (7)	0	2 (2)	0
Dyspnoea	0	0	0	0	46 (22)	14 (7)	21 (20)	8 (7)
Musculoskeletal and connective tissue disorders								
Musculoskeletal pain	8 (26)	1 (3)	1 (6)	0	48 (23)	4 (2)	23 (21)	2 (2)
Myalgia	8 (26)	1 (3)	0	0	48 (23)	4 (2)	11 (10)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Tumour pain	6 (19)	3 (10)	3 (19)	1 (6)	64 (31)	17 (8)	23 (21)	9 (8)
Psychiatric disorders								
Anxiety	4 (13)	0	0	0	16 (8)	2 (<1)	8 (7)	1 (<1)
Insomnia	2 (6)	0	1 (6)	0	20 (10)	1 (<1)	6 (6)	0
Cardiac disorders								
Left ventricular dysfunction	3 (10)	0	0	0	16 (8)	4 (2)	5 (5)	0

*: Adverse events with an incidence of ≥10%

In the pazopanib group, adverse events reported ≥10% more frequently in the Japanese population than in the foreign population were constipation, exfoliative rash, pruritis, hair colour changes, skin disorder, alopecia, chest pain, weight decreased, decreased appetite, dysgeusia, nasopharyngitis, and hypertension. Grade 3 or higher adverse events reported ≥5% more frequently in the Japanese population than in the foreign population were oedema peripheral and hypertension.

It is difficult to compare the adverse event profile of pazopanib properly between Japanese and foreign populations, since the above safety information was obtained from a small number of Japanese subjects, but decreased appetite, nasopharyngitis, and hypertension were also reported frequently in Japanese subjects in the placebo group. Among 31 subjects in the Japanese population treated with pazopanib, serious adverse events, and adverse events leading to treatment discontinuation, dose reduction and dose interruption were reported by 11 subjects (35%), 5 subjects (16%), 14 subjects (45%), and 17 subjects (55%), respectively. Of 209 subjects in the foreign population treated with pazopanib, these adverse events were reported by 88 subjects

(42%), 43 subjects (21%), 63 subjects (30%), and 103 subjects (49%), respectively. These results indicated no marked difference in incidence. There were no adverse events reported specifically in Japanese subjects. Therefore there is no clear difference in the safety profile of pazopanib between Japanese and foreign populations.

PMDA considers as follows:
Adverse events reported more frequently in the pazopanib group than in the placebo group, i.e. fatigue, diarrhoea, nausea, weight decreased, hypertension, decreased appetite, hair colour changes, vomiting, dysgeusia, gastrointestinal pain, headache, myalgia, exfoliative rash, alopecia, skin disorder, skin hypopigmentation, dyspnoea, ALT increased, AST increased, γ-GTP increased, haemoglobin decreased, pneumothorax, embolism, left ventricular dysfunction, and hypertension, require close monitoring as adverse events caused by pazopanib. It is necessary to appropriately provide relevant information to healthcare professionals.
Although there were some differences in incidence for some adverse events, it is difficult to compare the incidences properly between Japanese and foreign populations, since the sample size of Japanese subjects was small. However, for information about the adverse events reported ≥10% more frequently in the Japanese population than in the foreign population, and ≥ Grade 3 adverse events reported ≥5% more frequently in the Japanese population than in the foreign population, and the finding that all of the 3 subjects (1%) with a urine protein creatinine (UPC) ratio of ≥3 in the pazopanib group were Japanese [see "4.(iii).B.(3).9) Proteinuria and nephrotic syndrome"], it is necessary to appropriately provide the information to healthcare professionals as information about the differences in adverse event profile between Japanese and foreign populations.

4.(iii).B.(3).2) Hepatic function disorder

The applicant explained hepatic function disorder as follows:

Abnormal liver function test values reported in Study VEG110727 and combined data from the pazopanib group in Study VEG110727 and Study VEG20002 are shown in the following table. Fatal liver events were reported by 3 of 375 subjects (1%). All of the 3 subjects had Grade 4 ALT increased, and 2 subjects of them developed hepatic failure. All of the deaths occurred in foreign subjects.

Liver function test abnormal (Study VEG110727, combined data)

Laboratory criteria[*1]	Number of subjects (%)		
	VEG110727		Combined data[*2]
	Pazopanib (N = 237)[*3]	Placebo (N = 123)[*3]	Pazopanib (N = 375)[*3]
Possible Hy's Law: ALT > 3 × ULN and total bilirubin[*4] > 2 × ULN, (ALP < 3 × ULN or ALP missing)	5 (2)[*5]	1 (<1)	6 (2)
ALT > 3 × ULN and total bilirubin[*4] > 2 × ULN	5 (2)	1 (<1)	7 (2)
ALT/ALP ratio elevations			
ALT (× ULN)/ALP (× ULN) > 5	22 (9)	3 (2)	28 (7)
ALT or AST elevations			
ALT or AST > 3 × ULN	48 (20)	6 (5)	63 (17)
ALT or AST > 5 × ULN	27 (11)	5 (4)	33 (9)
ALT or AST > 8 × ULN	17 (7)	2 (2)	21 (6)
ALT or AST > 20 × ULN	6 (3)	1 (<1)	6 (2)
ALT elevations			
ALT > 3 × ULN	42 (18)	6 (5)	54 (14)
ALT > 5 × ULN	23 (10)	4 (3)	29 (8)
ALT > 8 × ULN	13 (5)	2 (2)	16 (4)
ALT > 20 × ULN	5 (2)	1 (<1)	5 (1)
ALT > 3 × ULN and baseline ALT < 3 × ULN (or baseline ALT missing)	42 (18)	6 (5)	54 (14)
Total bilirubin elevations			
Total BIL > 2 × ULN	12 (5)	3 (2)	28 (7)
Total BIL > 2 × ULN and baseline total BIL < 2 × ULN (or baseline total BIL missing)	12 (5)	3 (2)	27 (7)
ALP elevation			
ALP > 3 × ULN	13 (5)	5 (4)	33 (9)
ALP > 3 × ULN and baseline ALP < 3 × ULN (or baseline ALP missing)	10 (4)	2 (2)	24 (6)

ULN: Upper Limit of Normal

*1: Subjects may be counted in more than one category.

*2: Combined data of VEG110727 (pazopanib group) and VEG20002

*3: Number of subjects with at least one post-baseline value. (n = 122 for total bilirubin in placebo group)

*4: Bilirubin value can occur up to 28 days on or after ALT value.

*5: One subject was reported as Hy's law case (defined by U.S. Department of Health and Human Services, Food and Drug Administration in the Guidance for industry — Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009), but the bilirubin value of the subject on the day of onset of abnormal liver function was not reported. This subject is included in the number.

Liver function test abnormal classified by Grade (Study VEG110727 and combined data)

	Number (%) of subjects						
	VEG110727				Combined data*2 (N = 375)*1		
	Pazopanib (N = 237)*1			Placebo (N = 123)*1			
	All Grades	Grade 3	Grade 4	All Grades	All Grades	Grade 3	Grade 4
ALT	110 (46)	18 (8)	5 (2)	22 (18)	174 (46)	24 (6)	5 (1)
AST	122 (51)	13 (5)	6 (3)	27 (22)	176 (47)	18 (5)	6 (2)
ALP	77 (32)	7 (3)	0	28 (23)	125 (33)	10 (3)	0
Total bilirubin	68 (29)	3 (1)	0	9 (7)	117 (31)	8 (2)	2 (<1)

*1: Number of subjects with at least one post-baseline value. (n = 122 for total bilirubin in placebo group)
*2: Combined data of VEG110727 (pazopanib group) and VEG20002

In combined data from Study VEG110727 and Study VEG20002, the median time from the baseline measurement to the first event of ALT increased to >3 times ULN of laboratory reference range was 50 days (range: 4-565 days), with no specific trend in the time of occurrence. In 3 subjects with fatal liver events, Grade 4 ALT increased occurred on Days 60, 118, and 213. Abnormal hepatic function values that meet the Hy's Law criteria occurred between Days 56 and 213 in 6 subjects.

In combined data from Study VEG110727 and Study VEG20002, 54 of 375 subjects (14%) treated with pazopanib had increased ALT to ≥3 times ULN, and ALT recovered* in 46 subjects of them. The median time from dose interruption to recovery was 22 days (range: 5-39 days). Of these, 16 subjects were rechallenged after dose interruption. Of the 16 subjects, increased ALT did not exceed 3 times ULN in 10 subjects and exceeded 3 times ULN in 6 subjects. In these 6 subjects, the median time to recurrence of increased ALT was 12 days (range: 7-45 days). Of the 6 subjects, ALT recovered after treatment discontinuation in 5 subjects, and 1 subject was rechallenged after interruption and no increased ALT occurred.

Most of these abnormal liver function test values were reversible, and the subjects were able to remain on pazopanib by dose interruption or reduction. In order to control abnormal liver function test values properly, a caution statement will be included in the package insert stating that if any abnormal liver function test value is found during treatment with pazopanib, dose interruption, reduction, or treatment discontinuation should be considered according to the criteria for dose interruption and reduction, and treatment discontinuation used in Study VEG110727.

*: ALT decreases to ≤ Grade 1 (<2.5 times ULN) at 2 consecutive tests, or if there is no data, to ≤ Grade 1 once.

PMDA considers as follows:
The occurrence of hepatic function disorder and hepatic failure leading to fatal cases considered to be related to pazopanib were reported, and hepatic function disorder did not tend to develop at a specific time. Taking these into account, caution and information on the incidence of hepatic function disorder reported in the clinical studies of pazopanib should be provided in the package insert, and hepatic function disorder should be monitored closely by performing periodic serum chemistry test before and during treatment with pazopanib. In addition, it is necessary to appropriately provide information on the criteria for dose interruption and reduction, and treatment discontinuation with regard to hepatic function disorder used in Study VEG110727, in order to allow appropriate actions taken at onset of hepatic function disorder according to the criteria.

4.(iii).B.(3).3) Hypertension

The applicant explained hypertension associated with pazopanib as follows:

In Study VEG110727, hypertension* was reported by 101 of 240 subjects (42%) in the pazopanib group and 7 of 123 subjects (6%) in the placebo group during treatment with study drug. Grade 3 hypertension was observed in 16 subjects (7%) in the pazopanib group, but no ≥ Grade 4 hypertension was observed. Study treatment was withdrawn, or the dose was reduced or interrupted due to hypertension in 3 subjects (1%), 16 subjects (7%), and 24 subjects (10%), respectively in the pazopanib group. Maximum systolic blood pressure and diastolic blood pressure values from baseline are shown in the following table.

*: Hypertension reported as adverse event (MedDRA preferred term)

Maximum systolic and diastolic blood pressure from baseline (Study VEG110727)

		Number of subjects (%)	
		Pazopanib (N = 239)*	Placebo (N = 123)
Systolic BP from baseline (mmHg)	150-169	67 (28)	13 (11)
	≥170	29 (12)	0
Diastolic BP from baseline (mmHg)	90-109	119 (50)	22 (18)
	≥110	15 (6)	0

*: Except for 1 subject (died after 9 days from pazopanib treatment) with no post-baseline blood pressure value.

In combined data from Study VEG110727 and Study VEG20002, the median time to the first event of hypertension (systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg) was 28 days (range: 4-1434 days). The analysis of cumulative incidence of hypertension showed that 40.1% of the events occurred by Day 9 and 90.1% occurred in the first 18 weeks.

Based on the above, pazopanib could cause hypertension frequently or exacerbate pre-existing hypertension. Hypertension should be controlled before starting treatment with pazopanib. Patients should be monitored for hypertension in the early stage after starting treatment, and when hypertension occurs, an antihypertensive therapy or appropriate actions including dose reduction, interruption, or discontinuation of pazopanib should promptly be taken.

PMDA considers as follows:

The incidence of hypertension associated with pazopanib was high and some subjects were withdrawn from study treatment, thus caution is required. Blood pressure should be monitored periodically before and during treatment with pazopanib to ensure blood pressure control.

4.(iii).B.(3).4) Cardiovascular events (including venous thromboembolic events)

a. Myocardial dysfunction

The applicant explained myocardial dysfunction ("myocardial dysfunction" includes left ventricular dysfunction, pulmonary oedema, cardiac failure, and restrictive cardiomyopathy, as MedDRA preferred terms) caused by pazopanib as follows:

The incidences of myocardial dysfunction-related adverse events in Study VEG110727 are shown in the following table. There were no myocardial dysfunction-related adverse events resulting in death.

The incidences of myocardial dysfunction-related adverse events (Study VEG110727)

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)			
	Pazopanib (N = 240)		Placebo (N = 123)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	21 (9)	4 (2)	6 (5)	0
Left ventricular dysfunction	19 (8)	4 (2)	5 (4)	0
Cardiac failure	1 (<1)	0	0	0
Pulmonary oedema	1 (<1)	0	1 (<1)	0
Restrictive cardiomyopathy	1 (<1)	0	0	0

Left ventricular dysfunction was reported as a serious adverse event in 5 of 240 subjects (2%) in the pazopanib group. Of them, 3 subjects recovered, but 2 subjects did not recover.

In Study VEG110727, left ventricular ejection fraction (LVEF) was determined at baseline and Week 12*, or when necessary in the clinical judgment of the investigator, and myocardial dysfunction was evaluated based on changes in LVEF. LVEF data were obtained from 140 of 240 subjects (58%) in the pazopanib group and 39 of 123 subjects (32%) in the placebo group. Myocardial dysfunction** defined based on the LVEF was reported by 15 of 140 subjects (11%) in the pazopanib group and 1 of 39 subjects (3%) in the placebo group, and of them, 2 subjects in the pazopanib group had symptomatic LVEF decline.

Of the 15 subjects with myocardial dysfunction in the pazopanib group, 4 subjects completely resolved (returned to within 5% of baseline LVEF), 5 subjects partially resolved (higher than the lower limit of normal [LLN], and ≥5% lower than baseline LVEF), 5 subjects had insufficient follow-up data, and 1 subject did not resolve. In 13 of the 15 subjects with LVEF decline, the first event of LVEF decline was observed after the occurrence of hypertension or the start of new anti-hypertensive medications. Pazopanib were not resumed in 7 of 15 subjects after LVEF decline, but 3 of 15 subjects continued on pazopanib and 5 of 15 subjects were resumed after dose interruption. In 6 of these 8 subjects who continued on pazopanib or were resumed, the dose of pazopanib was reduced to 600 mg, and it was further reduced to 400 mg in 1 subject because of the recurrence of LVEF decline. In 1 subject whose dose was reduced to 400 mg, hypertension recurred every time LVEF declined.

In patients with prior anthracycline therapy, hypertension and associated increase in cardiac load may have resulted from the exacerbation of left ventricular dysfunction, which had been asymptomatic before pazopanib treatment. Myocardial dysfunction observed in the pazopanib group was able to be managed by blood pressure control and dose adjustment of pazopanib. When pazopanib is administered to patients with risk for myocardial dysfunction (e.g., those with prior anthracycline therapy), LVEF monitoring, strict blood pressure control, and dose adjustment of pazopanib are recommended.

* In the protocol version 3 (revised on [redacted], 20[redacted]), the time points for LVEF measurement were added, i.e. LVEF should also be determined every 2 scheduled visits (every 16 weeks) after Week 12 until withdrawal from study treatment.

**Myocardial dysfunction was defined according to the following criteria: (1) symptoms of myocardial dysfunction, (2) ≥15% absolute decline in LVEF compared with baseline or, (3) ≥10% absolute decline in LVEF compared with baseline that is also below the lower limit of normal (LLN) of laboratory reference range.

PMDA asked the applicant to explain the predictive factors of pazopanib-induced myocardial dysfunction and safety measures against myocardial dysfunction.

The applicant responded as follows:
In Study VEG110727, LVEF was determined at baseline, Week 12, and every 2 scheduled visits (every 16 weeks) thereafter until withdrawal from study treatment, and myocardial dysfunction was assessed by changes in LVEF. The time when myocardial dysfunction occurs frequently could not be accurately identified and the relationship to treatment with pazopanib (duration or cumulative dose) could not be evaluated. Fifteen subjects who developed myocardial dysfunction had normal LVEF at baseline and a history of anthracycline therapy.

According to the safety information (data cut-off date: [redacted], 20[redacted]) updated after the preparation of Clinical Study Report (Version 1), cumulative dose data were obtained from 13 of 16 subjects with myocardial dysfunction and 79 of 115 subjects without myocardial dysfunction in the pazopanib group and the median cumulative doses of doxorubicin were 360 mg/m^2 (range: 145-679 mg/m^2) and 240 mg/m^2 (19-643 mg/m^2), respectively. As a risk factor for myocardial dysfunction, prior mediastinal radiotherapy, a history of or current hypertension, diabetes mellitus, dyslipidaemia, myocardial infarction, angina unstable, peripheral vascular disease, and stroke, and a history of angioplasty/stenting and coronary artery bypass graft surgery were assessed. As a result, a history of or current hypertension was present in 7 of 16 subjects with myocardial dysfunction (44%) and 30 of 115 subjects without myocardial dysfunction (26%). These findings indicate that myocardial dysfunction that had been asymptomatic may be exacerbated in patients with prior anthracycline therapy or patients with prior or current hypertension, if hypertension develops or is exacerbated during pazopanib treatment.

The applicant considered that patients should be monitored for hypertension beforeand in the early stage after starting treatment with pazopanib and frequently thereafter to ensure blood pressure control and be treated promptly with an appropriate antihypertensive therapy as needed. Baseline and periodic evaluation of LVEF by echocardiography, etc. is required in patients at risk for cardiac dysfunction (e.g. patients with prior anthracycline therapy, prior chest radiotherapy, or hypertension).

PMDA considers as follows:
At present, the predictive factors of pazopanib-induced myocardial dysfunction cannot be identified because of insufficient information. It is difficult to determine whether pazopanib induces cardiotoxicity or not, as it is known that cardiotoxicity is a class effect of anthracyclines and that anthracyclines increase the risk for cardiomyopathy and congestive heart failure when the cumulative dose reaches a certain level (*Cancer Principles and Practice of Oncology*. 7th ed. PA, USA: Lippincott Williams & Wilkins; 2005: 384-388), and most patients have prior anthracycline therapy before pazopanib treatment. However, the possibility that pazopanib increases the risk of cardiotoxicity cannot be ruled out, since assessment based on LVEF changes showed more frequent occurrence of myocardial dysfunction in the pazopanib group than in the placebo group. It is therefore necessary to provide a caution about the need for baseline and subsequent periodic cardiac evaluation by echocardiography, etc. Additionally, information about the occurrences of myocardial dysfunction reported in the clinical studies of pazopanib should be provided to healthcare professionals, and if a patient develops myocardial dysfunction, appropriate measures, such as dose reduction or interruption, should be taken promptly.

b. Arrhythmia
The applicant explained arrhythmia ("arrhythmia" includes sinus tachycardia, palpitations, sinus bradycardia, atrial fibrillation, supraventricular tachycardia, atrial flutter, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular extrasystoles, atrioventricular block first degree, tachycardia, ventricular extrasystoles, and cardio-respiratory arrest, as MedDRA preferred terms) associated with the use of pazopanib as follows:
The incidences of arrhythmia-related adverse events in Study VEG110727 are listed in the following table.

The incidences of arrhythmia-related adverse events (Study VEG110727)

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)			
	Pazopanib (N = 240)		Placebo (N = 123)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	15 (6)	4 (2)	11 (9)	1 (<1)
Electrocardiogram QT prolonged	5 (2)	2 (<1)	0	0
Sinus bradycardia	4 (2)	0	1 (<1)	0
Supraventricular extrasystoles	3 (1)	0	0	0
Palpitations	2 (<1)	0	2 (2)	0
Sinus tachycardia	2 (<1)	1 (<1)	3 (2)	0
Atrioventricular block first degree	1 (<1)	0	0	0
Tachycardia	1 (<1)	0	0	0
Ventricular extrasystoles	1 (<1)	0	0	0
Cardio-respiratory arrest	1 (<1)	1 (<1)	0	0
Atrial fibrillation	0	0	2 (2)	0
Supraventricular tachycardia	0	0	2 (2)	0
Atrial flutter	0	0	1 (<1)	1 (<1)
Ventricular tachycardia	0	0	1 (<1)	1 (<1)

As a serious adverse event, cardio-respiratory arrest was reported by 1 of 240 subjects (<1%) in the pazopanib group. This subject died, but the applicant considered that this event was related to disease progression and not related to pazopanib. In the placebo group, atrial fibrillation, atrial flutter, and sinus bradycardia were reported by 1 subject each.

In combined data from Study VEG110727 and Study VEG20002, arrhythmia-related adverse events were reported by 24 of 382 subjects (6%) in the pazopanib group. QT interval prolongation was reported by 5 subjects (all were in the pazopanib group in Study VEG110727), and there were no events of Torsade de pointes (TdP) or sudden death. In the clinical study in patients with renal cell carcinoma, QT interval prolongation (≥ 500 msec) was reported by 11 of 558 subjects (2%) and TdP suggestive of causal relationship to pazopanib in 2 of 558 subjects (<1%). Therefore pazopanib should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrythmics or other medications that may potentially prolong QT interval, or patients with cardiac disease causing QT interval prolongation. The applicant considers that it is necessary to perform the periodic monitoring of electrocardiograms and measurement of electrolytes (calcium, magnesium, potassium) before and during treatment with pazopanib to control the level within normal range as needed.

PMDA considers as follows:
Taking into account that arrhythmias including QT interval prolongation occurred in pazopanib-treated subjects with soft tissue sarcoma, and TdP was reported in the foreign clinical study in patients with renal cell carcinoma, caution should be exercised. Therefore, electrolyte monitoring and electrocardiography should be performed before and during pazopanib treatment, and any electrolyte abnormality at baseline should be corrected before starting pazopanib treatment. It is necessary to provide a caution that if QT/QTc interval prolonggation or arrhythmia occurs during pazopanib treatment, appropriate measures, including dose interruption, should be taken.

c. Thromboembolic events
The applicant explained venous thromboembolic events and arterial thrombotic events associated with the use of pazopanib as follows:

The incidences of venous thromboembolism-related adverse events in Study VEG110727 are shown in the following table.

Venous thromboembolism-related adverse events (Study VEG110727)

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)			
	Pazopanib (N = 240)		Placebo (N = 123)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event*	13 (5)	8 (3)	3 (2)	3 (2)
Pulmonary embolism	3 (1)	3 (1)	1 (<1)	1 (<1)
Deep vein thrombosis	7 (3)	3 (1)	1 (<1)	1 (<1)
Vena cava thrombosis and renal vein thrombosis	1 (<1)	1 (<1)	0	0
Vascular graft thrombosis	1 (<1)	0	0	0
Thrombosis vena cava inferior	1 (<1)	1 (<1)	0	0
Renal vein thrombosis	0	0	1 (<1)	1 (<1)

*: The number of venous thromboembolic events, which were determined by inquiries made by the applicant to the study sites about the pathology of all events coded as thromboembolic event.

In the pazopanib group, 2 of 3 subjects who developed pulmonary embolism died, but the pulmonary embolism in these 2 subjects was considered to be related to disease progression and not related to pazopanib.

In 6 of 13 subjects who developed venous thromboembolic events in the pazopanib group, history of thrombosis (3 subjects), complication of oedema lower limb, complication of venous insufficiency/varicose vein, and deep vein thrombosis/placement of an inferior vena cava filter (1 subject each) were identified as relevant past medical histories or risk factors.

During the study period of Study VEG20002, 8 of 142 subjects (6%) developed venous thromboembolic events, including pulmonary embolism (4 subjects), deep vein thrombosis (3 subjects), and pulmonary embolism/thrombosis vena cava inferior (1 subject), and all of them were non-fatal. As relevant past medical histories or risk factors, thrombophlebitis of the right leg (3 subjects), arterial thrombosis/aortic valve replacement, and thrombosis (1 subject each) were observed.

In Study VEG110727, arterial thromboembolic events were reported by 5 of 240 subjects (2%) only in the pazopanib group. Of them, 4 subjects developed Grade 1 to 3 myocardial ischemic events. Grade 4 cerebrovascular accident occurred in 1 subject 85 days after the last dose of pazopanib (12 days after 1 cycle of gemcitabine hydrochloride [gemcitabine] and docetaxel hydrate [docetaxel] administration) and resolved 4 days later. As relevant past medical histories or risk factors, hypertension/hyperlipidaemia (3 subjects), hypertension/diabetes mellitus (1 subject), and hypertension/diabetes mellitus/hyperlipidaemia/atherosclerotic cardiovascular disease/coronary artery calcification (1 subject) were observed.

During the study period of Study VEG20002, 2 of 142 subjects (1%) developed arterial thromboembolic events, including Grade 3 coronary artery disease (1 subject) and Grade 4 thrombosis of mechanical aortic valve (1 subject). As relevant past clinical histories or risk factors, hypertension/chest pain and embolism arterial/aortic valve replacement (1 subject each) were observed.

As patients with a history of any arterial thrombotic event in the past 6 months were excluded from the clinical studies of pazopanib, pazopanib should be used with caution in patients who are at increased risk of arterial thrombotic events, such as myocardial infarction, angina pectoris,

ischaemic stroke, and transient ischaemic attack or who have a history of arterial thrombotic events.

PMDA considers as follows:
Thromboembolic events have been reported with pazopanib and some cases were fatal. When using pazopanib, caution should be exercised against thromboembolism. It is therefore necessary to provide information about thromboembolic events reported in the clinical studies of pazopanib and background information about the patients who developed such events, and healthcare professionals should be advised to take appropriate measures when a thromboembolic event occurrs.

4.(iii).B.(3).5) Haemorrhagic events

The applicant explained haemorrhagic events associated with pazopanib as follows:
The incidences of haemorrhagic events in Study VEG110727 are shown in the following table. There were no haemorrhagic events resulting in death.

The incidences of haemorrhagic events (Study VEG110727)

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)[*1]					
	Pazopanib (N = 240)			Placebo (N = 123)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any event	54 (23)	3 (1)[*2]	3 (1)[*3]	10 (8)	1 (<1)	1 (<1)
Epistaxis	20 (8)	0	0	2 (2)	0	0
Mouth haemorrhage	6 (3)	0	0	0	0	0
Anal haemorrhage	5 (2)	0	0	0	0	0
Contusion	3 (1)	0	0	0	0	0
Pulmonary haemorrhage	3 (1)	0	0	5 (4)	0	1 (<1)
Haematoma	3 (1)	0	0	0	0	0
Gingival bleeding	2 (<1)	0	0	0	0	0
Rectal haemorrhage	2 (<1)	0	0	0	0	0
Urinary bladder haemorrhage	2 (<1)	0	0	1 (<1)	0	0
Vaginal haemorrhage	2 (<1)	0	0	0	0	0

*1: Adverse events reported by ≥2 subjects in the pazopanib group
*2: Upper gastrointestinal haemorrhage, haematuria, and haemorrhage
*3: Peritoneal haemorrhage, haemorrhage intracranial, and subarachnoid haemorrhage

In Study VEG110727, 8 subjects developed ≥ Grade 3 haemorrhagic events (6 of 240 subjects [3%] in pazopanib group, 2 of 123 subjects [2%] in placebo group), and all of them were serious adverse events. In 7 of the 8 subjects, neoplastic lesions were observed in organs probably associated with the haemorrhage, at the time of screening or examination following the onset of the adverse events. More specifically, metastases were observed in the liver in a patient with peritoneal haemorrhage, in the right inguinal lymph node in a patient with right inguinal haemorrhage, and in the lungs in patients with pulmonary haemorrhage or haemoptysis at screening, and in the brain in a patient with haemorrhage intracranial, in the stomach in a patient with upper gastrointestinal haemorrhage, and in the bladder in a patient with heamaturia at examinations after the event occurred. Based on these findings, one of the predictive factors of haemorrhagic events is neoplastic lesions in organs that may be associated with the haemorrhage.

Patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months were excluded from the clinical studies of pazopanib. As pazopanib may induce haemorrhagic events, pazopanib should be used with caution in patients with significant risk of haemorrhage.

PMDA considers as follows:
As serious haemorrhagic events have been reported with pazopanib, it should be used carefully as with other anti-angiogenic agents. It is therefore necessary to provide information about haemorrhagic events including serious tumour haemorrhage reported in the clinical studies of pazopanib, and provide a caution statement that haemorrhagic events should be treated with appropreate measures upon occurrence.

4.(iii).B.(3).6) Pneumothorax

The applicant explained pneumothorax associated with pazopanib as follows:
In Study VEG110727, pneumothorax was reported by 8 of 240 subjects (3%) in the pazopanib group, and none in the placebo group. In combined data from Study VEG110727 and Study VEG20002, 15 of 382 subjects (4%) treated with pazopanib developed pneumothorax, and 5 subjects of them had ≥ Grade 3 events. Of them, 14 subjects had pulmonary or pleural lesion before starting pazopanib. The median time to the first event of pneumothorax was 40 days (range: 12-614 days). Pneumothorax events reported by 11 of 15 subjects were serious adverse events, and 1 subject of them was withdrawn from pazopanib because of Grade 4 pneumothorax, and another subject developed Grade 2 serious pneumothorax associated with the past pleurodesis, and died of pneumonia approximately 5 months later. Pneumothorax was also reported by 2 patients in the compassionate use program (Study VEG115859) in patients with soft tissue sarcoma. Of them, 1 patient had pulmonary lesion before starting pazopanib, and it was unknown whether there was any pulmonary or pleural lesion in the other patient.

In Study VEG110727, 191 of 240 subjects (80%) in the pazopanib group had a pulmonary or pleural lesion before the start of pazopanib, and 8 of 191 subjects (4%) developed pneumothorax. In the placebo group, 103 of 123 subjects (84%) had a pulmonary or pleural lesion before starting the study drug, but none of them developed pneumothorax. In Study VEG20002, 35 of 142 subjects (25%) had a pulmonary or pleural lesion before starting pazopanib, and 6 of 35 subjects (17%) developed pneumothorax.

In the clinical studies of pazopanib conducted in the US and Europe in patients with advanced renal cell carcinoma, 4 of 586 subjects (<1%) administered pazopanib developed pneumothorax. All of the 4 subjects had a pulmonary or pleural lesion before starting pazopanib. Since October 2009, when pazopanib was approved for the treatment of advanced renal cell carcinoma in the US, approximately 2800 patients/year were treated with pazopanib. Pneumothorax was reported by 2 patients as of May 21, 2012. One patient of them, with whom pazopanib was used off-label for synovial sarcoma, had a pulmonary lesion before starting pazopanib. It is unknown whether there was any pulmonary or pleural lesion in the other patient.

As shown in the above, the incidence of pneumothorax was higher in patients with soft tissue sarcoma than in those with renal cell carcinoma. It has been reported that patients with soft tissue sarcoma are at a high risk of pneumothorax, because pneumothorax may be related to anti-cancer agent-induced necrosis of pulmonary or pleural lesions (*Chest.* 2010; 138: 510-8). However, the primary metastatic site for renal cell carcinoma is the lungs as with soft tissue sarcoma, and there have been no reports suggesting any differences in metastasis between these tumors. The reason why there was a difference in the incidence of pneumothorax between the 2 populations is unknown.

PMDA considers as follows:
Serious pneumothorax has been reported with pazopanib in soft tissue sarcoma patients with a pulmonary or pleural lesion at baseline. Based on that, careful monitoring of pneumothorax is especially needed for patients with a pulmonary or pleural lesion.

4.(iii).B.(3).7) Thyroid function abnormalities

The applicant explained thyroid function abnormalities associated with pazopanib as follows:
The incidences of thyroid function abnormal in Study VEG110727 and Study VEG20002 are shown in the following table. All events were Grade 1 or 2, and none were serious.

TSH elevations and thyroid replacement therapy after initiation of study drug (Study VEG110727 and combined data)

	Number of subjects (%)		
	VEG110727		Combined data[*1]
	Pazopanib (N = 240)	Placebo (N = 123)	Pazopanib(N = 382)
Post-baseline TSH lab value elevation[*2]			
Any TSH above 5 mU/L	82 (34)	3 (2)	112 (29)
5 < TSH ≤ 10 mU/L	39 (16)	3 (2)	52 (14)
10 < TSH ≤ 20 mU/L	28 (12)	0	38 (10)
TSH > 20 mU/L	15 (6)	0	22 (6)
Confirmation of hypothyroidism[*2]			
5 < TSH ≤ 10 mU/L and T4 < LLN	3 (1)	0	4 (1) [*3]
TSH > 10 mU/L and T4 < LLN	7 (3)	0	11 (3) [*4]
Confirmation of hyperthyroidism[*2]			
TSH < 0.3 mU/L and T4 > ULN	5 (2)	0	5 (1)
TSH elevation by thyroid replacement therapy[*5]			
Yes	17 (7)	1 (<1)	19 (5)
No	223 (93)	122 (>99)	363 (95)

*1: Combined data of VEG110727 (pazopanib group) and VEG20002
*2: Only those subjects with no TSH value abnormal at baseline were counted.
*3: Subjects 188, 254 and 322 for VEG110727 and Subject 35 for VEG20002.
*4: Subjects 21, 44, 115 (This subject is not included in the table because TSH value abnormal [defined as TSH >5 and T4< LLN] was found at baseline), 142, 166, 178, 260, and 264 for VEG110727, and subjects 10, 20, 84, and 120 for VEG20002.
*5: Subjects with no TSH value abnormal at baseline, but was administered thyroid hormone replacement therapy after initiation of the study drug treatment and had an elevated TSH (>5 mU/L).

In combined data from Study VEG110727 and Study VEG20002, hypothyroidism was reported as an adverse event in 20 of 382 subjects (5%) and hyperthyroidism in 2 of 382 subjects (<1%).

PMDA considers as follows:
Some patients received thyroid hormone replacement therapy because TSH exceeded 5 mU/L after pazopanib treatment. Therefore, periodic monitoring of thyroid function should be performed during the pazopanib treatment.

4.(iii).B.(3).8) Gastrointestinal perforations and fistula

The applicant explained gastrointestinal perforations and fistula associated with pazopanib as follows:
In combined data from Study VEG110727 and Study VEG20002, 4 of 382 subjects (1%) developed gastrointestinal perforations or fistula, including Grade 3 gastrointestinal fistula, Grade 3 enterocutaneous fistula, Grade 4 ileal perforation, and Grade 5 small intestinal perforation. These 4 subjects had abdominal metastasis at the time of participation in the studies. In the 2 subjects with gastrointestinal perforations, perforations were developed at metastatic sites. Of these two, 1 subject died of peritonitis, and the other was recovered by surgery. Gastrointestinal fistula in the other 2 subjects resolved. Of these, 1 subject had gastrointestinal fistula at baseline, and developed another event of gastrointestinal fistula during the study, but both events resolved.

Pazopanib should be used with caution in patients with abdominal metastasis or a lesion near the gastrointestinal tract because they are at risk for gastrointestinal perforation or fistula.

PMDA considers as follows:
Caution should be exercised because ≥ Grade 3 gastrointestinal perforations and fistula occurred and deaths were also reported with pazopanib. It is therefore necessary to appropriately provide information that includes deaths due to gastrointestinal perforations and fistula, which were reported in the clinical studies of pazopanib, and caution that appropriate measures should be taken if gastrointestinal perforations or fistula occurrs.

4.(iii).B.(3).9) Proteinuria and nephrotic syndrome

The applicant explained proteinuria associated with pazopanib as follows:
In Study VEG110727, proteinuria was evaluated by monitoring of adverse events and urine protein creatinine (UPC) ratio*.

*: It is specified in the protocol that proteinuria should be monitored for 24 hours when UPC ratio is ≥3, study drug should be interrupted when urinary protein is ≥3 g, and restarted at a reduced dose when UPC ratio returns to <3. If UPC ratio becomes ≥3 even after the dose of study drug is further reduced, study drug should be withdrawn.

In combined data from Study VEG110727 and Study VEG20002, 2 adverse events of proteinuria were reported and they were ≤ Grade 2. Grade 4 nephrotic syndrome with a UPC ratio of ≥3 was reported by 1 subject in the pazopanib group in Study VEG110727, and this subject was withdrawn from pazopanib due to this event.

In Study VEG110727, 3 of 240 subjects (1%) in the pazopanib group had a UPC ratio of ≥3 and 3 of 123 subjects (3%) in the placebo group. All the 3 subjects in the pazopanib group were Japanese, and 24-hour urinary protein was ≥3 g. After dose interruption, these 3 subjects were restarted with pazopanib at a reduced dose but withdrawn because UPC ratio became ≥3. Proteinuria was not reported as an adverse event in these 3 subjects.

PMDA considers as follows:
Caution about proteinuria and nephrotic syndrome should be exercised because these were reported with pazopanib, and some Japanese patients were withdrawn from the treatment due to increased UPC ratio. Periodic urinalysis is recommended during pazopanib treatment, and if any abnormality is observed, appropriate actions including dose interruption should be taken.

4.(iii).B.(3).10) Skin disorder

PMDA asked the applicant to explain about the incidence of skin disorders including hand and foot syndrome and exfoliative rash, and the necessity of a caution statement.

The applicant responded as follows:
In Study VEG110727, skin disorders (including hand and foot syndrome) were reported by 27 of 240 subjects (11%, 31 events) in the pazopanib group and 1 of 123 subjects (<1%, 1 event) in the placebo group, and exfoliative rash by 44 of 240 subjects (18%, 52 events) and 11 of 123 subjects (9%, 11 events), respectively.

In the pazopanib group, the median time to the first event of skin disorder was 32.0 days (range: 6-300 days), and the median duration was 50.5 days (range: 4-379 days) for 26 events for which the date of onset and the date of recovery were available. The median time to the first event of exfoliative rash was 45.0 days (range: 1-370 days), and the median duration was 32.0 days (range: 1-300 days) for 45 events for which the date of onset and the date of recovery were available.

In the pazopanib group, 27 of 31 events (87%) of skin disorder and 45 of 52 events (87%) of exfoliative rash resolved, and the rest did not resolve by the end of the study period. The dose of pazopanib was interrupted or reduced for 10 events of skin disorder and 3 events of exfoliative rash, but no subjects were withdrawn from pazopanib.

In Study VEG109693, 6 events of palmar-plantar erythrodysaestheia syndrome occurred in 5 subjects and 4 events of skin exfoliation in 2 subjects, and all of them were in Part B where pazopanib and lapatinib were concomitantly used. All of these events resolved without dose withdrawal, interruption, or reduction.

There were no specific rules for the treatment of skin symptoms in the protocol of each clinical study. Skin symptoms reported with pazopanib were treated individually by physicians and none resulted in treatment discontinuation Therefore, it is not necessary to provide a caution about these skin disorders.

PMDA considers as follows:
None of the events of skin disorders including hand and foot syndrome and exfoliative rash associated with pazopanib resulted in treatment discontinuation, and most of them resolved by dose reduction or interruption. Skin disorders are manageable when treatment, dose reduction of pazopanib, etc., are appropriately performed. However, information about skin disorders reported in the clinical studies of pazopanib should be provided.

4.(iii).B.(3).11) Hair colour changes and skin hypopigmentation

PMDA asked the applicant to explain hair colour changes and skin hypopigmentation associated with pazopanib.

The applicant responded as follows:
In Study VEG110727, 94 events (27 events for Grade 2, rest of all for Grade 1) of hair colour changes were reported by 93 of 240 subjects in the pazopanib group and 3 events (all Grade 1) in 3 of 123 subjects in the placebo group, and 27 events (6 events for Grade 2, rest of all for Grade 1) of skin hypopigmentation were reported by 27 subjects in the pazopanib group and none in the placebo group. There were no serious adverse events.

Thirty of 94 events (32%) of hair colour changes resolved, and 64 of 94 events (68%) did not resolve by the end of study period. The dose of pazopanib was reduced in 1 subject, but not due to hair colour changes. Eleven of 27 events (41%) of skin hypopigmentation resolved, but 16 of 27 events (59%) did not resolve by the end of study period. There were some unresolved hair colour changes and skin hypopigmentation seen in the follow-up period, but most of them were Grade 1, and no subjects except 1 subject resulted in discontinuation, interruption, or reduction of pazopanib.

PMDA considers as follows:
Hair colour changes and skin hypopigmentation rarely led to withdrawal or interruption of pazopanib, but they were reported at a constant rate and some events did not resolve. Taking these into account, it is necessary to provide information about these events reported in the clinical studies of pazopanib to healthcare professionals.

4.(iii).B.(3).12) Wound healing delayed

The applicant explained wound healing delayed associated with pazopanib as follows:
In Study VEG109693, Grade 1 wound healing delayed was reported by 1 subject. In the foreign clinical studies of pazopanib in patients with renal cell carcinoma, postoperative wound

complication was reported by 3 of 586 subjects (<1%) and skin graft failure in 1 of 586 subjects (<1%).

Although information about pazopanib-induced impaired healing is limited, caution should be exercised because wound healing delayed has also been reported with VEGF signaling pathway inhibitors, such as bevacizumab (genetical recombinant), similarily to pazopanib.

PMDA considers as follows:
As for impaired wound healing associated with pazopanib, considering that (1) pazopanib has anti-angiogenic activity and wound healing delayed has been reported with other antineoplastic agents with a similar mechanism of action to pazopanib, and (2) the safety of pazopanib is unknown in "patients who had major surgery or significant traumatic injury within 28 days before registration" because such patients were excluded from the enrollment in Study VEG110727 and Study VEG109693, the administration of pazopanib should be interrupted before major surgery,. and whether or not the re-administration of pazopanib is appropriate should be determined carefully depending on the patient's condition including wound healing. It is therefore necessary to provide information about the criteria for enrollment defined in the clinical studies of pazopanib to healthcare professionals.

4.(iii).B.(4) Clinical positioning
The following foreign and Japanese clinical practice guidelines were reviewed for the treatment strategy for soft tissue sarcoma. There was no description about pazopanib in these clinical practice guidelines.

- National Institute Physician Data Query (NCI-PDQ) Adult Soft Tissue Sarcoma Treatment (revised on February 16, 2012)

- NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma (Ver 1. 2012) (hereinafter "NCCN Guideline")

- Clinical Practice Guideline for Soft Tissue Sarcoma 2012 (The Japanese Orthopedic Association ed. Nankodo Co., Ltd.; 2012) (hereinafter "Japanese practice guideline")

PMDA asked the applicant to explain the clinical positioning of pazopanib in the treatment of metastatic soft tissue sarcoma.

The applicant responded as follows:
According to the Japanese practice guideline, regarding soft tissue sarcoma, systemic chemotherapy should be considered for the treatment of non-round cell sarcoma (leiomyosarcoma, malignant fibrous histiocytoma, synovial sarcoma, etc.), both for locally advanced and metastatic cases. As systemic chemotherapy, doxorubicin monotherapy is a standard therapy, and ifosfamide is also used. In addition to doxorubicin and ifosfamide, cyclophosphamide hydrate, dacarbazine, gemcitabine, docetaxel, and trabectedin, etc. are expected to be effective in treating metastatic cases. However, in Japan, only doxorubicin and ifosfamide are indicated for soft tissue sarcoma and generally used, and there are no approved drugs indicated for soft tissue sarcoma that progressed after chemotherapy with these agents.

Pazopanib was shown to be effective in patients with metastatic soft tissue sarcoma that progressed after anthracycline therapy, and its safety profile was manageable in Study VEG110727. Therefore pazopanib is expected to be used for the treatment of metastatic soft tissue sarcoma after the standard chemotherapy with doxorubicin, etc. As doxorubicin is known to have cumulative cardiotoxicity, ifosfamide or pazopanib will be a therapeutic option for soft tissue

sarcoma patients, who are not suitable for doxorubicin.

Based on "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety" sections and the review in this section, PMDA concluded that pazopanib can be one of the options for a second-line chemotherapy for metastatic soft tissue sarcoma that progressed after the standard chemotherapy with doxorubicin, etc.

4.(iii).B.(5) Indication

The proposed indication was for "advanced soft tissue sarcoma".

PMDA concluded as follows:

Based on "4.(iii).B.(2) Efficacy", "4.(iii).B.(3) Safety," and "4.(iii).B.(4) Clinical positioning" sections and the review described in this section, (1) pazopanib should be indicated for "soft tissue sarcoma", (2) the histology subtypes, included in and excluded from the clinical studies of pazopanib, should be appropriately listed in the Clinical Studies section of the package insert, and (3) the caution statements described below should be included in the Precautions for Indications section. The proposed indication contains "advanced", but it is better not to confine the indication to advanced cases, because the histology subtypes, resectability, and prior chemotherapy cannot be specified in detail for the selection of patients with soft tissue sarcoma suitable for pazopanib treatment.

- The efficacy and safety of pazopanib in patients who have not received prior chemotherapy have not been established.

- Patients for pazopanib treatment should be selected after obtaining full knowledge of the information provided in the Clinical Studies section with regard to the histologic subtypes of soft tissue sarcoma in patients enrolled in the clinical studies, as well as full understanding of the efficacy and safety of pazopanib.

4.(iii).B.(5).1) Patient populations and tumor histology

The applicant explained how the study population of Study VEG110727 was selected as follows: In Study VEG20002, of patients with high or intermediate grade malignant soft tissue sarcoma that is incurable by surgery or radiotherapy, those who were not eligible for chemotherapy, or received one combination, or a maximum of two single-agent chemotherapy regimen for advanced disease were enrolled. Subjects were stratified into 4 strata according to the WHO classification of soft tissue sarcoma:

- Leiomyosarcoma (uterine, skin, or non organ origin)
- Adipocytic tumors (liposarcoma dedifferentiated, myxoid/round cell, pleomorphic, mixed type, not otherwise specified [NOS])
- Synovial sarcoma
- Other types of soft tissue sarcoma (high or intermediate grade malignant soft tissue sarcoma)

In Study VEG20002, Simon two stage testing procedure (optimal design) was used. In Stage 1 of the study, 17 patients each were to be included in the following strata according to their tumor histology: "adipocytic sarcoma," "leiomyosarcoma," "synovial sarcoma," and "other soft tissue sarcoma than adipocytic sarcoma, leiomyosarcoma, or synovial sarcoma." If CR, PR, or SD were observed in ≥4 subjects in a stratum at Week 12 (i.e., PF rate, ≥20%), the study was to progress to Stage 2. In Stage 2, after further recruitment of subjects up to 37, the efficacy of pazopanib was to be considered promissing if PF rate was ≥40%.

In Study VEG20002, the anti-tumor activity of pazopanib was suggested in patients with leiomyosarcoma, synovial sarcoma, and other types of soft tissue sarcoma, but not in patients with adipocytic sarcoma (liposarcoma dedifferentiated, myxoid/round cell, pleomorphic, mixed type, and others). Therefore, leiomyosarcoma, synovial sarcoma and other types of soft tissue sarcoma were selected as the histology subtypes to be evaluated in Study VEG110727.

In Study VEG110727, of patients with high or intermediate grade malignant soft tissue sarcoma, those who had received prior anthracycline therapy and no more than 4 prior lines of systemic chemotherapy for the advanced disease and had metastasis were enrolled. The following histology subtypes of soft tissue sarcoma, according to the WHO classification, were eligible.

- Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumor)
- So-called fibrohistiocytic (pleomorphic malignant fibrous histocytoma [MFH], giant cell MFH, inflammatory MFH)
- Leiomyosarcoma
- Malignant glomus tumor
- Skeletal muscles (alveolar, pleomorphic rhabdomyosarcoma)
- Vascular (epithelioid haemangioendothelioma, angiosarcoma)
- Uncertain differentiation (synovial sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma, desmoplastic small round cell, extra-renal rhabdoid , malignant mesenchymoma, perivascular epithelioid cell tumor [PEComa], intimal sarcoma) excluding chondrosarcoma and Ewing tumors/primitive neuroectodermal tumor (PNET).
- Malignant peripheral nerve sheath tumor
- Undifferentiated soft tissue sarcomas not otherwise specified
- Other types of soft tissue sarcoma

In Study VEG110727, histology subtypes listed in the following table were excluded.

Ineligible tumour types in Study VEG110727

Ineligible tumour types	Reason for the ineligibility
Adipocytic sarcoma (all subtypes)	In the intrim analysis in Study VEG20002, adipocytic sarcoma did not meet the criteria to progress to stage 2, which was performed based on the investigator -assessed tumor pathology review, therefore, further accrual was stopped. *1 Since Study VEG110727 was planned according to the intrim analysis, adipocytic sarcoma was not eligible for Study VEG110727.
All rhabdomyosarcoma that were NOT alveolar or pleomorphic	Although these tumours are classified as STS, they occur predominantly in pediatric and young adult populations.
Chondrosarcoma Bone sarcoma Ewing tumors/primitive neuroectodermal tumor (PNET)	These tumours are classified as bone tumor. They have different standard chemotherapies for the patients with metastasis from STS.
Gastrointestinal stromal tumor (GIST)	Although GIST is classified as STS, it has an established standard therapy different from those for other STS. Imatinib mesilate (imatinib) and sunitinib malate (sunitinib) are used in the standard therapy.
Dermatofibrosarcoma protuberans (DFSP)	Although DFSP is classified as STS, it has an established standard therapy different from those for other STS. The standard drug (imatinib) for the therapy has been approved in the foreign countries. There is no approved drug for the treatment of DFSP in Japan.
Inflammatory myofibroblastic sarcoma	Inflammatory myofibroblastic sarcoma is classified as STS and has same standard therapy as other STS. However, it progresses locally and typically non-metastatic, and shows different mechanism from malignant tumours.
Malignant mesothelioma	Malignant mesothelioma is classified as mesothelioma. Established therapy (cisplatin and pemetrexed sodium hydrate) is available.
Mixed mesodermal tumors of the uterus	Mixed mesodermal tumors of the uterus is classified as uterine cancer and it has different standard therapy from STS (combination therapy with ifosfamide and paclitaxel is recommended).

*1: For the liposarcoma stratum, CR, PR, or SD was confirmed in 2 of 17 subjects in the intrim analysis performed based on the investigator-assessed tumor pathology review. This result did not meet the criteria defined in the protocol, to progress to stage 2 (CR, PR, or SD in ≥4 of 17 subjects are needed at week 12 to meet the criteria). Therefore, further accrual was stopped. Based on the subsequent evaluation at central pathology review, however, SD was confirmed in 5 of 19 subjects, which met the criteria to progress to stage 2.

The applicant explained as follows: based on the study population in Study VEG20002 and Study VEG110727, it is stated in the Precautions for Indications section, "Adipocytic sarcoma and gastrointestinal stromal tumor were excluded from the phase III clinical study, and gastrointestinal stromal tumor from the phase II study."

PMDA asked the applicant to explain, (a) histology subtypes that were eligible for the study but not actually treated with pazopanib, and (b) the clinical usefulness of pazopanib for the ineligible histology subtypes of soft tissue sarcoma in the study.

The applicant responded as follows:
Vascular endothelial growth factor receptor (VEGF) is overexpressed in many histology subtypes of soft tissue sarcoma, such as leiomyosarcoma, malignant fibrous histiocytoma, and dermatofibrosarcoma protuberans (*Anticancer Res.* 2004; 24: 333-7), and other angiogenic factors, for example, platelet-derived growth factor (PDGF), are also overexpressed. These factors are associated with the tumor grade and tumor cell proliferation (*Cancer Res.* 1994; 54: 560-4, *J Surg Res.* 2006; 135: 282-90). Pazopanib mainly inhibits kinases for VEGFR-1, -2 and -3, PDGFR-α and -β, and stem cell factor receptor. Based on this mechanism of action, pazopanib is expected to be effective against all histology subtypes of soft tissue sarcoma. Non-clinical pharmacology data suggested that pazopanib inhibits adipocytic sarcoma and synovial sarcoma, which are

the major histology subtypes of soft tissue sarcoma [see "3.(i).A.(1) Primary pharmacodynamics"]. Moreover, neovascularization is likely to play an important role in the progression of soft tissue sarcoma regardless of the histology subtype (*Virchows Arch.* 2001; 438: 13-22, *Oncologist.* 2008; 13: 1193-200). Therefore, pazopanib is expected be effective against various histology subtypes of soft tissue sarcoma.

a. Histology subtypes that were eligible for the study but not actually treated with pazopanib

Patients with inflammatory MFH, malignant glomus tumor, alveolar or pleomorphic rhabdomyosarcoma, malignant mesenchymoma, and intimal sarcoma were to be included in Study VEG110727, but no subjects with these subtypes were actually treated with pazopanib [see"4.(iii).B.(2).4) Efficacy by tumor histology"]. Soft tissue sarcoma has various histology subtypes and some of them are very rare to occur. For that reason, considering the feasibility of clinical studies, it is impractical to evaluate the efficacy of pazopanib in each of all histology subtypes. In Study VEG110727, pazopanib was shown to be effective in the subpopulation of "other STS" including the histology subtypes that are eligible for the study but not actually treated with pazopanib. Pazopanib is therefore also expected to be clinically useful for the histology subtypes eligible for the Study VEG110727 but not actually treated with pazopanib.

b. Ineligible histology subtypes in the clinical studies

All ineligible histology subtypes in Study VEG110727 except adipocytic sarcoma were also excluded from Study VEG20002. Therefore, the clinical usefulness of pazopanib for those histology subtypes is unknown. For adipocytic sarcoma, pazopanib is clinically useful to some extent for the following reasons:

- In the non-clinical pharmacology study, pazopanib showed tumor growth inhibition in human liposarcoma tumor xenograft in mice.

- In the interim analysis of efficacy performed based on the investigator-assessed tumor pathology review in Study VEG20002, the adipocytic sarcoma stratum did not meet the prespecified criteria (i.e., 2 of 17 subjects for SD, PF rate of 11%) to progress to Stage 2, and further accrual was stopped. However, subsequently, some of those that were originally assessed as "others" (other soft tissue sarcomas than adipocytic sarcoma, leiomyosarcoma, or synovial sarcoma) were re-assessed by central pathology review as "adipocytic sarcoma" stratum. In these subjects, efficacy of pazopanib was seen, and the "adipocytic sarcoma" stratum met the prespecified criteria to progress to Stage 2 (i.e., 5 of 19 subjects for SD, PF rate of 26%) in the final analysis. The efficacy of pazopanib in adipocytic sarcoma was not denied.

PMDA considers as follows:

The applicant explained that pazopanib is expected to be effective against various histology subtypes of soft tissue sarcoma because pazopanib inhibits angiogenesis and angiogenesis is involved in the growth of some soft tissue sarcoma cell lines [see "3.(i).B. Mechanism of action and efficacy of pazopanib in soft tissue sarcoma with various tumor types"]. This explanation remains a matter of inference because the efficacy of pazopanib was not evaluated in histology subtypes of soft tissue sarcoma other than synovial sarcoma or liposarcoma in the non-clinical pharmacodynamic studies.

However, it is difficult to evaluate the efficacy of pazopanib in each of all histology subtypes of soft tissue sarcoma because of its variety and scarcity. This applicant's explanation is understandable. Based on the following review *a*. and *b*., pazopanib should be indicated for "soft tissue sarcoma" including rare histology subtypes. It is necessary to provide caution statements

and relevant information in the package insert, etc., so that prescribing physicians can select patients suitable for pazopanib treatment considering the efficacy data, etc. for each histology subtype of soft tissue sarcoma obtained from the clinical studies. In the Precautions for Indications section, it is necessary not only to call attention to adipocytic sarcoma and gastrointestinal stromal tumor but also to provide precise information about the histology subtypes included in the clinical studies.

a. Histology subtypes that were eligible for the study but not actually treated with pazopanib

- In the subgroup analysis by tumor histology in Study VEG110727, "leiomyosarcoma," "synovial sarcoma," and "other STS" showed a statistically significant improvement in PFS in the pazopanib group compared with the placebo group as seen in the entire population, and PR or some reduction in tumor size from baseline was observed in many histology subtypes classified to "other STS". Based on these findings, the clinical benefit of pazopanib for some of these histology subtypes should not be denied just because the subtypes were not actually treated with pazopanib in Study VEG110727.

b. Ineligible histology subtypes in the clinical studies

- Adipocytic sarcoma was excluded from Study VEG110727, but the clinical usefulness of pazopanib for adipocytic sarcoma can be expected based on the results of Study VEG20002, in which adipocytic sarcoma was eligible.

- For other ineligible histology subtypes in the clinical studies, the clinical usefulness of pazopanib is unknown. Considering the circumstance that pazopanib is expected to be used by physicians with adequate knowledge and experience in cancer chemotherapy, patients suitable for pazopanib treatment will be selected properly if precise information about the histology subtypes included in the clinical studies is provided.

4.(iii).B.(5).2) Locally advanced soft tissue sarcoma

In Study VEG110727, soft tissue sarcoma patients with metastatic lesion were enrolled, but those with locally advanced lesion only were excluded.

PMDA asked the applicant to explain the efficacy of pazopanib in locally advanced disease.

The applicant responded as follows:

Pazopanib is recommended for use in locally advanced disease for the following reasons:

- According to the Japanese practice guideline, systemic chemotherapy should be considered in patients with locally advanced soft tissue sarcoma not suitable for radical resection as in patients with metastatic soft tissue sarcoma, and doxorubicin monotherapy is a standard therapy. In the treatment of soft tissue sarcoma, therefore, there is no clear difference in chemotherapy between locally advanced and metastatic cases.

- In Study VEG110727, patients with metastatic soft tissue sarcoma (metastatic plus locally advanced disease, metastatic disease only) were included. This criterion was set for the evaluation of the primary endpoint, PFS, but not due to an assumed difference in the therapeutic efficacy of pazopanib between metastatic disease and locally advanced disease.

- In Study VEG110727, it turned out that 4 patients with "locally advanced soft tissue sarcoma without metastatic disease" were enrolled, but the efficacy and safety of pazopanib could not be evaluated in this population because of the small sample size. However, since both metastatic disease and locally advanced disease result from the growth of cells derived from the primary tumor, pazopanib is expected to be similarly effective against locally

advanced disease. Thus, the efficacy and safety profiles of pazopanib in patients with locally advanced soft tissue sarcoma without metastatic disease are not considered to be significantly different from those obtained in Study VEG110727.

- In Study VEG110727, patients with both metastatic and locally advanced soft tissue sarcoma were included. It is therefore inappropriate to limit the indication of pazopanib to metastatic soft tissue sarcoma only. Pazopanib should also be indicated for soft tissue sarcoma only with locally advanced disease.

PMDA considers as follows:
According to the Japanese practice guideline, there is no difference in the therapeutic strategy between soft tissue sarcoma only with locally advanced disease and soft tissue sarcoma only with metastatic disease. The exclusion of locally advanced soft tissue sarcoma without metastatic disease, which was ineligible in Study VEG110727, from the indication, has little significance. However, it is necessary to provide information that the study population was patients with metastatic soft tissue sarcoma.

4.(iii).B.(5).3) Neoadjuvant/adjuvant chemotherapy
PMDA asked the applicant to explain the necessity of a caution statement about neoadjuvant and adjuvant chemotherapy with pazopanib.

The applicant responded as follows:
Neoadjuvant chemotherapy for soft tissue sarcoma may be performed aiming at the reduction of tumor weight for the effective resection of resectable soft tissue sarcoma (NCCN Guideline). However, in the Japanese practice guideline, the significance of neoadjuvant chemotherapy is not clearly stated, and the positioning of neoadjuvant chemotherapy is unknown in the treatment of soft tissue sarcoma.

The Japanese practice guideline indicates that adjuvant chemotherapy with doxorubicin and ifosfamide, etc. should be considered for resectable Stage III non-round cell sarcoma in extremities, and that it should be performed after the risk and benefit based on the patient's condition are fully explained to the patient. The clinical positioning of adjuvant chemotherapy is not clarified.

As described above, the clinical positioning of neoadjuvant and adjuvant chemotherapy is not clear in the treatment of soft tissue sarcoma. It was once proposed to include a statement "The efficacy and safety of pazopanib for adjuvant chemotherapy have not been established.", but it may cause misunderstanding that there is established neoadjuvant and adjuvant chemotherapy in the treatment of soft tissue sarcoma. Therefore this statement will not be included in the Precautions for Indications section of the package insert.

PMDA confirmed that the neoadjuvant and adjuvant chemotherapy for soft tissue sarcoma is not an established treatment in the Japanese or overseas guidelines (NCCN Guideline, etc.), and accepted the applicant's explanation.

4.(iii).B.(5).4) Prior chemotherapy
PMDA asked the applicant to explain the precaution for pazopanib treatment in patients who have not received prior chemotherapy.

The applicant responded as follows:
The proposed indication for pazopanib in the EU includes "patients who are unsuited for such therapy" and this population includes metastatic soft tissue sarcoma patients who have not received prior chemotherapy. In the EU, the approved indication of trabectedin (not approved in Japan) includes this population. Trabectedin and pazopanib were evaluated in their pivotal clinical

studies in similar study populations, that is, patients with soft tissue sarcoma who had been treated with anthracycline, ifosfamide, or other chemotherapy. Trabectedin serves as a precedent, and the proposed indication for pazopanib in the EU includes patients unsuited for chemotherapy.

On the other hand, in Japan, doxorubicin and ifosfamide are indicated for soft tissue sarcoma, but doxorubicin and ifosfamide are contraindicated in some patients who have not received prior chemotherapy with metastatic soft tissue sarcoma, because doxorubicin has cumulative cardiotoxicity (package insert of Adriacin Injection 10/50), and ifosfamide has a risk of adverse events in the urinary system such as renal disorder and haemorrhagic cystitis (package insert of Ifomide Injection 1 g). However, the efficacy and safety of pazopanib have not been established in patients who have not received prior chemotherapy. In Japan, therefore, the proposed indication for pazopanib does not include a statement about patients unsuited for chemotherapy," and a caution statement "The efficacy and safety of the product have not been established in patients who have not received prior chemotherapy." will be included in the Precautions for Indications section.

PMDA considers as follows:
Considering the circumstances that doxorubicin is established as standard first line therapy for metastatic soft tissue sarcoma (NCCN Guideline, etc.), and that pazopanib is used by physicians with adequate knowledge and experience in cancer chemotherapy, pazopanib will hardly be used in patients who have not been treated with chemotherapy including doxorubicin. Therefore, it is not absolutely essential to include "pretreated patients" in the indication. However, it is necessary to include "The efficacy and safety of pazopanib have not been established in patients who have not received prior chemotherapy." in the Precautions for Indications section, because the efficacy and safety of pazopanib are unknown in patients who have not received prior chemotherapy.

4.(iii).B.(6) Dosage and administration
The proposed dosage and administration for pazopanib was "The usual adult dosage is 800 mg of pazopanib orally administered once daily. The dose may be adjusted according to the patient's condition, but the daily dose should not exceed 800 mg."

PMDA concluded that the dosage and administration for pazopanib should be modified as "The usual adult dosage is 800 mg of pazopanib orally administered once daily, at least 1 hour before or at least 2 hours after a meal. The dose may be adjusted according to the patient's condition." and to add the caution statements below in the Precautions for Dosage and Administration section, based on the facts stated in "4.(i).B.(1) Effect of food" and the following review. Precautions against crushed tablets, concomitant use with antiacids, and concomitant use with CYP3A4 inhibitors are discussed under "4.(i).A.(3) Foreign phase I study," "4.(i).B.(2) Effect of gastric pH," and "4.(ii).B.(2) Pharmacokinetic drug interactions," respectively.

- The efficacy and safety of the concomitant use of pazopanib with other antineoplastic drugs have not been established.

- It has been reported that administration of pazopanib after a meal results in increase in C_{max} and AUC. In order to avoid the effect of food, pazopanib should be taken in compliance with Dosage and Administration.

- If dose reduction of pazopanib is necessary due to the onset of adverse reaction, it should be in 200 mg decrements in a stepwise fashion. Additionally, if dose escalation is considered after dose reduction, it should be in 200 mg increments in a stepwise fashion, but should not exceed 800 mg.

- In patients with moderate or severe hepatic impairment, the dose of pazopanib should be reduced, and patients should be closely monitored for the onset of adverse events.

- If abnormal liver function test values are observed during pazopanib treatment, the following criteria should be considered.

Criteria for dose interruption and reduction, and treatment discontinuation for abnormal liver function test values

Liver function test value	Treatment
3.0 × ULN ≤ ALT ≤ 8.0 × ULN	Pazopanib may be continued (with weekly monitoring of liver function until ALT returns to ≤ Grade1 or baseline).
ALT > 8.0 × ULN	Pazopanib should be interrupted until ALT returns to ≤ Grade 1 or baseline. If administration of pazopanib is resumed, the dose should be reduced to 400 mg. Following reintroduction of pazopanib, if abnormalities in liver function test (ALT > 3.0 × ULN) recur, then pazopanib should be permanently discontinued.
ALT > 3.0 × ULN, and total bilirubin elevations > 2.0 × ULN (direct bilirubin >35%)	Pazopanib should be permanently discontinued (patients should be monitored until ALT returns to ≤ Grade 1 or baseline).

4.(iii).B.(6).1) Dosage and administration of pazopanib

The applicant explained the rationale for the dosage and administration of pazopanib as follows: Pazopanib 800 mg QD was selected as the recommended dose in foreign countries, because in the foreign phase I study (Study VEG10003), (1) the safety profile of pazopanib 800 mg QD was confirmed to be manageable, (2) there was no further increase found in systemic exposure at oral doses above 800 mg QD, (3) the plasma pazopanib concentration at 24 hours after administration (C_{24}), which is the target level for pharmacodynamic effect, was ≥15 μg/mL, and this concentration is similar to the trough concentration (17.5 μg/mL) at which inhibitory action of angiogenesis was observed in the non-clinical study [see "3.(i).A.(1).2).i) Inhibition of phosphorylation"], and (4) C_{24} was 15 μg/mL in 93% of subjects (13 of 14 subjects) treated orally with pazopanib at 800 mg QD.

The recommended dose of 800 mg QD in foreign countries is also appropriate for Japanese patients, because in Japanese phase I study (Study VEG109693), (1) pazopanib 800 mg and 1000 mg QD were confirmed to be well tolerated, (2) there appears to be no clear difference in the safety profile of pazopanib between the Japanese and foreign populations, (3) SD was observed as best response in 3 of 10 subjects treated orally at 800 mg QD, and lasted for ≥ 6 months in 2 of the 3 subjects, and (4) the geometric mean C_{24} of pazopanib at 800 mg and 1000 mg QD (22.0, 21.1 μg/mL, respectively) was higher than the target C_{24} level (15 μg/mL) for the clinical effect of pazopanib.

Furtheremore, in the global phase III study (Study VEG110727), in which pazopanib was administered orally at 800 mg QD, the efficacy and safety of pazopanib were demonstrated in patients with metastatic soft tissue sarcoma (entire population, Japanese subpopulation).

Therefore, the dosage and administration for pazopanib were proposed as "The usual dosage of pazopanib is 800 mg orally administered once daily."

PMDA accepted the applicant's explanation.

4.(iii).B.(6).2) Dose adjustment of pazopanib

Dose adjustment procedure when the dose of pazopanib needs to be reduced due to adverse reactions, and the guideline for dose interruption, reduction, or treatment discontinuation when any abnormal liver function test value is observed during treatment with pazopanib, are provided in the Precautions for Dosage and Administration section in the proposed package insert.

The applicant explained the rationale as follows:

In Study VEG110727, the starting dose of pazopanib was 800 mg QD, and the dose was interrupted or reduced (to 600 mg, 400 mg, and 200 mg in a stepwise fashion), if any adverse event possibly related to pazopanib was observed. When the adverse event did not recur or get worse after dose reduction, the dose of pazopanib was allowed to be increased in 200 mg increments in a stepwise fashion up to 800 mg. Adverse events were able to be managed by this stepwise dose adjustment. Therefore, the following statement is included in the Precautions for Dosage and Administration section; "If dose reduction of pazopanib is necessary due to the onset of adverse drug reactions, it should be in 200 mg decrements in a stepwise fashion based on individual symptoms, severity, etc. Additionally, if dose escalation is considered after dose reduction, it should be in 200 mg increments in a stepwise fashion, but should not exceeded 800 mg."

In Study VEG110727, many of the abnormal liver function test values were reversible, and the subjects were able to remain on pazopanib by appropriate dose interruption or reduction. In order to control abnormal liver function test values properly, as in Study VEG110727, a statement "If abnormal liver function test values are observed during treatment with the product, the dose should be interrupted or reduced, or the treatment should be discontinued in accordance with the following criteria." and the "Criteria for dose interruption and reduction, and treatment discontinuation for abnormal liver function test values" are provided in the Precautions for Dosage and Administration section. In Study VEG110727, in addition to abnormal liver function test values, the criteria for dose interruption and reduction, and treatment discontinuation was also defined for such adverse events as hypertension, proteinuria, and haemorrhage. However, the criteria were not included in the proposed package insert, because in practice, the dose of pazopanib should be adjusted by the clinical judgment based on each adverse events and patient's condition, concomitant medications, risk-benefit considerations, etc.

PMDA asked the applicant to explain the safety profile of pazopanib in the subjects whose dose was increased after dose reduction in Study VEG110727.

The applicant responded as follows:

In Study VEG110727, the dose of pazopanib was increased in 24 of 240 subjects (10%), of whom, after dose reduction due to an adverse event or laboratory test abnormality, the dose of pazopanib was increased in 19 subjects. Of them, the causative adverse event recurred or got exacerbated in 4 subjects but none resulted in withdrawal. In 1 of these 4 subjects, the dose of pazopanib was reduced again because of the recurrence of the adverse event (diarrhoea), but the dose was increased again later. In 1 of the 19 subjects in whom the dose of pazopanib was increased after dose reduction, the reason for dose reduction was reported only as non-hematologic toxicity, and the term of adverse event is unknown.

Based on the above, when the dose of pazopanib is reduced due to an adverse event or laboratory test abnormality, and then the adverse event or laboratory abnormality value resolves or does not get worse, there is no significant safety concern after the dose increase. Therefore dose increase after dose reduction can be recommended.

PMDA considers as follows:

PMDA largely accepted the applicant's explanation about the dose adjustment of pazopanib, but

the number of subjects who experienced dose increase after dose reduction is limited. Post-marketing safety information should be obtained from patients in whom the dose of pazopanib is reincreased after dose reduction, and relevant information should be provided to healthcare professionals [see "4.(iii).B.(7) Post-marketing investigations"].

Based on the review in "4.(iii).B.(6).3) Dose adjustment of pazopanib in patients with hepatic impairment," it is appropriate to provide the criteria for dose interruption and reduction, and treatment discontinuation for hepatic function disorder, which was established in Study VEG110727, in the Precautions for Dosage and Administration section so that appropriate measures can be taken in the event of hepatic function disorder during treatment with pazopanib. Since the criteria for dose adjustment will also be useful as a reference in the event of an adverse event other than hepatic function disorder, it is recommended to provide relevant information to clinical practice. Particularly, for adverse events requiring attention during treatment with pazopanib, a concrete guideline for dose interruption, reduction, treatment discontinuation, and dose increase after dose reduction should be appropriately provided with an information leaflet, etc.

4.(iii).B.(6).3) Dose adjustment of pazopanib in patients with hepatic impairment

In the Precautions for Dosage and Administration section of the proposed package insert, it is stated that the starting dose of pazopanib should be reduced to 200 mg QD in patients with moderate hepatic impairment (total bilirubin, 1.5-3.0 times ULN), and that pazopanib is not recommended in patients with severe hepatic impairment (total bilirubin, >3 times ULN).

The applicant explained the rationale as follows:

In Study NCI-8063, in which the pharmacokinetics of pazopanib was evaluated in patients with hepatic impairment, dose limiting toxicities (Grade 4 ALT increased in 1 subject; Grade 4 AST increased, Grade 4 ALT increased, Grade 3 hyperbilirubinaemia in 1 subject) were observed in 2 of 4 patients with moderate hepatic impairment in the 400 mg QD cohort, and the maximum tolerated dose of pazopanib in patients with moderate or severe hepatic impairment was 200 mg QD [see "4.(ii).A.(6) Foreign phase I study in patients with hepatic impairment"]. In patients with severe hepatic impairment, it is suggested that pazopanib exposure may not reach the therapeutically effective concentration because in Study NCI-8063, when patients with moderate and severe hepatic impairment received multiple oral dose of pazopanib 200 mg QD, the steady state trough concentrations of pazopanib were 16.2 μg/mL (range, 3.1-24.2 μg/mL) and 5.7 μg/mL (range, 1.5-18.4 μg/mL), respectively, and the trough concentration required to inhibit angiogenesis was 17.5 μg/mL in the non-clinical study to evaluate the ability of pazopanib to inhibit phosphorylation of VEGFR-2 [see "3.(i).A.(1).2).i) Inhibition of phosphorylation"].

PMDA considers as follows:

Based on the results of Study NCI-8063, patients with moderate or severe hepatic impairment should not be treated at a dose higher than the maximum tolerated dose of 200 mg QD. In addition, the evidence is not sufficient to recommend adjustment of the starting dose of 200 mg QD because the relationship between pazopanib exposure and efficacy is still unknown in patients with soft tissue sarcoma [see "4.(ii).A.(4).2) Relationship between exposure and changes in blood pressure or efficacy"].

It is therefore necessary to appropriately provide a precaution and relevant information in the package insert, etc. about the results of Study NCI-8063 including the fact that the maximum tolerated dose of pazopanib was 200 mg QD in patients with moderate or severe hepatic impairment, so that whether pazopanib should be used or not and its dosage can be considered carefully with a full understanding of the results of Study NCI-8063 before pazopanib is used in

patients with moderate or severe hepatic impairment.

4.(iii).B.(6).4) Concomitant use of pazopanib with other antineoplastic drugs

The applicant explained the concomitant use of pazopanib with other antineoplastic drugs as follows:

A caution statement that pazopanib should not be used in combination with other antineoplastic drugs will be provided in the package insert, because at present, the safety and efficacy of pazopanib when used in combination with other antineoplastic drugs have not been established. A phase I study (Study VEG109603) with pazopanib and anthracycline therapy (doxorubicin or epirubicin hydrochloride) is ongoing in foreign patients with solid tumors.

PMDA accepted this explanation.

4.(iii).B.(7) Post-marketing investigations

The applicant explained the post-marketing surveillance plan as follows:

Post-marketing surveillance will be conducted in all patients treated with pazopanib to assess the actual status of use of pazopanib and identify (1) unknown adverse drug reactions, (2) the types and incidences of adverse drug reactions, and (3) factors affecting the safety of pazopanib.

The priority surveillance items will be incidence, severity, time of onset, etc., of hepatic function disorder, hypertension, and cardiac dysfunction (cardiac failure, cardiomyopathy, etc.), because severe cases of these adverse events were reported more frequently in the pazopanib group than in the placebo group, and reported in the Japanese subgroup in the global phase III study (Study VEG110727).

Based on the incidence of ≥ Grade 3 hepatic function disorder, hypertension, and cardiac dysfunction, which are the priority surveillance items, the target number of patients for analysis will be set at 200 to allow the detection of ≥1 case of each adverse event with a 95% probability. The target number of patients for registration will be 300. According to the Japanese Orthopedic Association's patient registry and marketing research, approximately 100 to 140 patients will be treated with pazopanib in 6 months, and the registration period will be 1.5 years.

The observation period will be 1 year, because (1) the first event of each adverse event of the priority surveillance items occurred within 1 year except in 1 subject who experienced hypertension more than 1 year after the first dose of pazopanib, and (2) there was no adverse event that occurred more than 1 year after the first dose of pazopanib for the first time in >1 subject, in the global phase III study (Study VEG110727) and foreign phase II study (Study VEG20002).

PMDA considers the submitted post-marketing surveillance plan as follows:

Post-marketing surveillance should be conducted in all patients treated with pazopanib because pazopanib is the first VEGF inhibitor approved for the indication of soft tissue sarcoma in Japan, although other VEGF inhibitors have been approved, and it is necessary to collect post-marketing safety information as rapidly as possible because the safety information of pazopanib obtained so far from Japanese patients is limited.

In addition to the adverse events of priority surveillance items listed by the applicant, the following information should be obtained and assessed:

- Administration status and safety of pazopanib in patients with hepatic impairment
- QT interval prolongation and arrhythmias including TdP
- Thromboembolism
- Haemorrhagic events

- Pneumothorax
- Thyroid function abnormal
- Gastrointestinal perforations and gastrointestinal fistula
- Proteinuria and nephrotic syndrome
- Complications due to wound healing delayed
- Safety when pazopanib is used for the tumor types not treated in the clinical studies
- Safety when the dose of pazopanib is reincreased after dose reduction

The target number of patients for analysis should be changed in order to allow the collection of the above information. The proposed observation period is acceptable. Since metastatic soft tissue sarcoma has various histology subtypes, it is recommended to take appropriate measures not to gather information only from the most prevalent histology subtypes.

4.(iii).B.(8) Clinical development in children

PMDA asked the applicant to explain the status of development of dosage regimen for pediatric patients with soft tissue sarcoma.

The applicant responded as follows:

At present, the Children's Oncology Group (COG) is conducting and planning some clinical studies of pazopanib in pediatric patients with solid tumors under the support of the Cancer Therapy Evaluation Program (CTEP). In the ongoing phase I study (Study ADVL0815), the recommended dosage regimen in pediatric patients with solid tumors were selected as 450 mg/m^2, QD, and oral dose, and a phase II study in pediatric patients with solid tumors will be conducted in several arms (rhabdomyosarcoma, non-rhabdomyosarcoma, Ewing's sarcoma, etc.).

In Japan, there is no clinical development plan in pediatric patients with solid tumors, and the progress of the above COG studies is awaited.

PMDA considers as follows:

The applicant should take appropriate measures so that pediatric dosage can be developed against soft tissue sarcoma in Japan without delay, after gathering and analyzing relevant information about the need for development of pazopanib for pediatric patients in Japan and obtaining information about foreign clinical development plan, etc. as soon as possible. The measures include participation of Japanese patients in global studies.

4.(iv) Adverse events observed in clinical studies

Based on the clinical study data submitted for safety evaluation, deaths reported in the clinical studies are described under "4.(iii) Summary of efficacy and safety." Frequently reported adverse events other than death are described below.

4.(iv).(1) Japanese phase I study (Study VEG109693)

1) Part A

Adverse events were reported by 3 of 3 subjects (100%) in the P400/800 mg group, 7 of 7 subjects (100%) in the P800 mg group, and 3 of 3 subjects (100%) in the P1000 mg group. Adverse events for which a causal relationship to pazopanib can not be ruled out were reported by 3 of 3 subjects (100%), 6 of 7 subjects (86%), and 3 of 3 subjects (100%), respectively. Adverse events reported by ≥2 subjects in any group are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)*					
	P400/800 mg (N = 3)		P800 mg (N = 7)		P1000 mg (N = 3)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any events	3 (100)	3 (100)	7 (100)	2 (29)	3 (100)	1 (33)
Gastrointestinal disorders						
Diarrhoea	1 (33)	0	4 (57)	0	2 (67)	0
Nausea	1 (33)	0	1 (14)	0	3 (100)	0
Vomiting	1 (33)	0	1 (14)	0	2 (67)	0
Investigations						
AST increased	2 (67)	0	3 (43)	0	0	0
ALT increased	2 (67)	0	2 (29)	0	0	0
Lipase increased	2 (67)	0	2 (29)	1 (14)	1 (33)	0
Platelet count decreased	0	0	4 (57)	0	0	0
Blood alkaline phosphatase increased	1 (33)	0	0	0	2 (67)	0
Blood thyroid stimulating hormone increased	2 (67)	0	1 (14)	0	0	0
Neutrophil count decreased	0	0	3 (43)	0	0	0
White blood cell count decreased	0	0	3 (43)	0	0	0
Blood thyroid stimulating hormone decreased	0	0	2 (29)	0	0	0
Skin and subcutaneous tissue disorders						
Rash	1 (33)	0	3 (43)	0	1 (33)	0
Skin hypopigmentation	2 (67)	0	0	0	1 (33)	0
Hair colour changes	0	0	2 (29)	0	0	0
Blood and lymphatic system disorders						
Leukopenia	3 (100)	0	1 (14)	0	1 (33)	1 (33)
Neutropenia	3 (100)	2 (67)	1 (14)	0	1 (33)	1 (33)
Lymphopenia	2 (67)	0	1 (14)	1 (14)	1 (33)	0
Thrombocytopenia	3 (100)	0	0	0	1 (33)	0
General disorders and administration site conditions						
Fatigue	0	0	1 (14)	0	2 (67)	0
Vascular disorders						
Hypertension	3 (100)	1 (33)	1 (14)	0	1 (33)	0
Renal and urinary disorders						
Proteinuria	1 (33)	0	2 (29)	0	0	0

*: Adverse events reported by ≥2 subjects in any of the treatment groups

Serious adverse events were reported by 1 of 3 subjects (33%) in the P400/800 mg group, 4 of 7 subjects (57%) in the P800 mg group, and 1 of 3 subjects (33%) in the P1000 mg group. These were hepatic function abnormal in 1 subject (33%) in the P400/800 mg group, enterocolitis infectious, ileus, lower respiratory tract infection, and pneumonitis in 1 subject each (14%) in the P800 mg group, and hepatic function abnormal in 1 subject (33%) in the P1000 mg group. Of these serious adverse events, a causal relationship to pazopanib was not ruled out for hepatic function abnormal (1 subject) reported in the P400/800 mg group, pneumonitis (1 subject) in the P800 mg group, and hepatic function abnormal (1 subject) in the P1000 mg group.

Adverse events leading to discontinuation of pazopanib were reported by 1 of 3 subjects (33%) in the P400/800 mg group, 2 of 7 subjects (29%) in the P800 mg group, and 0 of 3 subjects (0%) in the P1000 mg group. These were hepatic function abnormal (1 subject, 33%) in the

P400/800 mg group, and ileus, hepatic function abnormal, and lower respiratory tract infection (1 subject each, 14%) in the P800 mg group. Of these adverse events, a causal relationship to pazopanib was not ruled out for hepatic function abnormal (1 subject) reported in the P400/800 mg group.

2) Part B

Adverse events were reported by 4 of 4 subjects (100%) in the P400 mg + L1000 mg group, 3 of 3 subjects (100%) in the P800 mg + L1000 mg group, 3 of 3 subjects (100%) in the P400 mg + L1500 mg group and 7 of 7 (100%) in the P600 mg + L1250 mg group, and adverse events for which a causal relationship to the study drug can not be ruled out were reported by all subjects. Adverse events reported by ≥2 subjects in any group are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)*							
	P400mg + L1000 mg (N = 4)		P800 mg + L1000 mg (N = 3)		P400 mg + L1500 mg (N = 3)		P600 mg + L1250 mg (N = 7)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	4 (100)	3 (75)	3 (100)	3 (100)	3 (100)	1 (33)	7 (100)	4 (57)
Gastrointestinal disorders								
Diarrhoea	4 (100)	0	3 (100)	0	3 (100)	0	7 (100)	1 (14)
Nausea	3 (75)	0	1 (33)	0	2 (67)	0	3 (43)	0
Stomatitis	0	0	1 (33)	0	2 (67)	0	4 (57)	1 (14)
Vomiting	3 (75)	0	1 (33)	1 (33)	1 (33)	0	2 (29)	0
Ileus	2 (50)	1 (25)	0	0	0	0	0	0
Investigations								
Blood thyroid stimulating hormone increased	1 (25)	0	3 (100)	0	1 (33)	0	5 (71)	0
Weight decreased	3 (75)	1 (25)	2 (67)	0	1 (33)	0	2 (29)	0
ALT increased	1 (25)	0	1 (33)	0	3 (100)	0	2 (29)	0
Blood amylase increased	2 (50)	0	2 (67)	1 (33)	0	0	2 (29)	0
AST increased	1 (25)	0	1 (33)	0	3 (100)	0	0	0
Blood alkaline phosphatase increased	1 (25)	0	2 (67)	0	1 (33)	0	1 (14)	0
Blood lactate dehydrogenase increased	0	0	2 (67)	0	3 (100)	0	0	0
Platelet count decreased	3 (75)	0	0	0	1 (33)	0	1 (14)	0
Lipase increased	2 (50)	2 (50)	0	0	1 (33)	1 (33)	1 (14)	1 (14)
C-reactive protein increased	2 (50)	0	0	0	1 (33)	0	0	0
Haemoglobin decreased	1 (25)	0	0	0	0	0	2 (29)	0
Gamma-glutamyl transferase increased	0	0	0	0	2 (67)	0	0	0
Skin and subcutaneous tissue disorders								
Rash	3 (75)	0	1 (33)	0	2 (67)	0	5 (71)	0
Skin hypopigmentation	2 (50)	0	2 (67)	0	1 (33)	0	2 (29)	0
Hair colour changes	1 (25)	0	1 (33)	0	0	0	4 (57)	0
Alopecia	1 (25)	0	1 (33)	0	1 (33)	0	2 (29)	0
Dry skin	0	0	0	0	2 (67)	0	3 (43)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	1 (33)	0	1 (33)	0	3 (43)	0
Nail disorder	2 (50)	0	0	0	1 (33)	0	1 (14)	0
Eczema	0	0	0	0	0	0	2 (29)	0

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)*							
	P400mg + L1000 mg (N = 4)		P800 mg + L1000 mg (N = 3)		P400 mg + L1500 mg (N = 3)		P600 mg + L1250 mg (N = 7)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and lymphatic system disorders								
Neutropenia	2 (50)	0	3 (100)	0	2 (67)	0	4 (57)	0
Leukopenia	2 (50)	0	3 (100)	1 (33)	0	0	4 (57)	0
Lymphopenia	2 (50)	0	1 (33)	0	1 (33)	0	3 (43)	1 (14)
Thrombocytopenia	0	0	2 (67)	0	0	0	5 (71)	0
General disorders and administration site conditions								
Fatigue	3 (75)	1 (25)	2 (67)	0	2 (67)	0	4 (57)	0
Metabolism and nutrition disorders								
Decreased appetite	3 (75)	0	1 (33)	0	3 (100)	0	5 (71)	0
Hypoalbuminaemia	1 (25)	0	1 (33)	0	0	0	3 (43)	0
Hyperkalaemia	0	0	0	0	2 (67)	0	0	0
Nervous system disorder								
Dysgeusia	1 (25)	0	1 (33)	0	3 (100)	0	4 (57)	0
Headache	2 (50)	1 (25)	0	0	1 (33)	0	0	0
Infections and infestations								
Nasopharyngitis	2 (50)	0	0	0	2 (67)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Epistaxis	1 (25)	0	1 (33)	0	0	0	2 (29)	0
Vascular disorders								
Hypertension	2 (50)	2(50)	1 (33)	0	2 (67)	0	4 (57)	1 (14)
Renal and urinary disorders								
Proteinuria	1 (25)	0	2 (67)	0	1 (33)	0	2 (29)	0
Musculoskeletal and connective tissue disorders								
Arthralgia	1 (25)	0	0	0	1 (33)	0	3 (43)	0
Muscle spasms	0	0	0	0	1 (33)	0	2 (29)	0
Hepatobiliary disorders								
Hyperbilirubinaemia	0	0	1 (33)	0	0	0	3 (43)	0
Psychiatric disorders								
Insomnia	0	0	0	0	1 (33)	0	2 (29)	0
Reproductive system and breast disorders								
Menstruation irregular	1 (25)	0	0	0	0	0	2 (29)	0

*: Adverse events reported by ≥2 subjects in any of the treatment groups

Serious adverse events were reported by 4 of 4 subjects (100%) in the P400 mg + L1000 mg group, 1 of 3 subjects (33%) in the P800 mg + L1000 mg group, 0 of 3 subjects (0%) in the P400 mg + L1500 mg group, and 2 of 7 subjects (29%) in the P600 mg + L1250 mg group. These were ileus (2 subjects, 50%), pericoronitis, urinary tract infection, headache, and syncope (1 subject each, 25%) in the P400 mg + L1000 mg group, dysuria and pyrexia (1 subject each, 33%) in the P800 mg + L1000 mg group, hepatic function abnormal, pneumonia, and liver function test abnormal (1 subject each, 14%) in the P600 mg + L1250 mg group. Of these serious adverse events, a causal relationship to pazopanib was not ruled out for hepatic function abnormal, pneumonia, and liver function test abnormal (1 subject each) reported in the P600 mg + L1250 mg group.

Adverse events leading to discontinuation of study treatment were reported by 1 of 4 subjects (25%) in the P400 mg + L1000 mg group, 1 of 3 subjects (33%) in the P800 mg + L1000 mg group,

0 of 3 subjects (0%) in the P400 mg + L1500 mg group, and 1 of 7 subjects (14%) in the P600 mg + L1250 mg group. Adverse events reported were ileus (1 subject, 25%) in the P400 mg + L1000 mg group, fatigue, ALT increased, and AST increased (1 subject each, 33%) in the P800 mg + L1000 mg group, and hepatic function abnormal and pneumonia (1 subject each, 14%) in the P600 mg + L1250 mg group. Of these adverse events, a causal relationship to pazopanib was not ruled out for fatigue, ALT increased, and AST increased (1 subject each) in the P800 mg + L1000 mg group, and hepatic function abnormal and pneumonia (1 subject each) in the P600 mg + L1250 mg group.

4.(iv).(2) Foreign phase II study (Study VEG20002)

Adverse events were reported by 138 of 142 subjects (97%), and adverse events for which a causal relationship to pazopanib can not be ruled out in 127 of 142 subjects (89%). Adverse events reported by ≥20% of subjects are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA 13.1)	Number of subjects (%)*	
	Pazopanib (N = 142)	
	All Grades	≥ Grade 3
Any event	138 (97)	73 (51)
Gastrointestinal disorders		
Diarrhoea	64 (45)	9 (6)
Nausea	59 (42)	2 (1)
Vomiting	49 (35)	4 (3)
Constipation	33 (23)	0
General disorders and administration site conditions		
Fatigue	82 (58)	21 (15)
Skin and subcutaneous tissue disorders		
Skin hypopigmentation	52 (37)	0
Vascular disorders		
Hypertension	60 (42)	10 (7)
Respiratory, thoracic and mediastinal disorders		
Cough	32 (23)	1 (<1)
Dyspnoea	31 (22)	7 (5)
Nervous system disorder		
Headache	29 (20)	3 (2)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	32 (23)	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour pain	51 (36)	12 (8)
Investigations		
Weight decreased	44 (31)	1 (<1)
Metabolism and nutrition disorders		
Decreased appetite	46 (32)	1 (<1)

*: Adverse events with an incidence of ≥20%

Serious adverse events were reported by 41 of 142 subjects (29%), and those reported by ≥2 subjects were pulmonary embolism and pneumothorax (5 subjects each, 4%), abdominal pain (4 subjects, 3%), diarrhoea, vomiting, general physical health deterioration, and hypertension (3 subjects each, 2%), and chest pain, fatigue, pyrexia, pneumonia, and back pain (2 subjects each, 1%). Of these serious adverse events, a causal relationship to pazopanib was not ruled out for

pulmonary embolism (5 subjects), hypertension (3 subjects), pneumothorax (2 subjects), abdominal pain, diarrhoea, vomiting, chest pain, fatigue, pyrexia, pneumonia, and general physical health deterioration (1 subject each).

No adverse events leading to discontinuation of pazopanib treatment were collected in Study VEG20002.

4.(iv).(3) Global phase III study (Study VEG110727)

Adverse events were reported by 237 of 240 subjects (99%) in the pazopanib group and 110 of 123 subjects (89%) in the placebo group, and adverse events for which a causal relationship to study drug can not be ruled out were reported by 219 of 240 subjects (91%) and 78 of 123 subjects (63%), respectively. Adverse events reported by ≥10% of subjects in any group are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA 13.1/J 13.1)	Number of subjects (%)*			
	Pazopanib (N = 240)		Placebo (N = 123)	
	All Grade	≥ Grade 3	All Grade	≥ Grade 3
Any event	237 (99)	149 (62)	110 (89)	34 (28)
Gastrointestinal disorders				
Diarrhoea	141 (59)	11 (5)	19 (15)	1 (<1)
Nausea	135 (56)	8 (3)	27 (22)	2 (2)
Vomiting	80 (33)	8 (3)	14 (11)	1 (<1)
Gastrointestinal pain	55 (23)	6(3)	11 (9)	5 (4)
Constipation	38 (16)	1 (<1)	21 (17)	3 (2)
Stomatitis	27 (11)	1 (<1)	4 (3)	0
General disorders and administration site conditions				
Fatigue	157 (65)	33 (14)	59 (48)	6 (5)
Oedema peripheral	33 (14)	5 (2)	11 (9)	2 (2)
Chest pain	25 (10)	4 (2)	7 (6)	0
Pyrexia	25 (10)	0	12 (10)	1 (<1)
Investigations				
Weight decreased	116 (48)	9 (4)	18 (15)	0
Ear, nose and throat examination abnormal	29 (12)	4 (2)	3 (2)	0
Skin and subcutaneous tissue disorders				
Hair colour changes	93 (39)	0	3 (2)	0
Exfoliative rash	44 (18)	1 (<1)	11 (9)	0
Alopecia	28 (12)	0	1 (<1)	0
Skin disorder	27 (11)	4 (2)	1 (<1)	0
Skin hypopigmentation	27 (11)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	48 (20)	15 (6)	21 (17)	8 (7)
Cough	41 (17)	1 (<1)	15 (12)	1 (<1)
Nervous system disorder				
Dysgeusia	66 (28)	0	4 (3)	0
Headache	56 (23)	2 (<1)	10 (8)	0
Dizziness	27 (11)	2 (<1)	5 (4)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	56 (23)	5 (2)	24 (20)	2 (2)

System Organ Class Preferred term (MedDRA 13.1/J 13.1)	Number of subjects (%)*			
	Pazopanib (N = 240)		Placebo (N = 123)	
	All Grade	≥ Grade 3	All Grade	≥ Grade 3
Myalgia	56 (23)	5 (2)	11 (9)	0
Vascular disorders				
Hypertension	101 (42)	16 (7)	7 (6)	0
Metabolism and nutrition disorders				
Decreased appetite	97 (40)	14 (6)	23 (19)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Tumour pain	70 (29)	20 (8)	26 (21)	10 (8)

*: Adverse events with an incidence of ≥10%

Serious adverse events were reported by 99 of 240 subjects (41%) in the pazopanib group and 29 of 123 subjects (24%) in the placebo group, and those reported by ≥2 subjects were dyspnoea (10 subjects, 4%), ALT increased (9 subjects, 4%), haemoglobin decreased (8 subjects, 3%), AST increased, γ-GTP increased, and pneumothorax (6 subjects each, 3%), fatigue, and left ventricular dysfunction (5 subjects each, 2%), pleural effusion, gastrointestinal pain, chest pain, tumor pain, and vomiting (4 subjects each, 2%), platelet count decreased, pneumonia, pulmonary embolism, thrombosis, and performance status decreased (3 subjects each, 1%), blood bilirubin increased, neutrophil percentage*, AST**, neutrophil count decreased, weight decreased, lung disorder, small intestinal obstruction, malignant pleural effusion, decreased appetite, dehydration, myalgia, renal failure, and febrile neutropenia (2 subjects each, <1%) in the pazopanib group, dyspnoea, pyrexia, and tumor pain (3 subjects each, 2%), haemoglobin decreased, lymphocyte percentage*, respiratory failure, and gastrointestinal pain (2 subjects each, 2%) in the placebo group. Of these serious adverse events, a causal relationship to study drug was not ruled out for ALT increased (8 subjects), AST increased, and pneumothorax (5 subjects each), left ventricular dysfunction, γ-GTP increased, and fatigue (4 subjects each), thrombosis, haemoglobin decreased, gastrointestinal pain, and vomiting (3 subjects each), blood bilirubin increased, weight decreased, and dyspnoea (2 subjects each), pneumonia, chest pain, pulmonary embolism, dehydration, AST**, and decreased appetite (1 subject each) in the pazopanib group, and the gastrointestinal pain and pyrexia (1 subject each) in the placebo group.

Adverse events leading to discontinuation of study treatment were reported by 48 of 240 subjects (20%) in the pazopanib group and 6 of 123 subjects (5%) in the placebo group. These were dyspnoea, ALT increased, and left ventricular dysfunction (4 subjects each, 2%), vomiting, fatigue, and hypertension (3 subjects each, 1%), depressed mood, nausea, small intestinal obstruction, and pericardial effusion (2 subjects each, <1%), lung disorder, pneumonitis, pneumothorax, AST**, AST increased, haemoglobin decreased, platelet count decreased, urine protein/creatinine ratio**, diarrhoea, dysphagia, upper gastrointestinal haemorrhage, chest pain, death, multi-organ failure, performance status decreased, myocardial infarction, sinus tachycardia, pulmonary embolism, thrombosis, haemorrhage, tumour pain, metastases to skin, dysgeusia, haemorrhage intracranial, headache, subarachnoid haemorrhage, insomnia, nephrotic syndrome, renal failure, thrombotic microangiopathy, pneumonia, radiation injury, myalgia, and skin ulcer (1 subject each, <1%) in the pazopanib group, and dyspnoea (2 subjects, 2%), pulmonary haemorrhage, blood bilirubin increased, ileus, chest pain, and tumour pain (1 subject each, <1%) in the placebo group. Of these adverse events, a causal relationship to study drug was not ruled out for ALT increased (4 subjects), hypertension, fatigue, vomiting, and left ventricular dysfunction (3 subjects each), depressed mood and nausea (2 subjects each), upper gastrointestinal haemorrhage, thrombotic microangiopathy, skin ulcer, dysgeusia, insomnia, headache, nephrotic syndrome, urine protein/creatinine ratio**, diarrhoea, radiation injury, metastases to skin, myalgia, multi-organ failure, AST**, subarachnoid haemorrhage, AST increased,

haemoglobin decreased, haemorrhage, myocardial infarction, haemorrhage intracranial, pneumonitis, thrombosis, and pneumothorax (1 subject each) in the pazopanib group, and pulmonary haemorrhage and dyspnoea (1 subject each) in the placebo group.

*: Term based on MedDRA 13.1. Reported as the value “decreased” in the CRF.

**:Term based on MedDRA 13.1. Reported as the value “increased” in the CRF.

4.(iv).(4) Foreign phase I study (Study VEG10003)

Adverse events were reported by 61 of 63 subjects (97%), and adverse events for which a causal relationship to pazopanib can not be ruled out were reported by 48 of 63 subjects (76%). Adverse events reported by ≥20% of subjects are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA 10.0/J 10.0)	Number of subjects (%)*	
	Pazopanib (N = 63)	
	All Grade	≥ Grade 3
Any event	61 (97)	29 (46)
Gastrointestinal disorders		
Nausea	30 (48)	1 (2)
Diarrhoea	28 (44)	3 (5)
Vomiting	19 (30)	0
Constipation	13 (21)	1 (2)
Skin and subcutaneous tissue disorders		
Hair colour changes	21 (33)	0
General disorders and administration site conditions		
Fatigue	21 (33)	2 (3)
Metabolism and nutrition disorders		
Inappetence	24 (38)	0
Vascular disorders		
Hypertension	22 (35)	12 (19)

*: Adverse events with an incidence of ≥20%

Serious adverse events were reported by 15 of 63 subjects (24%), including cellulites and, pneumonia (2 subjects each, 3%), bone pain, bradycardia, deep vein thrombosis, electrocardiogram change, extrapyramidal disorder, hypertension, impaired gastric emptying, intestinal obstruction, nausea, pain, pelvic venous thrombosis, pneumonia klebsiella, postoperative ileus, pulmonary embolism, pyrexia, spinal cord compression, and tumour haemorrhage (1 subject each, 2%). Of these serious adverse events, a causal relationship to pazopanib was not ruled out for extrapyramidal disorder, nausea, hypertension, bradycardia, tumour haemorrhage, pulmonary embolism, deep vein thrombosis, pelvic venous thrombosis, and electrocardiogram change (1 subject each).

Adverse events leading to discontinuation of pazopanib treatment were reported by 10 of 63 subjects (16%), including extrapyramidal disorder, spinal cord compression, deep vein thrombosis, hypertension, pelvic venous thrombosis, impaired gastric emptying, hyperbilirubinaemia, cellulitis, postoperative ileus, ALT increased, AST increased, blood ALP increased, blood bilirubin increased, tumour haemorrhage, proteinuria, and pulmonary embolism (1 subject each, 2%). Of these adverse events, a causal relationship to pazopanib was not ruled out for tumour haemorrhage, extrapyramidal disorder, pulmonary embolism, hyperbilirubinaemia, deep vein thrombosis, pelvic venous thrombosis, proteinuria, and hypertension (1 subject each).

4.(iv).(5) Foreign phase I study (Study VEG10004)

Adverse events were reported by 3 of 3 subjects (100%) in Part A and 7 of 7 subjects (100%) in Part B, and adverse events for which a causal relationship to pazopanib was not ruled out in 3 of 3 subjects (100%) and 3 of 7 subjects (43%), respectively.

Adverse events reported by ≥2 subjects in Part A were ALT increased (2 subjects, 67%), which was < Grade 3 in both subjects. Adverse events reported by ≥30% of subjects in Part B were fatigue (6 subjects, 86%), nausea (4 subjects, 57%), hypertension (3 subjects, 43%), and the adverse event of ≥ Grade 3 was hypertension (1 subject, Grade 3).

Serious adverse events were reported by 1 of 3 subjects (33%) in Part A and 1 of 7 subjects (14%) in Part B, including cholangitis and biliary stent occlusion (1 subject each, 33%) in Part A, and mental status changes and pain (1 subject each, 14%) in Part B. A causal relationship to pazopanib was not ruled out for all events.

No adverse events leading to discontinuation of study treatment were reported.

4.(iv).(6) Foreign phase I study (Study VEG10005)

Adverse events were reported by 2 of 6 subjects (33%) in the lead-in cohort, 13 of 28 subjects (46%) in the food effect cohort, 6 of 9 subjects (67%) in the crushed tablet cohort, and 26 of 26 subjects (100%) in Part 2, and adverse events for which a causal relationship to pazopanib can not be ruled out were reported by 1 of 6 subjects (17%), 5 of 28 subjects (18%), 3 of 9 subjects (33%), and 21 of 26 subjects (81%), respectively.

Adverse events reported by ≥20% of subjects were none in the food effect cohort, diarrhoea and atrial fibrillation (1 subject each, 17%) in the lead-in cohort, erythemia, vomiting, and fatigue (2 subjects each, 22%) in the crushed tablet cohort, fatigue (15 subjects, 58%), inappetence (12 subjects, 46%), nausea (8 subjects, 31%) and vomiting (6 subjects, 23%) in Part 2. No adverse events were Grade 3 or higher.

Serious adverse events were reported by 1 of 6 subjects (17%) in the lead-in cohort, 7 of 28 subjects (25%) in the food effect cohort, 0 of 9 subjects in the crushed tablet cohort, and 2 of 26 subjects (8%) in Part 2. Serious adverse events reported were atrial fibrillation (1 subject, 17%) in the lead-in cohort, atrial fibrillation and congestive heart failure (2 subjects each, 7%), gastrointestinal haemorrhage, nausea, urinary tract infection, injury, road traffic accident, myocardial infarction, and back pain (1 subject each, 3%) in the food effect cohort, and ALT increased, AST increased, and deep vein thrombosis (1 subject each, 4%) in Part 2. Of these serious adverse events, a causal relationship to pazopanib was not ruled out for atrial fibrillation (1 subject) in the lead-in cohort and ALT increased, AST increased, and deep vein thrombosis (1 subject each) in Part2.

Adverse events leading to discontinuation of pazopanib treatment were reported by 0 of 6 subjects in the lead-in cohort, 4 of 28 subjects (14%) in the food effect cohort, 0 of 9 subjects in the crushed tablet cohort, and 2 of 26 subjects (8%) in Part 2. These were myocardial infarction and atrial fibrillation (1 subject each, 3%) in the food effect cohort, and diarrhoea, fatigue, and AST increased (1 subject, 4%) in Part 2. Of these adverse events, a causal relationship to pazopanib was not ruled out for diarrhoea, fatigue, and AST increased (1 subject each) in Part 2.

4.(iv).(7) Foreign phase I study (Study MD1103367)

Adverse events were reported by 6 of 6 subjects (100%) in the pazopanib group and 2 of 3 subjects (67%) in the placebo group, and adverse events for which a causal relationship to study drug can not be ruled out in 5 of 6 subjects (83%) and 1 of 3 subjects (33%), respectively.

Adverse events reported by ≥2 subject were ALT increased and AST increased (3 subjects each, 50%), headache (2 subjects, 33%) in the pazopanib group and none in the placebo group.

No serious adverse events were reported.

Adverse events leading to discontinuation of study treatment were reported by 5 of 6 subjects (83%) in the pazopanib group and 0 of 3 subjects in the placebo group. These were AST increased (2 subjects), ALT increased (3 subjects), sinus arrest and blood pressure increased (1 subject each), and a causal relationship to study drug was not ruled out for none of them.

4.(iv).(8) Foreign phase II study (Study VEG20006)

Adverse events were reported by 21 of 21 subjects (100%), and adverse events for which a causal relationship to pazopanib can not be ruled out were reported in 18 of 21 subjects (86%). Adverse events reported by ≥20% of subjects are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1	
	Pazopanib (N = 21)	
	All Grades	≥ Grade 3
Any event	21 (100)	10 (48)
Musculoskeletal and connective tissue disorders		
Muscle spasms	7 (33)	0
Arthralgia	5 (24)	0
Back pain	5 (24)	1 (5)
Gastrointestinal disorders		
Nausea	9 (43)	1 (5)
Diarrhoea	7 (33)	0
General disorders and administration site conditions		
Fatigue	9 (43)	2 (10)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	5 (24)	0
Vascular disorders		
Hypertension	6 (29)	0

*1: Adverse events with an incidence of ≥20%, *2: MedDRA version is unknown

Serious adverse events were reported by 5 of 21 subjects (24%), including upper respiratory tract infection bacterial (2 subjects, 10%), pneumonia, nausea/vomiting, abdominal pain, hypocalcemia, polyneuropathy, and sepsis (1 subject each, 5%). Of these serious adverse events, nausea/vomiting (1 subject) was considered to be possibly related to pazopanib.

Adverse events leading to discontinuation of pazopanib treatment were reported by 3 of 21 subjects (14%), including nausea/vomiting, fatigue, and abdominal pain (1 subject each, 5%). Of these adverse events, nausea/vomiting and fatigue (1 subject each) were considered to be possibly related to pazopanib.

4.(iv).(9) Foreign phase I study (NCI-8063 [Study VEG110827])

Adverse events were reported by 23 of 23 subjects (100%) in the normal liver function group, 23 of 23 subjects (100%) in the mild hepatic impairment group, 19 of 19 subjects (100%) in the moderate hepatic impairment group, and 32 of 32 subjects (100%) in the severe hepatic impairment group, and adverse events for which a causal relationship to pazopanib can not be

ruled out in 23 of 23 subjects (100%), 23 of 23 subjects (100%), 19 of 19 subjects (100%), and 32 of 32 subjects (100%), respectively.

Adverse events reported by ≥20% of subjects were diarrhoea and fatigue (10 subjects each, 43%), hypertension (8 subjects, 35%), AST increased, inappetence, and hyperalbuminaemia (7 subjects each, 30%), vomiting (6 subjects, 26%), anaemia, abdominal pain, nausea, ALT increased, hyperglycaemia, and hyponatraemia (5 subjects each, 22%) in the normal liver function group, fatigue (13 subjects, 57%), diarrhoea (10 subjects, 43%), anaemia (9 subjects, 39%), ALT increased, alkaline phosphatase increased, blood bilirubin increased, nausea, vomiting, and proteinuria (8 subjects each, 35%), lymphocyte count decreased, white blood cell decreased, and hypertension (7 subjects each, 30%), AST increased (6 subjects, 26%), platelet count decreased, inappetence, and hyponatraemia (5 subjects each, 22%) in the mild hepatic impairment group, blood bilirubin increased (11 subjects, 58%), fatigue (10 subjects, 53%), alkaline phosphatase increased and nausea (8 subjects each, 42%), diarrhoea (7 subjects), AST increased, vomiting, inappetence, and hypertension (6 subjects each, 32%), anaemia and ALT increased (5 subjects each, 26%), abdominal pain, INR increased, and platelet count decreased (4 subjects each, 21%) in the moderate hepatic impairment group, and fatigue (18 subjects, 56%), blood bilirubin increased (17 subjects, 53%), AST increased (13 subjects, 41%), alkaline phosphatase increased (12 subjects, 38%), hypoalbuminaemia and hyponatraemia (11 subjects each, 34%), nausea and inappetence (9 subjects each, 28%) in the severe hepatic impairment group. Adverse events of ≥ Grade 3 were fatigue (4 subjects), vomiting, anaemia, and hyponatraemia (2 subjects each), diarrhoea, hyperglycaemia, hyperalbuminaemia, abdominal pain, ALT increased, inappetence, and hypertension (1 subject each) in the normal liver function group, alkaline phosphatase increased and AST increased (5 subjects each), ALT increased and blood bilirubin increased (4 subjects each), fatigue, nausea, vomiting, lymphocyte count decreased, hypertension (2 subjects each) and anaemia, inappetence, and hyponatraemia (1 subject each) in the mild hepatic impairment group, blood bilirubin increased (7 subjects), alkaline phosphatase increased (6 subjects), AST increased and ALT increased (4 subjects each), abdominal pain (3 subjects), fatigue, hypertension, vomiting, and nausea (2 subjects each), inappetence, INR increased, and platelet count decreased (1 subject each) in the moderate hepatic impairment group, blood bilirubin increased (16 subjects), alkaline phosphatase increased and hyponatraemia (10 subjects each), AST increased (9 subjects), hypoalbuminaemia (8 subjects), fatigue (7 subjects), inappetence (2 subjects) in the severe hepatic impairment group.

Serious adverse events were reported by 7 of 23 subjects (30%) in the normal liver function group, 9 of 23 subjects (39%) in the mild hepatic impairment group, 7 of 19 subjects (37%) in the moderate hepatic impairment group, and 20 of 32 subjects (63%) in the severe hepatic impairment group. These were anaemia, bilirubin increased, hyperglycaemia, sinus tachycardia, gallbladder obstruction, and hypoalbuminaemia (2 subjects each, 9%), dyspnoea, hyponatraemia, hypophosphataemia, and pneumonitis (1 subject each, 4%) in the normal liver function group, generalised muscle weakness, depressed level of consciousness, ALT increased, weight decreased, intra-abdominal haemorrhage, dehydration, hyperkalaemia, hyponatraemia, nausea, voice alteration, colitis, bilirubin increased, cardiac arrest due to haemorrhage, and dyspnoea (1 subject each, 4%) in the mild hepatic impairment group, dehydration, hypotension, pain, hyperkalaemia, nausea, vomiting, peritoneal infection, hypertension, bandaemia, upper gastrointestinal haemorrhage, weight decreased, bilirubin increased, ALP increased, cholangitis, ALT increased, AST increased, renal failure acute, dehydration, and blood infection (1 subject each, 5%) in the moderate hepatic impairment group, and bilirubin increased (9 subjects, 28%), anaemia, hyponatraemia, creatinine increased, biliary tract infection, hypoalbuminaemia, gallbladder infection, encephalopathy, and upper gastrointestinal haemorrhage (2 subjects each, 6%), dysgeusia, ALP increased, fatigue, generalised muscle weakness, confusion, renal failure acute, depressed level of consciousness, somnolence, dyspnoea,

pleural effusion, pericardial effusion, abdominal pain, and dehydration (1 subject each, 3%) in the severe hepatic impairment group. Of these serious adverse events, a causal relationship to pazopanib was not ruled out for anaemia, sinus tachycardia, hypoalbuminaemia, hypophosphataemia, and pneumonitis (1 subject each) in the normal liver function group, ALT increased, weight decreased, intra-abdominal haemorrhage, hyperkalaemia, hyponatraemia, voice alteration, and colitis (1 subject each) in the mild hepatic impairment group, hypertension, weight decreased, ALT increased, and AST increased (1 subject each) in the moderate hepatic impairment group, and dysgeusia, upper gastrointestinal haemorrhage, and fatigue (1 subject each) in the severe hepatic impairment group.

Adverse events leading to treatment discontinuation of pazopanib were reported by 4 of 23 subjects (17%) in the normal liver function group, 5 of 23 subjects (22%) in the mild hepatic impairment group, 3 of 19 subjects (16%) in the moderate hepatic impairment group, and 7 of 32 subjects (22%) in the severe hepatic impairment group. These were vomiting (2 subjects, 9%), extraocular muscle paresis, constipation, inappetence, fatigue, and abdominal pain (1 subject each, 4%) in the normal liver function group, confusion, creatinine increased, proteinuria, leptomeningeal disease, abdominal fistula, and bilirubin increased (1 subject each, 4%) in the mild hepatic impairment group, bilirubin increased (3 subjects, 16%), ascites, diarrhoea, nausea, abdominal pain, alkaline phosphatase increased, ALT increased, AST increased, and lymphopenia (1 subject each, 5%) in the moderate hepatic impairment group, and abdominal pain (2 subjects, 6%), bilirubin increased, creatinine increased, paracentesis, AST increased, and encephalopathy (1 subject each, 3%) in the severe hepatic impairment group. Of these adverse events, a causal relationship to pazopanib was not ruled out for vomiting and constipation (1 subject each) in the normal liver function group, creatinine increased and proteinuria (1 subject each) in the mild hepatic impairment group, diarrhoea, nausea, ALT increased, AST increased, bilirubin increased, and lymphopenia (1 subject each) in the moderate hepatic impairment group, and AST increased (1 subject) in the severe hepatic impairment group.

4.(iv).(10) Foreign phase IV study (Study VEG113971)

1) Arm A

Adverse events were reported by 11 of 21 subjects (52%) in the pazopanib group and 17 of 21 subjects (81%) in the pazopanib + ketoconazole group, and adverse events for which a causal relationship to study drug can not be ruled out were reported by 8 of 21 subjects (38%) and 13 of 21 subjects (62%), respectively.

Adverse events reported by ≥20% of subjects were nausea (5 subjects, 24%) in the pazopanib group, and hyperglycaemia (5 subjects, 24%) in the pazopanib + ketoconazole group. No adverse events were ≥ Grade 3.

No serious adverse events were reported.

Adverse events leading to discontinuation of study treatment were reported by 0 of 21 subjects in the pazopanib group and 4 of 21 subjects (19%) in the pazopanib + ketoconazole group. These were vomiting and hypertension (2 subjects each, 10%) in the pazopanib + ketoconazole group. Of these adverse events, a causal relationship to study drug was not ruled out for vomiting (2 subjects) and hypertension (1 subject).

2) Arm B

Adverse events were reported by 2 of 13 subjects (15%) in the pazopanib group, and 8 of 13 (62%) in the pazopanib + esomeprazole group, and adverse events for which a causal relationship to study drug can not be ruled out were reported by 2 of 13 subjects (15%) and 7 of 13 subjects (54%), respectively.

Adverse events reported by ≥20% of subjects were none in the pazopanib group, and hypertension (3 subjects, 23%) in the pazopanib + esomeprazole group. Of these adverse events, hypertension reported by 2 subjects was ≥ Grade 3.

Neither serious adverse events nor adverse events leading to discontinuation of study treatment were reported.

4.(iv).(11) Foreign phase I study (Study VEG10006)

Adverse events were reported by 6 of 6 subjects (100%) in the P500 mg + L750 mg group, 4 of 4 subjects (100%) in the P250 mg + L750 mg group, 3 of 3 subjects (100%) in the P250 mg + L1000 mg group, 4 of 4 subjects (100%) in the P500 mg + L1000 mg group, 6 of 6 subjects (100%) in the P250 mg + L1250 mg group, 7 of 7 subjects (100%) in the P400 mg + L1250 mg group, 3 of 3 subjects (100%) in the P200 mg + L1500 mg group, 7 of 7 subjects (100%) in the P400 mg + L1500 mg group, 18 of 18 subjects (100%) in the P400 mg + L1000 mg group, and 17 of 17 subjects (100%) in the P800 mg + L1500 mg group. Adverse events for which a causal relationship to study drug can not be ruled out were reported by 6 of 6 subjects (100%), 4 of 4 subjects (100%), 3 of 3 subjects (100%), 4 of 4 subjects (100%), 6 of 6 subjects (100%), 6 of 7 subjects (86%), 3 of 3 subjects (100%), 7 of 7 subjects (100%), 18 of 18 subjects (100%), and 15 of 17 subjects (88%), respectively. Adverse events reported by ≥40% of subjects in any group are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1									
	P500 mg + L750 mg (N = 6)		P250 mg + L750 mg (N = 4)		P250 mg + L1000 mg (N = 3)		P500 mg + L1000 mg (N = 4)		P250 mg + L1250 mg (N = 6)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	6 (100)	5 (83)	4 (100)	3 (75)	3 (100)	2 (67)	4 (100)	4 (100)	6 (100)	5 (83)
Gastrointestinal disorders										
Diarrhoea	5 (83)	2 (33)	2 (50)	1 (25)	3 (100)	2 (67)	3 (75)	1 (25)	3 (50)	1 (17)
Nausea	4 (67)	0	2 (50)	1 (25)	3 (100)	1 (33)	3 (75)	0	4 (67)	0
Vomiting	5 (83)	0	1 (25)	1 (25)	2 (67)	1 (33)	2 (50)	0	4 (67)	1 (17)
Abdominal pain	3 (50)	0	2 (50)	0	2 (67)	0	2 (50)	1 (25)	1 (17)	0
Constipation	3 (50)	0	0	0	0	0	2 (50)	0	1 (17)	0
Dyspepsia	1 (17)	0	0	0	2 (67)	0	2 (50)	0	1 (17)	0
Flatulence	1 (17)	0	3 (75)	0	1 (33)	0	0	0	0	0
Skin and subcutaneous tissue disorders										
Rash	2 (33)	0	0	0	1 (33)	0	1 (25)	0	3 (50)	0
Hair colour changes	3 (50)	0	1 (25)	0	1 (33)	0	3 (75)	0	1 (17)	0
General disorders and administration site conditions										
Fatigue	3 (50)	0	2 (50)	0	2 (67)	0	4 (100)	0	4 (67)	2 (33)
Metabolism and nutrition disorders										
Inappetence	3 (50)	0	0	0	2 (67)	0	4 (100)	0	2 (33)	0
Musculoskeletal and connective tissue disorders										
Muscle spasms	2 (33)	0	2 (50)	0	2 (67)	0	1 (25)	0	0	0

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1									
	P500 mg + L750 mg (N = 6)		P250 mg + L750 mg (N = 4)		P250 mg + L1000 mg (N = 3)		P500 mg + L1000 mg (N = 4)		P250 mg + L1250 mg (N = 6)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Back Pain	0	0	0	0	0	0	2 (50)	0	1 (17)	0
Nervous system disorder										
Headache	4 (67)	0	1 (25)	0	0	0	2 (50)	0	1 (17)	0
Dysgeusia	1 (17)	0	0	0	2 (67)	0	0	0	0	0
Investigations										
ALT increased	1 (17)	1 (17)	1 (25)	1 (25)	0	0	2 (50)	1 (25)	0	0

*1: Adverse events reported by ≥40% of subjects in any of the treatment groups, *2: MedDRA version number is unknown

Adverse events (continued)

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1									
	P400 mg + L1250 mg (N = 7)		P200 mg + L1500 mg (N = 3)		P400 mg + L1500 mg (N = 7)		P400 mg + L1000 mg (N = 18)		P800 mg + L1500 mg (N = 17)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	7 (100)	5 (71)	3 (100)	1 (33)	7 (100)	4 (57)	18 (100)	7 (39)	17 (100)	11 (65)
Gastrointestinal disorders										
Diarrhoea	5 (71)	0	2 (67)	0	4 (57)	1 (14)	15 (83)	1 (6)	12 (71)	3 (18)
Nausea	5 (71)	0	1 (33)	0	5 (71)	0	10 (56)	0	5 (29)	0
Vomiting	3 (43)	0	1 (33)	0	5 (71)	0	10 (56)	0	5 (29)	0
Skin and subcutaneous tissue disorders										
Rash	3 (43)	0	1 (33)	0	3 (43)	0	5 (28)	0	5 (29)	0
Hair colour changes	3 (43)	0	0	0	1 (14)	0	6 (33)	0	3 (18)	0
General disorders and administration site conditions										
Fatigue	4 (57)	0	0	0	2 (29)	0	5 (28)	0	10 (59)	3 (18)
Metabolism and nutrition disorders										
Inappetence	4 (57)	0	3 (100)	0	3 (43)	0	7 (39)	0	7 (41)	0
Musculoskeletal and connective tissue disorders										
Back Pain	2 (29)	0	2 (67)	0	0	0	1 (6)	0	2 (12)	0
Respiratory, thoracic and mediastinal disorders										
Dyspnoea	4 (57)	0	1 (33)	0	1 (14)	0	1 (6)	0	4 (24)	0
Cough	3 (43)	0	0	0	0	0	1 (6)	0	1 (6)	0
Investigations										
Weight decreased	1 (14)	0	0	0	0	0	5 (28)	0	7 (41)	0

*1: Adverse events reported by ≥40% of subjects in any of the treatment groups, *2: MedDRA version is unknown

Serious adverse events were reported by 1 of 6 subjects (17%) in the P500 mg + L750 mg group, 1 of 4 subjects (25%) in the P250 mg + L750 mg group, 2 of 3 subjects (67%) in the P250 mg + L1000 mg group, 2 of 4 subjects (50%) in the P500 mg + L1000 mg group, 2 of 6 subjects (33%) in the P250 mg + L1250 mg group, 3 of 7 subjects (43%) in the P400 mg + L1250 mg group, 2 of 7 subjects (29%) in the P200 mg + L1500 mg group, 3 of 7 subjects (43%) in the P400 mg +

L1500 mg group, 5 of 18 subjects (28%) in the P400 mg + L1000 mg group, and 8 of 17 subjects (47%) in the P800 mg + L1500 mg group. These were hypertension (1 subject, 17%) in the P500 mg + L750 mg group, pericardial effusion, pleural effusion, akathisia, nausea, and vomiting (1 subject each, 25%) in the P250 mg + L750 mg group, nausea, vomiting, abdominal pain, diarrhoea, and ileus (1 subject each, 33%) in the P250 mg + L1000 mg group, ureteric obstruction and haemoptysis (1 subject each, 25%) in the P500 mg + L1000 mg group, intestinal obstruction and subileus (1 subject each, 17%) in the P250 mg + L1250 mg group, pneumonia, metastases to central nervous system, and bile duct obstruction (1 subject each, 14%) in the P400 mg + L1250 mg, hyponatraemia and progressive disease (1 subject each, 14%) in the P200 mg + L1500 mg group, pyrexia (2 subjects, 29%), confusional state, somnolence, hyperbilirubinaemia, malaise, vomiting, dehydration, and renal failure (1 subject each, 14%) in the P400 mg + L1500 mg group, renal failure, deep vein thrombosis, diarrhoea, vomiting, pyrexia, upper gastrointestinal haemorrhage, and musculoskeletal chest pain (1 subject each, 6%) in the P400 mg + L1000 mg group, abdominal pain and tumour pain (2 subjects each, 12%), upper gastrointestinal haemorrhage, tumour haemorrhage, hepatic function abnormal, condition aggravated, hypertension, proteinuria, thrombocytopenia, diarrhoea, dyspnoea, fatigue, blood creatinine increased, and anal fistula (1 subject each, 6%) in the P800 mg + L1500 mg group. Of these serious adverse events, a causal relationship to study drug was not ruled out for hypertension (1 subject) in the P500 mg + L750 mg group, diarrhoea (1 subject) in the P250 mg + L1000 mg group, confusional state, somnolence, vomiting, and dehydration (1 subject each) in the P400 mg + L1500 mg group, diarrhoea and upper gastrointestinal haemorrhage (1 subject each) in the P400 mg + L1000mg group, hypertension, thrombocytopenia, upper gastrointestinal haemorrhage, diarrhoea, and abdominal pain (1 subject each) in the P800 mg + L1500 mg group.

Adverse events leading to discontinuation of study treatment were reported by 1 of 6 subjects (17%) in the P500 mg + L750 mg group, 2 of 4 subjects (50%) in the P250 mg + L750 mg group, 0 of 3 subjects in the P250 mg + L1000 mg group, 1 of 5 subjects (20%) in the P500 mg + L1000 mg group, 1 of 6 subjects (17%) in the P250 mg + L1250 mg group, 1 of 7 subjects (14%) in the P400 mg + L1250 mg group, 0 of 3 subjects in the P200 mg + L1 500 mg group, 2 of 7 subjects (29%) in the P400 mg + L1500 mg group, 2 of 18 subjects (11%) in the P400 mg + L1000 mg group, and 1 of 17 subjects (6%) in the P800 mg + L1500 mg group. These were metastases to central nervous system (1 subject, 17%) in the P500 mg + L750 mg group, ALT increased, AST increased, dyspnoea, pericardial effusion, and pleural effusion (1 subject each, 25%) in the P250 mg + L750 mg group, inappetence, fatigue, pain, vomiting, ALT increased, AST increased, and wound necrosis (1 subject each, 20%) in the P500 mg + L1000 mg group, vomiting, abdominal pain, nausea, and subileus (1 subject each, 17%) in the P250 mg + L1250 mg group, pneumonia, aphasia, ataxia, confusional state, hemiparesis, metastases to central nervous system, blood bilirubin increased, and bile duct obstruction (1 subject each, 14%) in the P400 mg + L1250 mg group, hyperbilirubinaemia and renal failure (1 subject each, 14%) in the P400 mg + L1500 mg group, deep vein thrombosis and upper gastrointestinal haemorrhage (1 subject each, 6%) in the P400 mg + L1000 mg group, and fatigue (2 subjects, 11%), upper gastrointestinal haemorrhage, nausea, abdominal pain, ALT increased, AST increased, diarrhoea, tumour haemorrhage, tumour pain, and progressive disease (1 subject each, 9%) in the P800 mg + L1500 mg group. Of these adverse events, a causal relationship to study drug was not ruled out for ALT increased and AST increased (1 subject each) in the P250 mg + L750 mg group, ALT increased, AST increased, and wound necrosis (1 subject each) in the P500 mg + L1000 mg group, hyperbilirubinaemia (1 subject) in the P400 mg + L1500 mg group, upper gastrointestinal haemorrhage (1 subject) in the P400 mg + L1000 mg group, fatigue, upper gastrointestinal haemorrhage, nausea, abdominal pain, ALT increased, AST increased, and diarrhoea (1 subject each) in the P800 mg + L1500 mg group.

4.(iv).(12) Foreign phase I study (Study VEG10007)

Adverse events were reported by 11 of 24 subjects (46%) in the period when CYP substrates*

were administered, and 22 of 23 subjects (96%) in the period when pazopanib was administered. Of these, adverse events for which a causal relationship to study drug can not be ruled out were reported by 6 of 24 subjects (25%) and 21 of 23 subjects (91%), respectively. Adverse events reported by ≥3 subjects in either period are shown in the following table.

*: Midazolam and a mixed solution of caffeine, omeprazole, dextromethorphan, and warfarin

Adverse events

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1			
	CYP substrates dosing period*3 (N = 24)		Pazopanib dosing period*4 (N = 23)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	11 (46)	5 (21)	22 (96)	12 (52)
Gastrointestinal disorders				
Diarrhoea	1 (4)	0	12 (52)	1 (4)
Nausea	2 (8)	0	5 (22)	0
Vomiting	0	0	6 (26)	0
Abdominal distension	0	0	3 (13)	0
Vascular disorders				
Hypertension	0	0	16 (70)	1 (4)
General disorders and administration site conditions				
Fatigue	0	0	15 (65)	0
Pyrexia	3 (13)	0	3 (13)	0
Skin and subcutaneous tissue disorders				
Hair colour changes	0	0	7 (30)	0
Rash	0	0	6 (26)	0
Skin depigmentation	0	0	5 (22)	0
Blister	0	0	3 (13)	0
Dry skin	0	0	3 (13)	0
Investigations				
Blood bilirubin increased	0	0	5 (22)	0
AST increased	0	0	4 (17)	0
Blood alkaline phosphatase increased	1 (4)	0	3 (13)	1 (4)
Blood and lymphatic system disorders				
Anaemia	0	0	4 (17)	1 (4)
Neutropenia	0	0	3 (13)	0
Metabolism and nutrition disorders				
Inappetence	0	0	5 (22)	0
Hyponatraemia	0	0	3 (13)	2 (9)
Nervous system disorders				
Dizziness	0	0	3 (13)	0

*1: Adverse events reported by ≥3 subjects in either period, *2: MedDRA version is unknown, *3: Day 1 to 5 in Part 1, *4: Day 6 to 28 in Part 1, and Part 2

Serious adverse events were reported by 1 of 24 subjects (4%) in the CYP substrates dosing period, and 10 of 23 subjects (43%) in the pazopanib dosing period. These were pleural effusion and sepsis (1 subject each, 4%) in the CYP substrates dosing period, and hyponatraemia (2 subjects, 9%), upper gastrointestinal haemorrhage, hepatic failure, performance status decreased, lower respiratory tract infection, pneumonia, urinary tract infection, hypoglycaemia, dengue fever, pancreatitis, abdominal adhesions, hyperbilirubinaemia (1 subject each, 4%) in the pazopanib

dosing period. Of these adverse events, a causal relationship to study drug was not ruled out for hyponatraemia (2 subjects), performance status decreased and pancreatitis (1 subject each) in the pazopanib dosing period.

Adverse events leading to discontinuation of study treatment were reported by 1 of 24 subjects (4%) in the CYP substrates dosing period, and 5 of 23 subjects (22%) in the pazopanib dosing period. These were pleural effusion and sepsis (1 subject each) in the CYP substrates dosing period and hyponatraemia (2 subjects), upper gastrointestinal haemorrhage, abdominal distension, hepatic failure, performance status decreased, pneumonia (1 subject each) in the pazopanib dosing period. Of these adverse events, a causal relationship to study drug was not ruled out for hyponatraemia (2 subjects) and performance status decreased (1 subject) in the pazopanib dosing period.

4.(iv).(13) Foreign phase I study (Study VEG105427)

Adverse events were reported by 3 of 3 subjects (100%) in the paclitaxel 15 mg/m^2 + pazopanib 400 mg group, 3 of 3 subjects (100%) in the paclitaxel 15 mg/m^2 + pazopanib 800 mg group, 3 of 3 subjects (100%) in the paclitaxel 50 mg/m^2 + pazopanib 800 mg group, and 17 of 17 subjects (100%) in the paclitaxel 80 mg/m^2 + pazopanib 800 mg group, and adverse events for which a causal relationship to study drug can not be ruled out were reported by 2 of 3 subjects (67%), 3 of 3 subjects (100%), 3 of 3 subjects (100%) and 16 of 17 subjects (94%), respectively. Adverse events reported by ≥40% of subjects in any group are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1							
	Paclitaxel 15 mg/m^2 + Pazopanib 400 mg (N = 3)		Paclitaxel 15 mg/m^2 + Pazopanib 800 mg (N = 3)		Paclitaxel 50 mg/m^2 + Pazopanib 800 mg (N = 3)		Paclitaxel 80mg/m^2 + Pazopanib 800 mg (N = 17)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	3 (100)	2 (67)	3 (100)	3 (100)	3 (100)	2 (67)	17 (100)	13 (76)
Gastrointestinal disorders								
Diarrhoea	1 (33)	0	3 (100)	1 (33)	2 (67)	1 (33)	10 (59)	0
Nausea	2 (67)	0	2 (67)	0	2 (67)	0	12 (71)	1 (6)
Vomiting	1 (33)	0	3 (100)	0	1 (33)	0	8 (47)	1 (6)
General disorders and administration site conditions								
Fatigue	1 (33)	0	0	0	3 (100)	0	14 (82)	0
Skin and subcutaneous tissue disorders								
Alopecia	0	0	0	0	0	0	9 (53)	0
Rash	1 (33)	0	1 (33)	0	0	0	9 (53)	0
Musculoskeletal and connective tissue disorders								
Arthralgia	0	0	0	0	2 (67)	0	4 (24)	1 (6)
Respiratory, thoracic and mediastinal disorders								
Cough	0	0	0	0	3 (100)	0	3 (18)	0
Epistaxis	0	0	2 (67)	0	0	0	4 (24)	0
Metabolism and nutrition disorders								
Inappetence	1 (33)	0	1 (33)	0	1 (33)	0	7 (41)	1 (6)

*1: Adverse events with an incidence of ≥40% in any of the treatment groups, *2: MedDRA version is unknown

Serious adverse events were reported by 2 of 3 subjects (67%) in the paclitaxel 15 mg/m^2 + pazopanib 400 mg group, 1 of 3 subjects (33%) in the paclitaxel 15 mg/m^2 + pazopanib 800 mg group, 1 of 3 subjects (33%) in the paclitaxel 50 mg/m^2 + pazopanib 800 mg group, and

7 of 17 subjects (41%) in the paclitaxel 80 mg/m^2 + pazopanib 800 mg group. These were cerebrovascular accident, hydronephrosis, hypokalaemia, and small intestinal obstruction (1 subject each, 33%) in the paclitaxel 15 mg/m^2 + pazopanib 400 mg group, diarrhoea (1 subject, 33%) in the paclitaxel 15 mg/m^2 + pazopanib 800 mg group, abdominal distension and dyspnoea (1 subject each, 33%) in the paclitaxel 50 mg/m^2 + pazopanib 800 mg group, hepatitis acute, oesophageal obstruction, groin abscess, ascites, abdominal pain, back pain, convulsion, and gastrointestinal haemorrhage (1 subject each, 6%) in the paclitaxel 80 mg/m^2 + pazopanib 800 mg group. Of these adverse events, a causal relationship to study drug was not ruled out for hepatitis acute, groin abscess, and gastrointestinal haemorrhage (1 subject each) in the paclitaxel 80 mg/m^2 + pazopanib 800 mg group.

Adverse events leading to discontinuation of study treatment were reported by 1 of 3 subjects (33%) in the paclitaxel 15 mg/m^2 + pazopanib 400 mg group, 1 of 3 subjects (33%) in the paclitaxel 50 mg/m^2 + pazopanib 800 mg group, and 4 of 17 subjects (24%) in the paclitaxel 80 mg/m^2 + pazopanib 800 mg group. These were small intestinal obstruction (1 subject, 33%) in the paclitaxel 15 mg/m^2 + pazopanib 400 mg group, abdominal distension and dyspnoea (1 subject each, 33%) in the paclitaxel 50 mg/m^2 + pazopanib 800 mg group, and groin abscess, ascites, ALT increased, and gastrointestinal haemorrhage (1 subject each, 6%) in the paclitaxel 80 mg/m^2 + pazopanib 800 mg group. Of these adverse events, a causal relationship to study drug was not ruled out for groin abscess, ALT increased, and gastrointestinal haemorrhage (1 subject each) in the paclitaxel 80 mg/m^2 + pazopanib 800 mg group.

4.(iv).(14) Foreign Phase I/II Study (Study VEG102857)

1) Phase I

Adverse events were reported by 4 of 4 subjects (100%) in the pazopanib 200 mg + lapatinib 1500 mg group, 6 of 6 subjects (100%) in the pazopanib 800 mg + lapatinib 1500 mg group, 5 of 5 subjects (100%) in the pazopanib 800 mg + lapatinib 500 mg BID group, 6 of 7 subjects (86%) in the pazopanib 800 mg + lapatinib 750 mg BID group, 6 of 6 subjects (100%) in the pazopanib 800 mg + lapatinib 1000 mg BID group, and 6 of 6 subjects (100%) in the pazopanib 600 mg BID + lapatinib 1000 mg BID group. Adverse events for which a causal relationship to study drug can not be ruled out were reported by 2 of 4 subjects (50%), 6 of 6 subjects (100%), 4 of 5 subjects (80%), 4 of 7 subjects (57%), 6 of 6 subjects (100%), and 6 of 6 subjects (100%), respectively. Adverse events reported by ≥2 subjects in any group are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA[*2]/J 13.1)	Number of subjects (%)[*1]					
	Pazopanib 200 mg QD + Lapatinib 1500 mg QD (N = 4)		Pazopanib 800 mg QD + Lapatinib 1500 mg QD (N = 6)		Pazopanib 800 mg QD + Lapatinib 500 mg BID (N = 5)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	4 (100)	3(75)	6 (100)	5 (83)	5 (100)	3(60)
Gastrointestinal disorders						
Constipation	1 (25)	0	2 (33)	0	0	0
Diarrhoea	0	0	3 (50)	0	2 (40)	0
Nausea	0	0	3 (50)	0	2 (40)	1 (20)
Nervous system disorders						
Aphasia	0	0	2 (33)	1 (17)	0	0
Convulsion	0	0	1 (17)	0	2 (40)	0
Headache	2 (50)	1 (25)	3 (50)	0	1 (20)	0
General disorders and administration site conditions						
Fatigue	2 (50)	0	3 (50)	0	1 (20)	0

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1					
	Pazopanib 200 mg QD + Lapatinib 1500 mg QD (N = 4)		Pazopanib 800 mg QD + Lapatinib 1500 mg QD (N = 6)		Pazopanib 800 mg QD + Lapatinib 500 mg BID (N = 5)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Investigations						
AST increased	1 (25)	0	2 (33)	2 (33)	2 (40)	0
ALT increased	0	0	2 (33)	0	1 (20)	0
Vascular disorders						
Hypertension	0	0	3 (50)	0	0	0
Eye disorders						
Vision blurred	0	0	1 (17)	0	3 (60)	0
Musculoskeletal and connective tissue disorders						
Muscular weakness	0	0	2 (33)	1 (17)	1 (20)	0
Psychiatric disorders						
Insomnia	1 (25)	0	2 (33)	0	0	0

*1: Adverse events reported by ≥2 subjects in any of the treatment groups, *2: MedDRA version is unknown

Adverse events (continued)

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1					
	Pazopanib 800 mg QD + Lapatinib 750 mg BID (N = 7)		Pazopanib 800 mg QD + Lapatinib 1000 mg BID (N = 6)		Pazopanib 600 mg BID + Lapatinib 1000 mg BID (N = 6)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	6 (86)	5 (71)	6 (100)	5 (83)	6 (100)	4 (67)
Gastrointestinal disorders						
Diarrhoea	3 (43)	0	6 (100)	1 (17)	6 (100)	0
Nausea	0	0	3 (50)	0	3 (50)	0
Vomiting	0	0	3 (50)	1 (17)	1 (17)	0
Nervous system disorders						
Headache	0	0	4 (67)	2 (33)	0	0
Peripheral sensory neuropathy	0	0	2 (33)	0	0	0
General disorders and administration site conditions						
Fatigue	3 (43)	0	3 (50)	1 (17)	6 (100)	1 (17)
Investigations						
ALT increased	1 (14)	0	0	0	2 (33)	0
Vascular disorders						
Hypertension	0	0	2 (33)	0	4 (67)	0
Eye disorders						
Vision blurred	0	0	2 (33)	0	3 (50)	0
Skin and subcutaneous tissue disorders						
Rash	1 (14)	0	1 (17)	0	3 (50)	0
Blood and lymphatic system disorders						
Neurtopenia	0	0	2 (33)	2 (33)	1 (17)	1 (17)
Thrombocytopenia	1 (14)	1 (14)	2 (33)	1 (17)	1 (17)	0

*1: Adverse events reported by ≥2 subjects in any of the treatment groups, *2: MedDRA version is unknown

Serious adverse events were reported by 1 of 4 subjects (25%) in the pazopanib 200 mg QD + lapatinib 1500 mg QD group, 4 of 6 subjects (67%) in the pazopanib 800 mg QD + lapatinib

1500 mg QD group, 2 of 5 subjects (40%) in the pazopanib 800 mg QD + lapatinib 500 mg BID group, 3 of 7 subjects (43%) in the pazopanib 800 mg QD + lapatinib 750 mg BID group, 3 of 6 subjects (50%) in the pazopanib 800 mg QD + lapatinib 1000 mg BID group, and 2 of 6 subjects (33%) in the pazopanib 600 mg BID + lapatinib 1000 mg BID group. These were aspiration (1 subject, 25%) in the pazopanib 200 mg QD + lapatinib 1500 mg QD group, hemiparesis, ALT increased, AST increased, transaminases increased, lobar pneumonia, pneumonia streptococcal, and hyperglycaemia (1 subject each, 17%) in the pazopanib 800 mg QD + lapatinib 1500 mg QD group, nausea, vomiting, diarrhoea, femoral neck fracture, pubis fracture, and muscular weakness (1 subject each, 20%) in the pazopanib 800 mg QD + lapatinib 500 mg BID group, pyrexia, convulsion, and brain herniation (1 subject each, 14%) in the pazopanib 800 mg QD + lapatinib 750 mg BID group, nausea, vomiting, fatigue, syncope, dyspnoea, and tumour haemorrhage (1 subject each, 17%) in the pazopanib 600 mg BID + lapatinib 1000 mg BID group, and confusional state (2 subjects, 33%), vomiting, fatigue, pyrexia, diarrhoea, headache, thrombocytopenia, and hypothyroidism (1 subject each, 17%) in the pazopanib 800 mg QD + lapatinib 1000 mg BID group. Of these serious adverse events, a causal relationship to study drug was not ruled out for transaminases increased (1 subject) in the pazopanib 800 mg QD + lapatinib 1500 mg group, thrombocytopenia, diarrhoea, and hypothyroidism (1 subject each) in the pazopanib 800 mg QD + lapatinib 1000 mg BID group, and nausea, vomiting, fatigue, dyspnoea, syncope, and tumour haemorrhage (1 subject each) in the pazopanib 600 mg BID + lapatinib 1000 mg BID group.

Adverse events leading to discontinuation of study treatment were reported by 0 of 4 subjects in the pazopanib 200 mg QD + lapatinib 1500 mg QD group, 1 of 6 subjects (17%) in the pazopanib 800 mg QD + lapatinib 1500 mg QD group, 1 of 5 subjects (20%) in the pazopanib 800 mg QD + lapatinib 500 mg BID group, 0 of 7 subjects in the pazopanib 800 mg QD + lapatinib 750 mg BID group, 2 of 6 subjects (33%) in the pazopanib 800 mg QD + lapatinib 1000 mg BID group, and 2 of 6 subjects (33%) in the pazopanib 600 mg BID + lapatinib 1000 mg BID group. Adverse events reported were pneumonia streptococcal (1 subject, 17%) in the pazopanib 800 mg QD + lapatinib 1500 mg QD group, ALT increased (1 subject, 20%) in the pazopanib 800 mg QD + lapatinib 500 mg BID group, diarrhoea, fatigue, confusional state, headache, pyrexia, thrombocytopenia, and vomiting (1 subject each, 17%) in the pazopanib 800 mg QD + lapatinib 1000 mg BID group, and dyspnoea, fatigue, nausea, vomiting, syncope, and tumour haemorrhage (1 subject each, 17%) in the pazopanib 600 mg BID + lapatinib 1000 mg BID group. Of these serious adverse events, a causal relationship to study drug was not ruled out for diarrhoea (1 subject) in the pazopanib 800 mg QD + lapatinib 1000 mg BID group, ALT increased (1 subject) in the pazopanib 800 mg QD + lapatinib 500 mg BID group, dyspnoea, fatigue, nausea, vomiting, syncope, and tumour haemorrhage (1 subject each) in the pazopanib 600 mg BID + lapatinib 1000 mg BID group.

2) Phase II

Adverse events were reported by 18 of 19 subjects (95%) in the biomarker positive group and 22 of 22 subjects (100%) in the biomarker negative group, and adverse events for which a causal relationship to pazopanib can not be ruled out in 16 of 19 subjects (84%) and 19 of 22 subjects (86%), respectively. Adverse events reported by ≥20% of subjects in either group are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA*2/J 13.1)	Number of subjects (%)*1			
	Biomarker positive group (N = 19)		Biomarker negative group (N = 22)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
AAny event	18 (95)	12 (63)	22 (100)	13 (59)
Gastrointestinal disorders				
Diarrhoea	12 (63)	1 (5)	14 (64)	1 (5)
Nausea	5 (26)	0	3 (14)	1 (5)
Nervous system disorder				
Headache	7 (37)	0	8 (36)	1 (5)
Convulsion	3 (16)	1 (5)	7 (32)	4 (18)
Peripheral sensory neuropathy	3 (16)	0	5 (23)	1 (5)
Amnesia	5 (26)	0	1 (5)	0
General disorders and administration site conditions				
Fatigue	11 (58)	1 (5)	10 (45)	3 (14)
Skin and subcutaneous tissue disorders				
Rash	8 (42)	1 (5)	4 (18)	0
Dermatitis acneiform	1 (5)	0	5 (23)	0
Psychiatric disorders				
Confusional state	5 (26)	1 (5)	4 (18)	0
Metabolism and nutrition disorders				
Hyperglycaemia	3 (16)	1 (5)	6 (27)	0
Blood and lymphatic system disorders				
Lymphopenia	5 (26)	4 (21)	6 (27)	3 (14)
Vascular disorders				
Hypertension	3 (16)	1 (5)	9 (41)	1 (5)
Eye disorders				
Vision blurred	1 (5)	1 (5)	5 (23)	0

*1: Adverse events reported by ≥20% of subjects in either of the treatment groups, *2: MedDRA version is unknown

Serious adverse events were reported by 6 of 19 subjects (32%) in the biomarker positive group, and 8 of 22 subjects (36%) in the biomarker negative group. These were pancreatitis (2 subjects, 11%), convulsion, pulmonary embolism, speech disorder, confusional state, mental status changes, mood altered, and pneumonitis (1 subject each, 5%) in the biomarker positive group, and convulsion (4 subjects, 18%), pulmonary embolism, cerebral haemorrhage, partial seizures, abdominal pain, infection, pneumonia, asthenia, fatigue, ALT increased, AST increased, and deep vein thrombosis (1 subject each, 5%) in the biomarker negative group. Of these serious adverse events, a causal relationship to study drug was not ruled out for pancreatitis (2 subjects) and pneumonitis (1 subject) in the biomarker positive group, and ALT increased, AST increased, deep vein thrombosis, pulmonary embolism, asthenia, convulsion, fatigue, and cerebral haemorrhage (1 subject each) in the biomarker negative group.

Adverse events leading to discontinuation of study treatment were reported by 3 of 19 subjects (17%) in the biomarker positive group, and 2 of 22 subjects (9%) in the biomarker negative group. These were diarrhoeal haemorrhage, mood altered, and pulmonary embolism (1 subject each, 6%) in the biomarker positive group, and abdominal pain and convulsion (1 subject each, 5%) in the biomarker negative group. Of these adverse events, a causal relationship to study drug was not ruled out for diarrhoeal haemorrhage (1 subject) in the biomarker positive group.

4.(iv).(15) Foreign phase II study (Study VEG102616)

Adverse events were reported by 221 of 225 subjects (98%), and adverse events for which a causal relationship to pazopanib can not be ruled out in 215 of 225 subjects (96%). Adverse events reported by ≥20% of subjects are shown in the following table.

Adverse events

System Organ Class Preferred term (MedDRA 11.0/J 13.1)	Number of subjects (%)*	
	Pazopanib (N = 225)	
	All Grade	≥ Grade 3
Any event	221 (98)	124 (55)
Gastrointestinal disorders		
Diarrhoea	142 (63)	9 (4)
Nausea	94 (42)	2 (<1)
Vomiting	45 (20)	2 (<1)
Skin and subcutaneous tissue disorders		
Hair colour changes	97 (43)	0
General disorders and administration site conditions		
Fatigue	103 (46)	12 (5)
Nervous system disorders		
Dysgeusia	54 (24)	0
Headache	44 (20)	0
Vascular disorders		
Hypertension	93 (41)	20 (9)
Metabolism and nutrition disorders		
Inappetence	54 (24)	2 (<1)

*: Adverse events reported by ≥20% of subjects in any of the treatment groups

Serious adverse events were reported by 74 of 225 subjects (33%), and those reported by ≥2 subjects were pleural effusion (5 subjects, 2%), pulmonary embolism (4 subjects, 2%), abdominal pain, dyspnoea, dehydration, and ALT increased (3 subjects each, 1%), diarrhoea, gastrointestinal haemorrhage, large intestine perforation, vomiting, pneumothorax, hyponatraemia, chest pain, fatigue, intervertebral disc protrusion, transient ischaemic attack, AST increased, hypertension, and confusional state (2 subjects each, <1%). Of these serious adverse events, a causal relationship to pazopanib was not ruled out for ALT increased (3 subjects), hypertension, gastrointestinal haemorrhage, AST increased, pulmonary embolism, and hyponatraemia (2 subjects each), large intestine perforation, abdominal pain, vomiting, pneumothorax, and fatigue (1 subject each).

Adverse events leading to discontinuation of pazopanib were reported by 34 of 225 subjects (15%) and those reported by ≥2 subject were ALT increased (6 subjects, 3%), AST increased (4 subjects, 2%), dyspnoea (3 subjects, 1%), large intestine perforation, asthenia, fatigue, general physical health deterioration, and γ-GTP increased (2 subjects each, <1%). A causal relationship to pazopanib was ruled out for none of these adverse events.

4.(iv).(16) Foreign phase I study (Study VEG111485)

Adverse events were reported by 10 of 24 subjects (42%), 18 of 24 subjects (75%), 13 of 24 subjects (54%), and 17 of 24 subjects (71%) in Sequences 1, 2, 3, and 4*, respectively, and adverse events for which a causal relationship to study drug can not be ruled out in 6 of 24 subjects (25%), 15 of 24 subjects (63%), 7 of 24 subjects (29%), and 13 of 24 subjects (54%), respectively. Adverse events reported by ≥2 subjects in any group are shown in the following table.

*: Sequence 1: Day 1, placebo for moxifloxacin; Days 2 to 8, placebo for pazopanib

800 mg; Day 9, placebo for pazopanib 1600 mg
Sequence 2: Day 1, placebo for moxifloxacin; Days 2 to 8, pazopanib 800 mg; Day 9, pazopanib 1600 mg
Sequence 3: Day 1, moxifloxacin 400 mg; Days 2 to 8, placebo for pazopanib 800 mg; Day 9, placebo for pazopanib 1600 mg
Sequence 4: Day 1, moxifloxacin 400 mg; Days 2 to 8, pazopanib 800 mg; Day 9, pazopanib 1600 mg

Adverse events

System Organ Class Preferred term (MedDRA 10.0/J 13.1)	Number of subjects (%)*							
	Sequence 1 (N = 24)		Sequence 2 (N = 24)		Sequence 3 (N = 24)		Sequence 4 (N = 24)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any event	7 (29)	0	16 (67)	6 (25)	9 (38)	2 (8)	12 (50)	0
Gastrointestinal disorders								
Abdominal pain	0	0	2 (8)	0	0	0	0	0
Constipation	0	0	0	0	0	0	2 (8)	0
Frequent bowel movements	0	0	0	0	2 (8)	0	0	0
Haematochezia	0	0	0	0	2 (8)	0	0	0
Nausea	3 (13)	0	9 (38)	0	3 (6)	0	4 (17)	0
Diarrhoea	0	0	2 (8)	0	0	0	3 (13)	0
Vomiting	0	0	4 (17)	0	0	0	0	0
General disorders and administration site conditions								
Fatigue	2 (8)	0	8 (33)	0	3 (13)	0	6 (25)	0
Dysgeusia	2 (8)	0	0	0	0	0	0	0
Decreased appetite	0	0	0	0	0	0	3 (13)	0
Pyrexia	0	0	2 (8)	0	0	0	0	0
Metabolism and nutrition disorders								
Hyponatraemia	2 (8)	0	0	0	2 (8)	1 (4)	0	0
Decreased appetite	0	0	5 (21)	1 (4)	0	0	0	0
Nervous system disorder								
Dizziness	0	0	2 (8)	0	0	0	0	0
Paraesthesia	0	0	2 (8)	0	2 (8)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	2 (8)	0	2 (8)	0	0	0	0	0
Dysphonia	0	0	2 (8)	0	0	0	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	2 (8)	0	0	0	0	0	0	0
Back Pain	0	0	2 (8)	0	2 (8)	1 (4)	0	0
Investigations								
ALT increased	0	0	2 (8)	0	0	0	0	0
AST increased	0	0	2 (8)	2 (8)	0	0	0	0
Weight decreased	0	0	5 (21)	0	0	0	0	0
Vascular disorders								
Hypertension	0	0	6 (25)	3 (13)	0	0	0	0

*: Adverse events reported by ≥2 subjects in any of the treatment groups

Serious adverse events in Sequences 1, 2, 3, and 4 were reported by 1 of 24 subjects (4%), 1 of

24 subjects (4%), 1 of 24 subjects (4%), and 0 of 24 subjects, respectively. Serious adverse events reported were pulmonary haemorrhage in Sequence 1, upper gastrointestinal haemorrhage, cholestasis, biliary tract infection, ALT increased, AST increased, blood alkaline phosphatase increased, and blood bilirubin increased in Sequence 2, and back pain in Sequence 3. Of these serious adverse events, a causal relationship to study drug was not ruled out for pulmonary haemorrhage (1 subject, 4%) in Sequence 1.

Adverse event leading to discontinuation of study treatment was reported by 1 of 24 subjects (4%) in Sequence 3 only, which was an ear haemorrhage, and a causal relationship to study drug was ruled out.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of pazopanib in patients with soft tissue sarcoma has been demonstrated and its safety is acceptable based on the observed clinical benefit. Pazopanib is a drug with a new active ingredient, which inhibits tyrosine kinases, such as vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and stem cell factor receptor. Pazopanib has a clinical significance as one of the therapeutic options for soft tissue sarcoma. The proposed indication etc. will be further discussed at the Expert Discussion.

PMDA considers that pazopanib may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

August 28, 2012

I. Product Submitted for Registration

[Brand name]	Votrient Tablets 200 mg
[Non-proprietary name]	Pazopanib Hydrochloride
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	December 13, 2011

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

As a result of the review described in the Review Report (1) "4.(iii).B.(2) Efficacy," PMDA concluded that pazopanib hydrochloride (pazopanib) is expected to be effective in patients with metastatic soft tissue sarcoma progressed following prior chemotherapy because pazopanib prolonged progression-free survival (PFS), primary endpoint, in the global phase III study (Study VEG110727). In Study VEG110727, the primary analysis plan was changed, and the revised analysis plan was described only in the Statistical Analysis Plan. The protocol should also have been revised accordingly because the definition of PFS event, which was the primary endpoint, was changed and this is related to the reliability of the conclusion of the confirmatory Study VEG110727. Treatment with pazopanib, however, is expected to prolong PFS because the results obtained from all analyses, including those specified in the protocol, were consistent in Study VEG110727.

As a result of the review described in the Review Report (1) "4.(iii).B.(2).4) Efficacy by tumor histology," PMDA determined that it is difficult to judge the efficacy of pazopanib by each histology subtype because of the limited number of patients with each histology subtype.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors and the following comments were raised by the expert advisors:

- In Study VEG110727, the median OS [95% confidence interval (CI)] (months) tended to be longer in the placebo group (21.6 [6.6, 25.4]) than in the pazopanib group (8.7 [5.7, 14.6]) in the subgroup analysis for synovial sarcoma. However, the sample size of this subgroup was very small, and thus the hazard ratio was 1.62 with a large range of 95% CI, [0.79, 3.33]. It is therefore difficult to evaluate the effect of pazopanib on vital prognosis in patients with synovial sarcoma, based only on the above tendency.

(2) Safety

Based on the clinical study data submitted, PMDA determined that adverse events requiring attention during treatment with pazopanib were hepatic function disorder, hypertension, cardiac and vascular events (including venous thrombotic events), haemorrhagic events, pneumothorax, thyroid function abnormal, gastrointestinal perforations and fistula, proteinuria and nephrotic syndrome, skin disorder, hair colour changes and skin hypopigmentation, and wound healing delayed.

PMDA also considered as follows:
Occurrence of the above adverse events deserve attention when pazopanib is administered. However, pazopanib treatment is tolerable, as long as adverse events are monitored and controlled, and appropriate measures such as dose interruption, reduction, or treatment discontinuation are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors and the following comments were raised by the expert advisors:

- Since haemorrhagic events were reported in the clinical studies of pazopanib, caution should be exercised when pazopanib is used in patients with coagulation system disorder and those on an anticoagulant agent because pazopanib may aggravate haemorrhages.

- As wound healing delayed was reported in the clinical studies of pazopanib, when making a decision on whether a surgical procedure should be performed during, or after withdrawal from, pazopanib treatment, the risk of wound healing delayed, general condition, and other factors should be considered in a comprehensive manner. However, there is little data about an adequate duration between withdrawal from pazopanib treatment and scheduled surgery. It is desirable to provide healthcare professionals with reference data, if any.

Based on the above Expert Discussion, PMDA asked the applicant to explain (1) the incidences of hemorrhagic events by with or without use of anticoagulant agents in combination and by the presence or absence of coagulation test abnormalities, and (2) the background for providing a caution statement, “treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery” in the US and Europe.

The applicant responded as follows:
a. Haemorrhagic events:
The incidences of haemorrhagic events by with or without use of anticoagulant agents in combination and by the presence or absence of coagulation test abnormalities in Study VEG110727 were shown in the following table.

Eight of 10 subjects in the pazopanib group and 2 of 2 subjects in the placebo group were administered study drug concomitantly with an anticoagulant agent when haemorrhagic events occurred.

In subjects with coagulation test abnormalities, prothrombin time (PT) prolonged or international normalised ratio (INR) increased was observed at the occurrence of a haemorrhagic event in 5 of 8 subjects in the pazopanib group and 1 of 1 subject in the placebo group. Partial thromboplastin time (PTT) prolonged was observed at the occurrence of a haemorrhagic event in 6 of 14 subjects, and 0 of 2 subjects, respectively.

Haemorrhagic-related adverse events according to the clinical backgrounds of the patients (VEG110727 study)

With or without patient background	Number of patients (%)			
	Pazopanib group, 240 patients		Placebo group, 123 patients	
	With	Without	With	Without
Concomitant administration of an anticoagulant agent	49 (20)	191 (80)	15 (12)	108 (88)
With haemorrhagic events	10 (20)	44 (23)	2 (13)	8 (7)
Without haemorrhagic events	39 (80)	147 (77)	13 (87)	100 (93)
PT prolonged* or INR increased*	36 (15)	204 (85)	22 (18)	101 (82)
With haemorrhagic events	8 (22)	46 (23)	1 (5)	9 (9)
Without haemorrhagic events	28 (78)	158 (77)	21 (95)	92 (91)
PTT prolonged*	74 (31)	166 (69)	28 (23)	95 (77)
With haemorrhagic events	14 (19)	40 (24)	2 (7)	8 (8)
Without haemorrhagic events	60 (81)	126 (76)	26 (93)	87 (92)

For detailed adverse events considered as haemorrhagic events, see the Review Report (1) "4.(iii).B.(3).5) Haemorrhagic events." * Defined as above the ULN of laboratory reference range

b. Period between withdrawal from pazopanib and surgery:

The period from pazopanib withdrawal to surgery was set for 7 days, based on 5 times the $t_{1/2}$ of pazopanib, approximately 30 hours, in order to reduce the delaying effect of pazopanib on wound healing.

Based on the review at the Expert Discussion, PMDA considers as follows:

a) It is difficult to accurately compare the incidence of haemorrhagic events between the pazopanib group and placebo group by with or without use of anticoagulant agents in combination and by the presence or absence of coagulation test abnormalities, because the sample size is small, but there are no clear differences between the 2 groups. As described in the Review Report (1) "4.(iii).B.(3).5) Haemorrhagic events" and "4.(iii).B.(7) Post-marketing investigations", PMDA instructed the applicant to provide information about haemorrhagic events including serious tumour haemorrhage reported in the clinical studies of pazopanib, and include a caution statement that haemorrhagic events should be treated appropriately in the package insert, and collect information about haemorrhagic events during post-marketing surveillance. The applicant accepted this instruction.

b) Although the clinical pharmacological evidence for setting the period between withdrawal from pazopanib and scheduled surgery as "at least 7 days" is not sufficient, it is necessary to provide information about the $t_{1/2}$ of pazopanib properly, as one of the reference data for physicians to determine the withdrawal period before scheduled surgery, taking into account that there are no data currently available to evaluate the relationship between the withdrawal period and the reduction in the risk of wound healing delayed.

PMDA instructed the applicant to take the above action appropriately and the applicant accepted this.

During the preparation of the Review Report (1), PMDA asked the applicant to report the measures taken in Japan in response to the revised precautions for use of pazopanib after the regulatory submission in the US and Europe.

The applicant responded as follows:

After the regulatory submission in Japan, the safety information of pazopanib was updated 3 times

in the US (January, March, and April 2012), and 3 times in Europe (March, May, and August 2012). In the US and Europe, the safety information of pazopanib was also updated when pazopanib was approved for an additional indication, soft tissue sarcoma (April 2012, August 2012, respectively).

In the safety information of pazopanib revised in the US and Europe, 93 cases of infection were added as serious adverse reactions for which a causal relationshp to pazopanib can not be ruled out regardless of the presence of neutropenia (data lock on October 28, 2010). This new information should be provided in Japan. After the regulatory submission in Japan, there is no other new safety information requiring the revision of post-marketing safety measures in Japan. In the US, however, 7 cases of reversible posterior leukoencephalopathy syndrome (RPLS) were reported, and RPLS has been added to the safety information. Whether this information should be provided in Japan is under discussion with GlaxoSmithKline, UK. None of these 7 cases were soft tissue sarcoma.

As for interstitial lung disease, although this was not added to the safety information in the US and Europe, pneumonitis was reported by 1 of 240 subjects (0.4%) in the pazopanib group in Study VEG110727 and 1 of 30 subjects (3.3%) in Part A (pazopanib monotherapy group) in Study VEG109693, for which a causal relationship to pazopanib can not be ruled out. The two events that occurred in Japanese subjects were Grade 1 and 2, and eventually resolved or alleviated. If interstitial lung disease occurs, it may become serious. Therefore, this information will be included in the package insert in Japan.

PMDA considers as follows:
It is necessary to appropreately caution about infections and RPLS in the package insert, because cases for which a causal relationship to pazopanib can not be ruled out were reported.

As for interstitial lung disease, pneumonitis was reported as a serious adverse event in addition to the above 2 cases, in 1 of 23 subjects (4%) in the normal liver function group in Study NCI-8063 (VEG110827) and 1 of 19 subjects (5%) in the biomarker positive group in phase II (in combination with lapatinib) part of Study VEG102857. For these cases, a causal relationship to pazopanib can not be ruled out. Therefore, patients should be monitored closely for interstitial lung disease during treatment with pazopanib. It is necessary to provide information about the occurrence of interstitial lung disease-related events reported in the clinical studies of pazopanib and provide a caution statement that treatment with pazopanib should be stopped or an appropriate action should be taken if interstitial lung disease occurs, in the package insert, etc. Moreover, safety information about interstitial lung disease should be collected after the market launch, and if necessary, further caution and measure should be taken promptly and appropriately.

PMDA instructed the applicant to take the above action appropriately and the applicant accepted this.

(3) Clinical Positioning

Based on the review described in the Review Report (1) “4.(iii).B.(2) Efficacy,” “4.(iii).B.(3) Safety,” and “4.(iii).B.(4) Clinical positioning”, PMDA concluded that pazopanib can be used as one of the therapeutic options for second-line chemotherapy in patients with metastatic soft tissue sarcoma that progressed after chemotherapy with doxorubicin hydrochloride (doxorubicin), etc.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors. The following comments were raised by the expert advisors:

- Pazopanib has a clinical significance because no standard therapy has been established for

soft tissue sarcoma refractory to the existing chemotherapy.

- As doxorubicin and ifosfamide may not be used in elderly patients or patients with insufficient organ function, such as cardiac or renal impairment, pazopanib might be prescribed in patients who have not received prior chemotherapy. Information about the clinical positioning of pazopanib should be provided appropriately.

Based on the discussion at the Expert Discussion, PMDA instructed the applicant to appropriately provide information about the clinical positioning of pazopanib in the package insert, etc. [see "(4) Indication"], and to provide background information such as those about patients enrolled in Study VEG110727 in an information leaflet so that whether pazopanib should be used or not can be determined based on the patient's condition and prior therapy. The applicant accepted this instruction.

(4) Indications

Based on the review described in the Review Report (1) "4.(iii).B.(5) Indication," PMDA determined that the indication should be modified to "soft tissue sarcoma." In the Clinical Studies section of the package insert, the histology subtypes that were included in, and excluded from, Study VEG110727 and foreign phase II study (Study VEG20002) should be appropriately provided as well as the fact that only patients with metastatic disease were enrolled in the clinical studies. Furthermore, the following caution statements should be included in the Precautions for Indications section:

- The efficacy and safety of pazopanib in patients who have not received prior chemotherapy have not been established.

- Patients for pazopanib treatment should be selected based on full knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of pazopanib, with regard to the histologic subtypes of soft tissue sarcoma in patients enrolled in clinical trials.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors. The following comments were raised by the expert advisors:

- As soft tissue sarcoma has various histology subtypes and some histology subtypes are very rare, from the clinical point of view it is appropriate to define the indication collectively as "soft tissue sarcoma" that includes the histology subtypes ineligible to be enrolled in the clinical studies. However, relevant information need to be provided appropriately to clarify the reason why adipocytic sarcoma was excluded from Study VEG110727 and the histology subtypes that were ineligible in the clinical studies.

- It is not necessary to exclude adipocytic sarcoma from the indication, because there is no data to restrict the use of pazopanib for the treatment of adipocytic sarcoma, although pazopanib is not recommended for the treatment of lipogenic sarcoma in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Soft Tissue Sarcoma (Ver 2. 2012).

- It is important to include a caution statement "Patients for pazopanib treatment should be selected based on full knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of pazopanib, with regard to the histologic subtypes of soft tissue sarcoma in patients enrolled in clinical trials." in the package insert, in order to appropriately inform them of the histology subtypes included in the clinical studies of pazopanib. However, considering the difficulty in making an accurate

histopathological diagnosis in some cases of soft tissue sarcoma, it is not always possible to select patients suitable for pazopanib treatment based on the information about histology subtypes.

Based on the discussion at the Expert Discussion, PMDA considers as follows:
The description about pazopanib for lipogenic sarcoma added to the latest NCCN Guideline is based on the results of Study VEG20002, but PMDA does not consider that information obtained from Study VEG20002 ruled out the clinical benefit of pazopanib in the treatment of adipocytic sarcoma [see the Review Report (1) "4.(iii).B.(5).1) Patient populations and tumor histology"].

Taking account of the reasons below as well, the indication should be "soft tissue sarcoma". However, it is necessary to provide relevant information in the package insert and other information leaflets, so that physicians with adequate knowledge and experience in cancer chemotherapy are able to select patients considering the efficacy data for pazopanib obtained so far.

- Because of its rarity in incidence and variety of histology subtypes, soft tissue sarcoma cannot be investigated for all histology subtypes. It is therefore difficult to evaluate the efficacy of pazopanib in soft tissue sarcoma by histology subtype.

- It is difficult to make an accurate histopathological diagnosis in some subtypes of soft tissue sarcoma.

At the Expert Discussion, the following discussion was made on the necessity of a caution about neoadjuvant/adjuvant chemotherapy with pazopanib.

Based on the review described in the Review Report (1) "4.(iii).B.(5).3) Neoadjuvant/adjuvant chemotherapy," PMDA does not consider that it is necessary to include a caution statement that the efficacy and safety of pazopanib in neoadjuvant/adjuvant chemotherapy have not been established, because at present, the clinical positioning of neoadjuvant/adjuvant chemotherapy is not clear in the treatment of soft tissue sarcoma.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors and the following comments were raised by the expert advisors:

- Only rare cases of unresectable soft tissue sarcomas turns out to be radically resectable after complete response to chemotherapy and radiotherapy. In this disease area, it is considered that neoadjuvant/adjuvant chemotherapy has not been established for unresectable cases. Also, a caution statement will be included that the efficacy and safety of pazopanib in patients who have not received prior chemotherapy have not been established, in the Precautions for Indications section. Based on these, pazopanib is regarded as a drug to be used in second-line chemotherapy or thereafter, and it is not necessary to include a caution statement that the efficacy and safety of pazopanib in neoadjuvant/adjuvant chemotherapy have not been established.

- Considering that CR was not achieved as best response in Study VEG110727 [see Review report (1) "4.(iii).B.(2).4) Efficacy by tumor histology] and pazopanib is not so effective in reducing tumor size, there is no evidence to support the clinical use of pazopanib in neoadjuvant/adjuvant chemotherapy at present.

Based on the above, PMDA instructed the applicant to provide the following statements in the Indication and Precautions for Indications sections of the package insert, as well as information about the histology subtypes excluded from Study VEG110727 and Study VEG20002 in the

Clinical Studies section, etc. The applicant accepted this instruction.

[Indication]
Soft tissue sarcoma

[Precautions for indication]
- The efficacy and safety of pazopanib in patients who have not received prior chemotherapy have not been established.

- Patients for pazopanib treatment should be selected based on full knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of pazopanib, with regard to the histologic subtypes of soft tissue sarcoma in patients enrolled in clinical trials.

During the preparation of the Review Report (1), PMDA asked the applicant to report the evaluation of bioequivalency between the dosage forms for development used in Study VEG20002 (100 mg tablets, 500 mg tablets) and those used in Study VEG110727 (200 mg tablets, 400 mg tablets).

The applicant responded as follows:
The change between the development formulations used in Study VEG20002 and Study VEG110727 falls under "Level E" according to the "Partial Amendment to Guidelines for Bioequivalence Testing of Generic Drugs" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012), but no clinical bioequivalency study was conducted. However, the difference between the development formulations is considered to have no effect on the efficacy and safety evaluation in Study VEG20002, where the formulation used was different from the market formulation, because (1) there was no clear difference in dissolution behavior between the 2 development formulations, (2) in the foreign clinical studies to evaluate the PK of pazopanib, there were no clear differences in pazopanib exposure between administration of single or multiple oral dose of 800 mg of pazopanib as three 100 mg tablets and one 500 mg tablet (Study VEG10003, Study VEG10006 , Study VEG10007, Study VEG20006), and as two 400 mg tablets (Study VEG10004, Study VEG10005, Study VEG105427), and (3) the efficacy and safety profiles of pazopanib obtained in Study VEG20002 were similar to those in Study VEG110727.

As no bioequivalency study was conducted between the development formulations used in Study VEG110727 and Study VEG20002, PMDA considers that efficacy and safety data obtained from Study VEG20002 should be regarded as reference information. When efficacy data for adipocytic sarcoma are provided, it is also necessary to inform that they were obtained using a formulation different from the market formulation.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors. Based on the above, PMDA instructed the applicant to provide information that the results of Study VEG20002 were obtained using a formulation different from the market formulation, in the prescribing information. The applicant accepted this instruction.

(5) Dosage and Administration
Based on the review described in the Review Report (1) "4.(iii).B.(6) Dosage and administration," PMDA determined that the dosage and administration of pazopanib should be modified to "The usual adult dosage is 800 mg of pazopanib orally administered once daily, at least 1 hour before or at least 2 hours after a meal. The dose may be adjusted according to the patient's condition." PMDA concluded that the following statements should be included in the Precautions for Dosage and Administration section.

- The efficacy and safety of the concomitant use of pazopanib with other antineoplastic drugs have not been established.

- It has been reported that administration of pazopanib after a meal results in increase in C_{max} and AUC. In order to avoid the effect of food, pazopanib should be taken in compliance with Dosage and Administration.

- If dose reduction of pazopanib is necessary due to the onset of adverse reactions, it should be in 200 mg decrements in a stepwise fashion. Additionally, if dose escalation is considered after dose reduction, it should be in 200 mg increments in a stepwise fashion, but should not exceed 800 mg.

- In patients with moderate or severe hepatic impairment, dose reduction should be considered, and patients should be closely monitored for the onset of adverse events.

- If abnormal liver function test values are observed during pazopanib treatment, the criteria for dose interruption and reduction, and treatment discontinuation defined for abnormal liver function tests in Study VEG110727 should be considered.

Based on the review described under "4.(iii).B.(6).3) Dose adjustment of pazopanib in patients with hepatic impairment" in Review Report (1), PMDA considers that the dose of pazopanib should not exceed 200 mg QD in patients with moderate or severe hepatic impairment, because the maximum tolerated dose in patients with moderate hepatic impairment was 200 mg QD in Study NCI-8063. It is therefore necessary to adequately provide the results of Study NCI-8063 in the package insert so that whether pazopanib should be used or not in patients with moderate or severe hepatic impairment can be considered carefully with a full understanding of the results of Study NCI-8063.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors.

Based on the above, PMDA instructed the applicant to include the following Dosage and Administration and Precautions for Dosage and Administration in the package insert. The applicant accepted this instruction.

[Dosage and administration]
The usual adult dosage is 800 mg of pazopanib orally administered once daily, at least 1 hour before or at least 2 hours after a meal. The dose may be adjusted according to the patient's condition.

[Precautions for dosage and administration]
- The efficacy and safety of the concomitant use of the product with other antineoplastic drugs have not been established

- It has been reported that administration of the product after a meal results in increase in C_{max} and AUC. In order to avoid the effect of food, the product should be taken in compliance with Dosage and Administration.

- If dose reduction of pazopanib is necessary due to the onset of adverse reactions, it should be in 200 mg decrements in a stepwise fashion based on individual symptoms, severity, etc. Additionally, if dose escalation is considered after dose reduction, it should be in 200 mg increments in a stepwise fashion, but should not exceed 800 mg.

- In clinical trials, it has been demonstrated that the maximum tolerate dose of pazopanib

was 200 mg in patients with moderate hepatic impairment. In patients with moderate or severe hepatic impairment, therefore, a dose higher than 200 mg is not recommended. The dose of pazopanib in patients with moderate or severe hepatic impairment should be reduced, and the patients should be carefully monitored for the onset of adverse events.

- If abnormal liver function test values are observed during treatment with the product, the dose should be interrupted or reduced, or the treatment should be discontinued in accordance with the following criteria.

Criteria for dose interruption and reduction, and treatment discontinuation for abnormal liver function test values

Liver function test value	Treatment
3.0 × ULN ≤ ALT ≤ 8.0 × ULN	Pazopanib may be continued (with weekly monitoring of liver function until ALT returns to ≤ Grade 1 or baseline).
ALT > 8.0 × ULN	Pazopanib should be interrupted until ALT returns to ≤ Grade 1 or baseline. If administration of pazopanib is resumed, the dose should be reduced to 400 mg. Following reintroduction of pazopanib, if abnormalities in liver function test (ALT > 3.0 × ULN) recur, then pazopanib should be permanently discontinued.
ALT > 3.0 × ULN, and total bilirubin elevations > 2.0 × ULN (direct bilirubin >35%)	Pazopanib should be permanently discontinued (patients should be monitored until ALT returns to ≤ Grade 1 or baseline).

Grade is defined in NCI CTCAE
ULN: upper limit of normal

(6) Post-marketing investigations

The applicant plans to conduct post-marketing surveillance in all patients treated with pazopanib, with a planned statistical analysis population of 200 patients and a 1-year follow-up period. Priority surveillance items will be (1) hepatic function disorder and (2) hypertension and cardiac dysfunction (such as cardiac failure and cardiomyopathy) [see the Review Report (1) "4.(iii).B.(7) Post-marketing investigations"].

Based on the review described in the Review Report (1) "4.(iii).B.(7) Post-marketing investigations," PMDA concluded as follows:
The post-marketing surveillance should be conducted in all patients treated with pazopanib and safety information obtained should be provided to clinical practice as promptly as possible.
The target number of patients for analysis should be changed to allow the evaluation of 11 items listed in the Review Report (1) "4.(iii).B.(7) Post-marketing investigations" since those items should also be assessed appropriately, in addition to the adverse events of the priority surveillance items proposed by the applicant. It is also necessary to collect information about incidences of infections and RPLS as the priority surveillance items, because after the regulatory submission in Japan, serious infections and RPLS were reported and the safety information in the prescribing information of pazopanib was revised in the US and Europe [see "(2) Safety"]. As soft tissue sarcoma has various histology subtypes, it is recommended to take measures to avoid collecting information only from the most prevalent histology subtypes.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors. The following comments were raised by the expert advisors:

- Information about tumor subtypes and malignancy (Grade) should be collected via post-marketing surveillance.

- It is difficult to evaluate the efficacy of pazopanib via post-marketing surveillance, but it is recommended to obtain safety information for as many histology subtypes as possible. If

patients with some histology subtypes has not been registered when the number of patients for analysis reaches the target, it is necessary to take measures such as to extend the registration period in order to avoid collecting information only from the most prevalent histology subtypes.

Based on the discussion at the Expert Discussion, PMDA concluded as follows:
The proposed post-marketing surveillance plan should be revised to: (a) collect information about interstitial lung disease as a priority surveillance item since pneumonitis was reported in the clinical studies of pazopanib [see "(2) Safety"], (b) collect information about tumor subtypes and malignancy (Grade), and (c) perform an interim analysis so that the results of post-marketing surveillance can be reported immediately to clinical practice. The approximate number of patients to be registered should be determined for each of the major tumor histology (for example, leiomyosarcoma, synovial sarcoma, adipocytic sarcoma, and other soft tissue sarcoma than leiomyosarcoma, synovial sarcoma, or adipocytic sarcoma) and the post-marketing surveillance plan should include the measures to be taken in case the number of registered patients for a certain histology subtype is much smaller than expected.

PMDA instructed the applicant to take necessary action.

The applicant responded as follows:
Of the additional adverse events of priority surveillance items, except for RPLS with unknown incidence, arrhythmia including QT interval prolonged and Torsade de pointes, thromboembolism, haemorrhagic events, pneumothorax, thyroid function abnormal, gastrointestinal perforation and gastrointestinal fistula, proteinuria and nephrotic syndrome, infections, and interstitial lung disease were reported by about 1% of subjects in Study VEG110727, Study VEG20002, Study VEG109693, and foreign clinical studies in patients with renal cell carcinoma (Study VEG105192, Study VEG102616, Study VEG107769). Therefore, the target number of patients for analysis will be changed to 300 patients in order to detect ≥1 event of each of these adverse events with a probability of ≥95%. The approximate sample size by tumor histology will be 28 patients for leiomyosarcoma, 20 patients for synovial sarcoma, 99 patients for adipocytic sarcoma, and 153 patients for other soft tissue sarcoma than leiomyosarcoma, synovial sarcoma, or adipocytic sarcoma. The case report form will be designed to collect information about tumor subtypes and malignancy (Grade), in addition to the adverse events of priority surveillance items.

The interim analysis will be performed when the surveillance is completed in at least 100 patients (maximum follow-up period of 1 year), and the results will be reported to healthcare professionals. After making sure that sufficient information can be collected from the planned number of patients based on the number of registered patients and CRFs collected, etc., whether the surveillance should be changed to a patient registry without CRF collection will be considered. If the number of patients with one of the major histology subtypes is found to be much smaller than the assumed number, necessary measures will also be discussed, such as, continuing the surveillance only for that histology subtype.

PMDA accepted the applicant's response.

(7) Others
At the Expert Discussion, the following comments were raised by the expert advisors:

- (1) The applicant explained that the major mechanism of action of pazopanib is inhibition of vascular endothelial growth factor receptor (VEGFR), but the expression of VEGFR was not evaluated by histology subtype in the clinical studies, and (2) the applicant considers that pazopanib shows efficacy in soft tissue sarcoma by inhibiting angiogenesis,

based on the data from certain histology subtypes in the non-clinical studies [see Review Report (1) "3.(i).A.(1) Primary pharmacodynamics"]. Therefore it is difficult to discuss the efficacy of pazopanib by the expression of VEGFR or by histology subtype from the point of mechanism of action.

PMDA considers as follows:
It is difficult to conduct clinical studies to prove the efficacy of pazopanib for each histology subtype since soft tissue sarcoma has various histology subtypes and soft tissue sarcoma itself is a rare disease. However, non-clinical studies should have been conducted more extensively even during the clinical development phase in order to obtain non-clinical data supporting the efficacy of pazopanib in a wider range of histology subtypes as much as possible. As it was difficult to evaluate the efficacy of pazopanib in soft tissue sarcoma by histology subtype, in the future development, the applicant should conduct non-clinical and clinical studies more extensively to evaluate the efficacy of pazopanib in each histology subtype including those ineligible in the confirmatory clinical studies. New information obtained from these studies should be provided appropriately.

PMDA instructed the applicant to follow the above recommendation, and the applicant accepted it.

III. Overall Evaluation

Based on the result of review, PMDA has concluded that the product may be approved for the indications and dosage and administration that have been modified as shown below, with the following conditions for approval, provided that appropriate cautions will be included in the package insert and information concerning the proper use of pazopanib will be provided appropriately after market launch, and the compliance with the proper use of pazopanib will be ensured under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. The re-examination period is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]	Soft tissue sarcoma
[Dosage and administration]	The usual adult dosage is 800 mg of pazopanib orally administered once daily, at least 1 hour before or at least 2 hours after a meal. The dose may be adjusted according to the patient's condition.
[Condition for approval]	Because of the very limited number of subjects treated in the Japanese clinical trials, the applicant is required to conduct all-case surveillance until data from a certain number of patients are accumulated after market launch, in order to identify the background information of patients treated with the product and collect safety and efficacy data on the product in the early post-marketing period, thereby take necessary measures to ensure proper use of the product.

[Warnings]

1. The product should be administered only to patients considered appropriate to be given under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. Before the treatment, the patient or his/her family member should give the informed consent after being provided with a full explanation about the efficacy and possible risks of the product.
2. Serious hepatic function disorder may occur, and fatal outcomes associated with hepatic failure have been reported. Patients should be carefully monitored through periodic liver function tests before and during the treatment with pazopanib.
3. In patients with moderate or severe hepatic impairment, the maximum tolerated dose of the product is decreased. In this patient population, administration of the product should be decided with caution. If the product is administered, the dose should be reduced.

[Contraindications]

1. Patients with a history of hypersensitivity to pazopanib or any of the excipients
2. Pregnant women or women who may be pregnant

[Precautions for indications]

1. The efficacy and safety of the product have not been established in patients who have not received prior chemotherapy.
2. Patients for pazopanib treatment should be selected based on full knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of pazopanib, with regard to the histologic subtypes of soft tissue sarcoma in patients enrolled in clinical trials.

[Precautions for dosage and administration]

1. The efficacy and safety of the concomitant use of the product with other antineoplastic drugs have not been established.
2. It has been reported that administration of the product after a meal results in increase in C_{max} and AUC. In order to avoid the effect of food, the product should be taken in compliance with Dosage and Administration.
3. If dose reduction of pazopanib is necessary due to the onset of adverse reactions, it should be in 200 mg decrements in a stepwise fashion based on individual symptoms, severity, etc. Additionally, if dose escalation is considered after dose reduction, it should be in 200 mg increments in a stepwise fashion, but should not exceed 800 mg.
4. In clinical trials, it has been demonstrated that the maximum tolerate dose of pazopanib was 200 mg in patients with moderate hepatic impairment. In patients with moderate or severe hepatic impairment, therefore, a dose higher than 200 mg is not recommended since that exceeds the maximum tolerated dose. The dose of pazopanib in patients with moderate or severe hepatic impairment should be reduced, and the patients should be carefully monitored for the onset of adverse events.
5. If abnormal liver function test values are observed during treatment with the product, the dose should be interrupted or reduced, or the treatment should be discontinued in accordance with the following criteria.

Criteria for dose interruption and reduction, and treatment discontinuation for abnormal liver function test values

Liver function test value	Treatment
3.0 × ULN ≤ ALT ≤ 8.0 × ULN	Pazopanib may be continued (with weekly monitoring of liver function until ALT returns to ≤ Grade 1 or baseline).
ALT > 8.0 × ULN	Pazopanib should be interrupted until ALT returns to ≤ Grade 1 or baseline. If administration of pazopanib is resumed, the dose should be reduced to 400 mg. Following reintroduction of pazopanib, if abnormalities in liver function test (ALT > 3.0 × ULN) recur, then pazopanib should be permanently discontinued.
ALT > 3.0 × ULN, and total bilirubin elevations > 2.0 × ULN (direct bilirubin >35%)	Pazopanib should be permanently discontinued (patients should be monitored until ALT returns to ≤ Grade 1 or baseline).

Grade is defined in NCI CTCAE
ULN: upper limit of normal