Report on the Deliberation Results

January 26, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Lenvima Capsules 4 mg Lenvima Capsules 10 mg
[Non-proprietary name]	Lenvatinib Mesilate (JAN*)
[Applicant]	Eisai Co., Ltd.
[Date of application]	June 26, 2014

[Results of deliberation]
In the meeting held on January 21, 2015, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product 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.

[Conditions for approval]
The applicant is required to:

1. Develop a risk management plan and implement it appropriately.

2. Conduct a drug use-results survey involving all patients treated with the product after the market launch until data from a certain number of patients have been gathered in order to grasp the characteristics of treated patients, since the product has been studied in only a limited number of patients in clinical studies in Japan. At the same time, collect the safety and efficacy data of the product without delay and take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

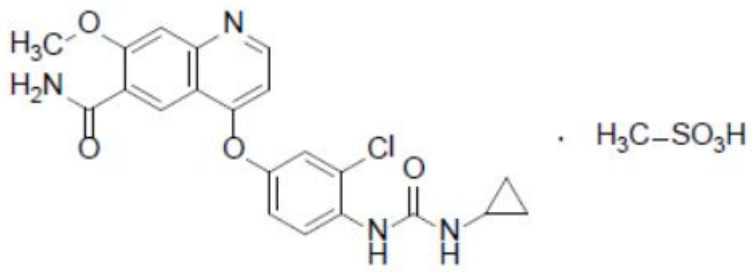
Review Report

January 9, 2015
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]	Lenvima Capsules 4 mg Lenvima Capsules 10 mg
[Non-proprietary name]	Lenvatinib Mesilate
[Name of applicant]	Eisai Co., Ltd.
[Date of application]	June 26, 2014
[Dosage form/Strength]	Each capsule contains 4.90 mg of Lenvatinib Mesilate (equivalent to 4 mg of lenvatinib) or 12.25 mg of Lenvatinib Mesilate (equivalent to 10 mg of lenvatinib).
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$
Molecular weight: 522.96
Chemical name:
4-{3-chloro-4-[(cyclopropylcarbamoyl)amino]phenoxy}-7-methoxyquinoline-6-carboxamide monomethanesulfonate

[Items warranting special mention]
Orphan drug (Designation [24 yaku] No. 279; PFSB/ELD Notification No. 0816-6 issued from the Ministry of Health, Labour and Welfare, dated August 16, 2012)

[Reviewing office] Office of New Drug V

Review Results

January 9, 2015

[Brand name] Lenvima Capsules 4 mg
Lenvima Capsules 10 mg
[Non-proprietary name] Lenvatinib Mesilate
[Name of applicant] Eisai Co., Ltd.
[Date of application] June 26, 2014
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with unresectable thyroid cancer has been demonstrated and the safety is acceptable in view of its observed benefits. The following events need to be further investigated via post-marketing surveillance etc.: hypertension/hypertensive crisis, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood thyroid stimulating hormone increased.

As a result of the regulatory review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication]
Unresectable thyroid cancer

[Dosage and administration]
The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition.

[Conditions for approval]
The applicant is required to:
1. Develop a risk management plan, and implement it appropriately.
2. Conduct a drug use-results survey involving all patients treated with the product after the market launch until data from a certain number of patients have been gathered in order to grasp the charasteristics of treated patients, since the product has been studied only in a limited number of patients in clinical studies in Japan. At the same time, collect the safety and efficacy data of the product without delay and take necessary measures to ensure proper use of the product.

Review Report (1)

December 9, 2014

I. Product Submitted for Registration

[Brand name]	Lenvima Capsules 4 mg Lenvima Capsules 10 mg
[Non-proprietary name]	Lenvatinib Mesilate
[Name of applicant]	Eisai Co., Ltd.
[Date of application]	June 26, 2014
[Dosage form/Strength]	Each capsule contains 4.90 mg of Lenvatinib Mesilate (equivalent to 4 mg of lenvatinib) or 12.25 mg of Lenvatinib Mesilate (equivalent to 10 mg of lenvatinib).
[Proposed indication]	Thyroid cancer
[Proposed dosage and administration]	The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition.

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) Overview of the product submitted for registration

Lenvatinib mesilate (hereinafter referred to as lenvatinib), discovered by Eisai Co., Ltd., is a chemical compound that inhibits multiple kinases. Lenvatinib is considered to suppress tumor growth by inhibiting kinases such as vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3; REarranged during Transfection proto-oncogene (RET); fibroblast growth factor receptors (FGFRs) 1, 2, 3, and 4; platelet-derived growth factor receptor (PDGFR) α; and stem cell factor receptor (KIT).

1.(2) Development history etc.

Out of Japan, a phase I study (Study E7080-E044-101) was initiated by Eisai Inc. (US) and Eisai Ltd. (UK) in [redacted] 20[redacted], in patients with solid cancer and malignant lymphoma. In addition, a phase II study (Study E7080-G000-201 [Study 201]) was initiated in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) or medullary thyroid carcinoma (MTC) in [redacted] 20[redacted]. Then, the global phase III study (Study E7080-G000-303 [Study 303]) was initiated in patients with locally advanced or metastatic RAI-refractory DTC in 21 countries, including Japan, in [redacted] 20[redacted].

As of November 2014, lenvatinib has not been approved in any country or region.

In Japan, a phase I study (Study E7080-J081-103) was initiated by the applicant in patients with solid cancer in [redacted] 20[redacted]. A phase II study (Study E7080-J081-208 [Study 208]) was initiated in patients with locally advanced or metastatic RAI-refractory DTC, MTC, and anaplastic thyroid carcinoma (ATC) in [redacted] 20[redacted]. In [redacted] 20[redacted], the enrollment of patient in Study 303 was started.

The application for lenvatinib including pivotal data from Study 201, Study 208, and Study 303 has now been filed.

Lenvatinib was designated as an orphan drug in August 2012 with the intended indication of thyroid cancer (Designation [24 yaku] No. 279).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to pale reddish yellow powder and the determined properties include description, solubility, dissociation constant, partition coefficient, melting point, hygroscopicity, and crystalline polymorphism. [redacted].

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

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

[redacted].

Using a quality-by-design (QbD) approach, the following investigations were mainly implemented.

- [redacted]
- Identification of critical process parameters based on the quality risk evaluation as well as manufacturing history and process knowledge accumulated during the development stage

[redacted].

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

[redacted].

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

The stability studies conducted on the drug substance were as shown in the table below. Photostability data showed that the drug substance is photostable.

Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	Commercial scale 3 batches	5°C	-	Polyethylene bag + aluminum-laminated bag	24 months
Accelerated testing	Commercial scale 3 batches	25°C	60%RH		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored refrigerated in a polyethylene bag in an aluminum-laminated bag, in accordance with the "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003) (ICH Q1E Guideline). The long-term testing will be continued up to [redacted] months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is immediate-release hard capsules each containing 4.90 mg or 12.25 mg of the drug substance (4 mg or 10 mg as lenvatinib, respectively). It contains precipitated calcium carbonate, D-mannitol, microcrystalline cellulose, hydroxypropylcellulose, low substituted hydroxypropylcellulose, and talc as excipients.

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

[redacted].

Using a QbD approach, the following investigations were mainly implemented.

- [redacted]
- Identification of critical process parameters by initial quality risk assessment and risk re-assessment based on the results obtained through the manufacturing process development

[redacted].

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

The proposed specifications for the drug product include content, description, identification (UV/VIS, HPLC), purity (related substances [HPLC]), water content, uniformity of dosage units (content uniformity [HPLC]), dissolution (absorbance), microbial limit, and assay (HPLC).

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

The stability studies conducted on the drug product were as shown in the table below. Photostability data showed that the drug product is photostable.

Stability studies on drug product

Content	Study	Primary batches	Temperature	Humidity	Storage form	Storage period
4 mg	Long-term testing	2 batches at a pilot scale 1 batch at a commercial scale	25°C	60%RH	PTP package (aluminum-laminated on both sides)	24 months
	Accelerated testing	2 batches at a pilot scale 1 batch at a commercial scale	40°C	75%RH		6 months
10 mg	Long-term testing	2 batches at a pilot scale 1 batch at a commercial scale	25°C	60%RH		24 months
	Accelerated testing	2 batches at a pilot scale 1 batch at a commercial scale	40°C	75%RH		6 months

Based on the above, a shelf-life of 36 months has been proposed for the drug product stored in a PTP package (aluminum-laminated on both sides) at room temperature, in accordance with the ICH Q1E Guideline. The long-term testing will be continued up to [redacted] months.

2.B Outline of the review by PMDA

Based on the review of the submitted data and the following considerations, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

Acceptance criteria for mutagenic impurities

The results from the reverse mutation test in bacteria suggest that Impurity B* contained in the drug substance and the drug product is mutagenic [see "3.(iii).A.(6).2).ii) Impurity A and Impurity B"]. [redacted]

[redacted]. For this impurity in the drug product, the acceptance criterion of ≤[redacted]% has been proposed in consideration of the acceptance criterion in the drug substance and stability data.

*: [redacted]

[redacted].

PMDA accepted the applicant's explanation.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) Inhibitory effect against various kinases (Reports W-20[redacted]0816, W-20[redacted]0814, W-20[redacted]0815, M[redacted]009 [Reference data])

The inhibitory effects of lenvatinib mesilate (hereinafter referred to as lenvatinib) and sorafenib tosylate (sorafenib) against phosphorylation of 66 human protein kinases were investigated by enzyme-linked immunoassay (ELISA) or electrophoretic mobility shift assay using these recombinant full length proteins or their recombinant kinase domains. Kinases inhibited by lenvatinib or sorafenib with IC_{50} values of <10,000 nmol/L were as shown in the table below.

Inhibitory effects of lenvatinib against various kinases

Kinase	IC_{50} value (nmol/L)		Kinase	IC_{50} value (nmol/L)	
	Lenvatinib	Sorafenib		Lenvatinib	Sorafenib
KIT^{V560G}	0.735	4.61	KIT^{V654A}	516	924
VEGFR3	2.32	15.7	MET	518	>10,000
VEGFR2	3.02	20.6	EGFR	623	>10,000
VEGFR1	4.67	21.0	PDGFR-α^{T674I}	628	85.6
RET	6.35	14.6	ABL	655	1050
RET^{M918T}	12.4	32.9	EPHB2	661	712
PDGFRα^{V561D}	24.7	5.35	FGR	909	1990
FGFR2	26.6	146	AurA	1130	2500
PDGFRα	28.8	1.64	RAF1	1610	46.4
FGFR4	43.3	3440	TIE2	2510	1730
FGFR3	51.6	339	CSK	2580	5330
FGFR1	60.8	335	FLT3	4100	57.2
KIT	85.4	144	EPHB4	4610	658
$FGFR3^{K650E}$	113	104	EPHA1	5090	1170
LCK	126	958	SRC	5740	4460
FRK	160	368	BRAF	8660	314
PDGFRβ	163	26.8	SYK	8670	>10,000
HER4	173	>10,000	MUSK	>10,000	68.3
BRK	175	8270	$BRAF^{V600E}$	>10,000	378
$FGFR3^{K650M}$	251	110	P70S6K	>10,000	460
HGK	403	3280	KIT^{D816V}	>10,000	1350
KIT^{T670I}	407	59.9	JAK2	>10,000	4410

n = 1

The inhibitory effect of lenvatinib against each activity of the following kinases was investigated by time-resolved fluorometry or ELISA: VEGFR1 and VEGFR2; FGFR1; epidermal growth factor receptor (EGFR); hepatocyte growth factor receptor (MET); and PDGFRβ. The IC_{50} value and 95% confidence interval (CI) against each kinase were as shown in the table below.

Inhibitory effects of lenvatinib against various kinases

Kinase	IC_{50} value [95% CI] (nmol/L)
VEGFR2	4.0 [1.8, 8.7]
VEGFR1	22 [11, 45]
PDGFRβ	39 [12, 130]
FGFR1	46 [18, 120]
MET	1900 [1500, 2500]
EGFR	6500 [5000, 8500]

n = 3

The inhibitory effect of lenvatinib against each activity of the following kinases was investigated by electrophoretic mobility shift assay: VEGFR1, 2 and 3; FGFR1, 2 and 3; K650E-variant FGFR3; K650M-variant FGFR3; rearranged during transfection proto-oncogene (RET); and stem cell factor receptor (KIT). The inhibition constants (K_i value) were as shown in the table below.

Inhibitory effects of lenvatinib against various kinases

Kinase	K_i value (nmol/L)	
	Lenvatinib	Sorafenib
VEGFR3	0.71	2.33
VEGFR2	0.74	3.89
VEGFR1	1.27	6.24
RET	1.52	3.15
FGFR2	8.15	21.3
KIT	11.3	9.63
FGFR3	14.6	77.0
FGFR1	21.8	31.3
$FGFR3^{K650E}$	28.1	25.4
$FGFR3^{K650M}$	62.4	26.9

n = 1

3.(i).A.(1).2) Effect on VEGFR2 (Reports W-20[redacted]0526, W-20[redacted]0522, M[redacted]008, M[redacted]006, M[redacted]005, W-20[redacted]0606 [Reference data], M[redacted]002)

- The enzyme reaction rate for the inhibitory effect of lenvatinib against a recombinant protein of VEGFR2 including kinase domain was measured using a reporter displacement assay. As a result, the equilibrium dissociation constant (K_d value) between lenvatinib and VEGFR2 was 2.07 nmol/L, and that between sorafenib and VEGFR2 was 33.1 nmol/L.

- The binding mode between VEGFR2 and lenvatinib was investigated by X-ray crystallography. The results suggested that lenvatinib bound to the adenosine triphosphate (ATP) binding site and the allosteric region of the kinase domain of VEGFR2.

- The inhibitory effects of lenvatinib against VEGF-induced VEGFR2 autophosphorylation, cell proliferation, and tube formation using human umbilical vein endothelial cells (HUVECs) were investigated by immunoblot, viable cell count measurement with a reducing dye, and microscopic measurement of lumen length, respectively. As a result, the IC_{50} values [95% CI] (nmol/L) of lenvatinib were 0.25 [0.21, 0.29], 3.4 [1.4, 8.4], and 2.1 [2.0, 2.3], respectively.

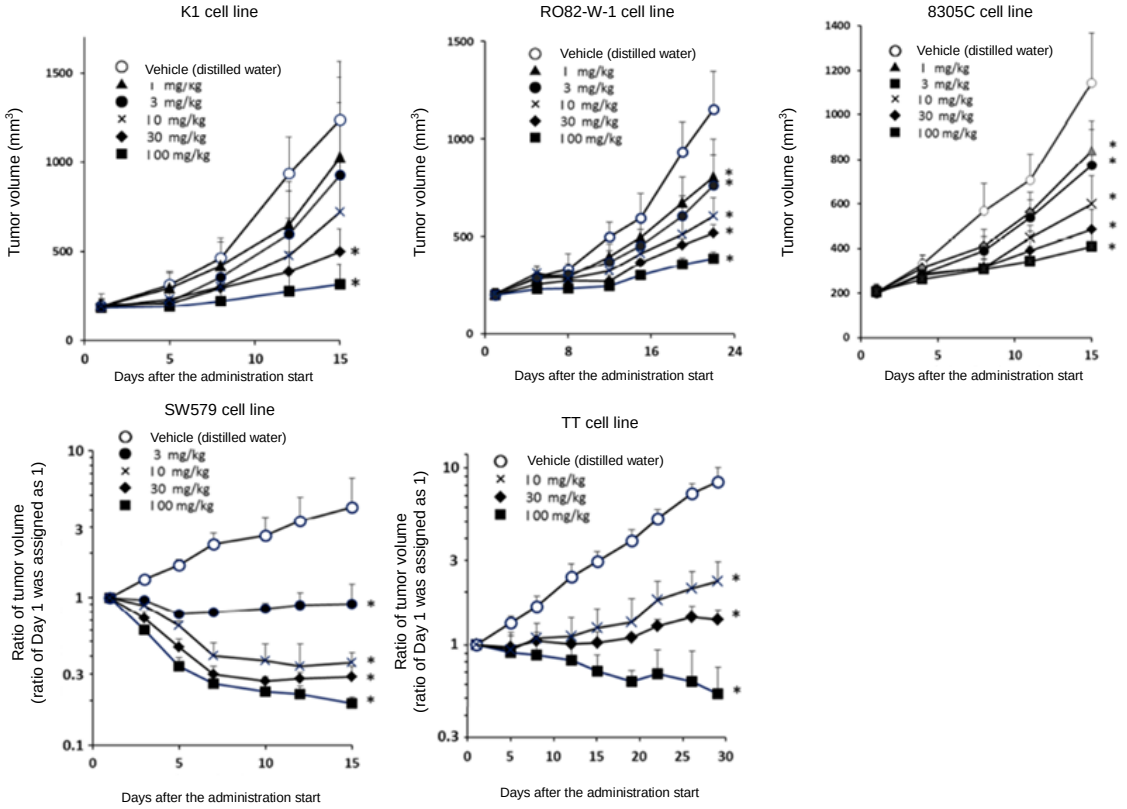
- The inhibitory effects of me88, me114, and me107, metabolites of lenvatinib [see "3.(ii).A.(3).1) *In vitro* metabolism"], against VEGF-induced proliferation of HUVECs were investigated. As a result, the IC_{50} values [95% CI] (nmol/L) were 57 [18, 180], 250 [240, 270], and 230 [120, 440], respectively.

3.(i).A.(1).3) Effects on malignant tumors (Reports M[redacted]007, A[redacted]004, M[redacted]012, M[redacted]013, M[redacted]003, W-20[redacted]0359, K[redacted]004, W-20[redacted]0793 [Reference data], M[redacted]012, M[redacted]011, K[redacted]038, JW[redacted]12, K[redacted]053, K[redacted]008)

i) Effects on thyroid cancer cell line

In vivo

- The tumor growth inhibitory effect of lenvatinib was investigated in athymic mice (nude mice) subcutaneously transplanted with human papillary thyroid cancer K1 cell line. Lenvatinib (1, 3, 10, 30, 100 mg/kg) was administered orally once daily for 14 days to the nude mice from 17 days after the transplantation (mean tumor volume, 377 mm^3) to determine the tumor volume. As a result, the significant tumor growth inhibitions in the lenvatinib 30 and 100 mg/kg groups were observed on Day 15 of the start of administration compared with the control (distilled water) group (the figures below). In addition, a similar investigation was performed in nude mice subcutaneously transplanted with a human thyroid follicular cancer RO82-W-1 cell line, a human anaplastic thyroid cancer 8305C cell line, a human thyroid squamous cancer SW579 cell line, or a human medullary thyroid carcinoma TT cell line. As a result, significant tumor growth inhibition and regression of all the cell lines transplanted were observed in the lenvatinib groups compared with the control (distilled water) group (the figures below).



Tumor growth inhibitory effect of lenvatinib (K1, RO82-W-1, 8305C, SW579, and TT cell lines)
Mean ± standard deviation (SD); n = 4 to 6/group; *, significantly different form the control group with $P < 0.05$ (Dunnett test)

- The effect of lenvatinib on the microvessel density (MVD) in the tumor tissue was investigated in nude mice (n = 6/group) subcutaneously transplanted with an 8305C cell line. Lenvatinib (1, 3, 10, 30, 100 mg/kg) was administered orally once daily for 14 days to the nude mice from 17 days after the transplantation (mean tumor volume, 194 mm^3). At 15 days after the start of administration, tumor tissues were immunohistochemically stained for CD31, a marker molecule of vascular endothelial cells, and MVD was measured by image analysis of these stained tissues. The results showed that the intratumoral MVD significantly decreased in the lenvatinib ≥3 mg/kg/day groups compared with that in the control (distilled water) group ($P < 0.05$, Dunnett test).

- The TT cell line has been reported to have an activating mutation in the RET kinase at C634W (*Biochem Biophys Res Commun.* 1995;207:1022-8). A single dose of lenvatinib (10, 30, 100 mg/kg) was administered orally to nude mice (n = 6/group) subcutaneously implanted with the TT cell line to investigate the effect of lenvatinib on the RET phosphorylation in the tumor tissue by Western blotting. The results showed that lenvatinib at a dose of ≥10 mg/kg inhibited autophosphorylation of RET.

ii) Effect on non-thyroid cancer cell lines

In vitro

Using a human non-small-cell lung cancer H460 cell line and a colon cancer Colo205 cell line, the inhibitory effect of lenvatinib against cell growth was investigated by viable cell count measurement using reducing dye. As a result, the IC_{50} values [95% CI] (nmol/L) were 14,000 [11,000, 17,000] and 26,000 [13,000, 51,000], respectively.

In vivo

Lenvatinib was administered alone or in combination with other antineoplastic drugs to nude mice subcutaneously transplanted with various human tumor cell lines, as shown below, to investigate the tumor growth inhibitory effect. As a result, lenvatinib administered alone and in combination with other antineoplastic drugs both significantly inhibited the tumor growth compared with the control or any of other antineoplastic drugs administered alone.

- Lenvatinib alone in mice transplanted with a human hepatocellular carcinoma PLC/PRF/5 cell line, H460 cell line, or Colo205 cell line

- Lenvatinib alone or in combination with temozolomide or eribulin mesilate in mice transplanted with a human malignant melanoma A375 cell line

- Lenvatinib alone or in combination with cisplatin or carboplatin in mice transplanted with a human non-small-cell lung cancer A549 cell line

- Lenvatinib alone or in combination with paclitaxel in mice transplanted with a human gastric cancer MKN-74 cell line

Lenvatinib weakly inhibited the growth of H460 cell line and Colo205 cell line *in vitro* but significantly inhibited growth of these tumor cell lines *in vivo.* The applicant explained this is because lenvatinib inhibited VEGFR2, thereby leading to inhibition of tumor angiogenesis *in vivo*.

In addition, data from a study of concomitant use of lenvatinib with a MET kinase inhibitor (unapproved in Japan) in a non-thyroid cancer cell line are not included in this review report, because the data are not particularly relevant to this regulatory application (Reports W-20[redacted]0607 [Reference data], W-20[redacted]1038 [Reference data]).

3.(i).A.(2) Secondary pharmacodynamics (Report 6633)

The binding properties of lenvatinib (1, 10 μmol/L) to 50 types of transporters, channels, and receptors other than receptor tyrosine kinase (RTK) were investigated based on their inhibitory effects against binding of radiolabeled ligand to these receptors etc. As a result, lenvatinib at 10 μmol/L inhibited ligand binding to serotonin 5-HT 1B receptor and norepinephrine transporter by 58% and 50%, respectively. The applicant explained that lenvatinib is unlikely to affect the central nervous system, because the estimated human intracerebral concentration of unbound lenvatinib at steady state following multiple administration at the clinical dose (24 mg/day) does not exceed the plasma concentration of unbound lenvatinib (16.7-41.3 nmol/L) calculated from the maximum plasma concentration (518 ng/mL) [see “4.(ii).A.(1).4 Japanese phase I study”].

Lenvatinib at 10 μmol/L did not inhibit binding of the ligand to the other 48 types of receptors, etc. by ≥50%.

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

3.(i).A.(3).1) Effects on the central nervous system (Report B[redacted]0401)

Following a single oral dose of lenvatinib (10, 30, 100 mg/kg) to rats (n = 6/group), its effects on the general symptoms and behavior were investigated. As a result, no effects of lenvatinib were observed.

3.(i).A.(3).2) Effects on the cardiovascular system and respiratory system (Reports [redacted]1029, B[redacted]0403, B[redacted]0402)

i) Effect on hERG current

In a human ether-a-go-go related gene (hERG)-transfected human embryonic kidney 293 (HEK293) cell line, the effect of lenvatinib (0.3, 1, 3, 10, 30 μmol/L) on hERG potassium current was investigated. As a result, lenvatinib at 10 and 30 μmol/L significantly suppressed hERG potassium current compared with the vehicle (0.1% DMSO) ($P < 0.01$, Dunnett test). The IC_{25}, IC_{50}, and IC_{75} values were 5.13, 11.89, and 25.70 μmol/L, respectively. The applicant explained that the finding was unlikely to raise issues in clinical use, because the human plasma concentration of unbound lenvatinib at steady state following multiple administration at a dose of 24 mg/day was estimated to be 41.3 to 16.7 nmol/L.

ii) Effect on cardiac action potential

The effect of lenvatinib (1, 10 μmol/L) on cardiac action potential was investigated in papillary muscle isolated from guinea pigs (n = 6 specimens/group). As a result, no effects of lenvatinib were observed.

iii) Effects on the cardiovascular system and body temperature

Each of single doses of lenvatinib at 6 and 30 mg/kg was administered orally to dogs (n = 6) with a 6-day washout period between the 2 doses to investigate the effects on heart rate, blood pressure, electrocardiogram (ECG) (PQ interval, QRS duration, QT interval), and body temperature. As a result, no effects of lenvatinib were observed.

3.(i).A.(3).3) Effect on the respiratory system (Report S[redacted]019)

Following a single oral dose of lenvatinib (10, 30, 100 mg/kg) to rats (n = 6/group), its effects on respiratory rate, tidal volume, and minute ventilation were investigated. As a result, no effects of lenvatinib were observed.

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

Based on the submitted data and the following review, PMDA concluded that the efficacy of lenvatinib against thyroid cancer is expected.

Efficacy of lenvatinib against thyroid cancer and its pharmacological properties

The applicant explained the efficacy of lenvatinib against thyroid cancer and its pharmacological properties as follows:

It has been reported that RTKs such as VEGFR, FGFR, KIT, and PDGFRα in various carcinomas are involved in tumor angiogenesis, lymphangiogenesis, and growth (*Nat Med.* 2003;9:669-76 etc.). Lenvatinib inhibits tumor growth by inhibiting these RTKs involved in tumor angiogenesis, etc.

In addition, it has been reported that (a) expression of VEGF is enhanced in thyroid cancer compared with normal tissue (*Am J Pathol.* 1999;155:1967-76), (b) expression of FGFR1, 3, and 4 is involved in malignant transformation of thyroid cancer (*Endocrinology.* 2005;146:1145-53), and (c) *RET* gene mutation is found in almost all patients with familial medullary cancer and about a half of those with acquired medullary cancer, and constitutive activation of RET caused by *RET* fusion gene is found in 13% to 43% of those with papillary cancer (*Clin Cancer Res.* 2010;16:5936-41 etc.). Furthermore, lenvatinib inhibited tumor growth of papillary cancer, follicular cancer, anaplastic cancer, medullary cancer, and squamous cell cancer cell lines in non-clinical studies [see "3.(i).A.(1).3) Effect on malignant tumors"]. Lenvatinib, therefore, is expected to have efficacy against various cell types of thyroid cancer.

The applicant explained differences and similarities in pharmacological properties between sorafenib, approved and indicated for thyroid cancer, and lenvatinib as follows:

Non-clinical studies indicated that both lenvatinib and sorafenib inhibit not only VEGFR2, thereby

inhibiting tumor angiogenesis, but also RET to a similar extent [see "3.(i).A.(1).1) Inhibitory effect against various kinases" and "3.(i).A.(1).2) Effect against VEGFR2"].

On the other hand, lenvatinib and sorafenib inhibit different kinases. The VEGFR2 inhibitory effect of lenvatinib is possibly more potent than that of sorafenib at the clinical dose, because the investigation by the applicant showed that the ratio of the plasma concentration of lenvatinib to the IC_{50} value against VEGF effect was 5.5, which was greater than 1.3, the corresponding ratio of sorafenib. In addition, only lenvatinib inhibited FGF-induced angiogenesis (*Vascular Cell.* 2014;6:18-30), and on the basis of applicant investigation, lenvatinib also possibly inhibits tumor angiogenesis by inhibiting FGFR, an inhibitory effect which has not been elucidated in sorafenib.

PMDA considers as follows:
PMDA largely accepted the applicant's explanation. The extent of involvement of levatinib-inhibited kinases in tumor growth, however, has remained largely unclear, and information on this matter is considered useful in identifying patients eligible for lenvatinib treatment. Therefore, it is necessary to continue the investigation and, when new findings become available, appropriately provide the information to healthcare providers in clinical settings.

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics (PK) of lenvatinib in animals were investigated in mice, rats, dogs, and monkeys. Biological samples from humans and animals were used to investigate the plasma protein binding of lenvatinib and its involvement in actions of drug-metabolizing enzyme, transporters, etc.

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

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

A single intravenous dose of 3 mg/kg of lenvatinib or a single oral dose of 3, 10, or 30 mg/kg of lenvatinib was administered to female mice to determine plasma lenvatinib concentrations (the table below). In the investigated dose range of oral administration, C_{max} of lenvatinib showed dose proportionality, while $AUC_{0\text{-}inf}$ tended to increase more than dose-proportionally. The applicant explained that the trend was considered attributable to inter-animal variability among blood samples taken from different mice at each timepoint. The absolute bioavailability (BA) of lenvatinib at a dose of 3 mg/kg was 64.4%.

A single intravenous dose of 3 mg/kg of lenvatinib or a single oral dose of 3, 10, or 30 mg/kg of lenvatinib was administered to male rats to determine plasma lenvatinib concentrations (the table below). C_{max} and $AUC_{0\text{-}inf}$ of lenvatinib after oral dose were dose-proportional between the 3 mg/kg group and the 10 mg/kg group, but increased less than dose-proportionally between the 10 mg/kg group and the 30 mg/kg group. The applicant explained that a less than dose-proportional increase in C_{max} and $AUC_{0\text{-}inf}$ of lenvatinib at high doses was considered attributable to decreased gastrointestinal absorption of poorly soluble lenvatinib with an increasing dose. The absolute BA of lenvatinib at a dose of 3 mg/kg was 68.7%.

A single intravenous or oral dose of 3 mg/kg of lenvatinib was administered to male dogs and monkeys to determine plasma lenvatinib concentrations (the table below). The absolute BA of lenvatinib was 70.4% in male dogs and 78.4% in male monkeys.

PK parameters of lenvatinib in various animal species

Animal species	Route of administration	Dose (mg/kg)	Sex	n	$AUC_{0\text{-}inf}$ (μg·h/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (h)	C_{max} [*1] (μg/mL)	t_{max} [*2] (h)
Mouse[*3]	Intravenous	3	Female	3[*4]	8.69	345	714.3	2.05	7.05	-
	Oral	3	Female	3[*4]	5.60	-	-	2.09	1.97	0.5
		10	Female	3[*4]	27.7	-	-	1.74	10.5	0.5
		30	Female	3[*4]	118	-	-	1.85	31.3	1
Rat	Intravenous	3	Male	4	30.1 ± 1.3	100 ± 4	392 ± 10	3.65 ± 0.09	14.1 ± 0.2	-
	Oral	3	Male	4	20.7 ± 3.1	-	-	3.61 ± 0.21	6.17 ± 1.37	0.5 (0.25, 0.5)
		10	Male	4	78.3 ± 6.6	-	-	5.27 ± 0.33	16.6 ± 1.2	0.5 (0.25, 1)
		30	Male	4	146 ± 18	-	-	4.95 ± 0.77	23.2 ± 4.8	1 (1, 2)
Dog	Intravenous	3	Male	4	8.42 ± 0.93	368 ± 36	1610 ± 249	5.27 ± 0.83	2.29 ± 0.09	-
	Oral	3	Male	4	5.48 ± 1.37	-	-	4.76 ± 0.94	1.27 ± 0.30	2 (0.5, 2)
Monkey	Intravenous	3	Male	4	12.9 ± 1.1	238 ± 21	794 ± 88	4.28 ± 0.34	4.64 ± 0.34	-
	Oral	3	Male	4	10.3 ± 1.5	-	-	4.07 ± 0.29	2.50 ± 0.45	2 (1, 2)

Mean ± standard error (SE); -, Not calculated; *1, Plasma concentration at 5 minutes after intravenous administration; *2, Mode (range); *3, PK parameters calculated from the arithmetic mean of plasma lenvatinib concentrations at each timepoint; *4, Number of animals at each timepoint

A single oral dose of 3 mg/kg of lenvatinib in which quinoline ring is radiolabeled with ^{14}C (^{14}C-lenvatinib) was administered to male rats to determine blood radioactivity concentrations. The radioactivity concentration peaked (3.10 μg eq./mL) at 0.5 hours after administration and then was eliminated in a triphasic manner ($t_{1/2}$ in the first, second, and third phases were 4.50 hours, 13.6 hours, and 1.90 days, respectively). $AUC_{0\text{-}inf}$ of the radioactivity concentrations was 25.34 μg eq.h/mL.

A single oral dose of 3 mg/kg of ^{14}C-lenvatinib or lenvatinib in which the chlorobenzene ring is radiolabeled with ^{14}C (CB-^{14}C-lenvatinib) was administered to male monkeys to determine the radioactivity concentrations in the blood, plasma, and erythrocytes (the table below). $AUC_{0\text{-}inf}$ and apparent $t_{1/2}$ of plasma radioactivity from either ^{14}C-lenvatinib or CB-^{14}C-lenvatinib were comparable to those of radioactivity in the blood and erythrocytes.

PK parameters of radioactivity (male monkeys, single oral dose)

Chemical compound administered	Specimens measured	$AUC_{0\text{-}inf}$ (μg eq.·h/mL)	C_{max} (μg eq./mL)	t_{max} [*1] (h)	Apparent $t_{1/2}$		
					First phase (h)	Second phase (day[*2])	Third phase (day[*2])
^{14}C-lenvatinib	Blood	13.22 ± 1.27	0.5367 ± 0.0854	6 (4, 6)	11.3 ± 2.6	1.18 ± 0.19	3.19 ± 0.35
	Plasma	13.86 ± 1.00	0.6821 ± 0.1176	4 (4, 6)	8.90 ± 1.81	1.15 ± 0.19	3.43 ± 0.41
	Erythrocyte	14.16 ± 1.28	0.4855 ± 0.0087	6 (4, 6)	13.1 ± 3.1	1.34 ± 0.29	4.27 ± 1.03
CB-^{14}C-lenvatinib	Blood	13.81 ± 0.64	2.0974 ± 0.2140	1 (1, 4)	5.01 ± 0.37	21.9 ± 1.9	76.5 ± 4.7
	Plasma	17.60 ± 0.11	3.2930 ± 0.4842	1 (1, 4)	4.28 ± 0.35	14.8 ± 0.9	88.8 ± 11.9
	Erythrocyte	12.30 ± 1.51	1.0724 ± 0.1076	1 (1, 4)	6.44 ± 0.39	42.3 ± 5.5	79.8 ± 2.3

Mean ± SE; n = 3; *1, Median (range); *2, Hours for the CB-^{14}C-lenvatinib group

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

Lenvatinib was administered orally to male and female rats once daily at 1 to 100 mg/kg for 4 weeks or at 0.4 to 10 mg/kg for 13 or 26 weeks to determine plasma lenvatinib concentrations. The PK parameters of lenvatinib following repeated administration for 4 or 26 weeks were as shown in the table below and did not show any clear gender-related difference. C_{max} and $AUC_{0\text{-}24h}$ of lenvatinib on Day 1 were dose-proportional in a dose range from 0.4 to 10 mg/kg, but tended to increase less than dose-proportionally at the doses of ≥10 mg/kg. In males and females in the 15, 30, and 100 mg/kg groups, C_{max} and $AUC_{0\text{-}24h}$ of lenvatinib decreased following repeated administration, but in the other groups, repeated administration did not affect C_{max} or $AUC_{0\text{-}24h}$ of lenvatinib. The applicant explained that the decreases in C_{max} and $AUC_{0\text{-}24h}$ of lenvatinib following repeated administration in the high-dose groups (15-100 mg/kg) were possibly attributable to decreased gastrointestinal absorption of lenvatinib that resulted from gastrointestinal disorders associated with repeated administration [see "3.(iii).A.(2).1) Four-week repeated oral dose toxicity study in rats"]. The PK of lenvatinib in the 13-week repeat-dose study tended to be similar to that in the 26-week repeat-dose study.

PK parameters of lenvatinib (male and female rats, 4- or 26-week repeated oral administration)

Treatment duration	Dose (mg/kg)	Timepoint (Day)	Sex	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{0-24h} (μg·h/mL)
4 weeks	1	1	Male	1.12 ± 0.40	1.00 (0.50, 2.00)	4.88 ± 0.80
			Female	2.21 ± 0.16	0.38 (0.25, 0.50)	7.49 ± 0.81
		27	Male	1.35 ± 0.70	1.00 (1.00, 8.00)	6.99 ± 0.69
			Female	2.75 ± 0.16	0.50 (0.50, 0.50)	9.16 ± 1.01
	10	1	Male	24.5 ± 2.2	0.50 (0.50, 0.50)	73.3 ± 7.1
			Female	24.9 ± 10.4	0.25 (0.25, 4.00)	69.5 ± 13.4
		27	Male	16.7 ± 3.3	1.00 (1.00, 1.00)	66.6 ± 2.5
			Female	25.0 ± 3.4	0.50 (0.25, 0.50)	64.5 ± 4.8
	15	1	Male	29.7 ± 6.4	0.50 (0.50, 1.00)	99.0 ± 17.4
			Female	47.9 ± 13.1	0.25 (0.25, 1.00)	147 ± 21
		27	Male	22.3 ± 5.7	1.50 (0.50, 2.00)	88.4 ± 15.7
			Female	41.5 ± 5.2	0.75 (0.25, 1.00)	137 ± 12
	30	1	Male	64.7 ± 7.2	0.50 (0.50, 1.00)	284 ± 31
			Female	48.0 ± 10.1	0.63 (0.25, 2.00)	246 ± 31
		27	Male	21.3 ± 12.3	3.00 (2.00, 8.00)	186 ± 41
			Female*2	28.3 ± 10.5	2.00 (1.00, 2.00)	186 ± 19
	100	1	Male	83.3 ± 15.1	2.00 (2.00, 2.00)	633 ± 139
			Female	103 ± 21	3.00 (2.00, 4.00)	790 ± 124
		27	Male*2	10.2 ± 7.7	8.00 (8.00, 24.00)	188 ± 149
			Female	11.8 ± 15.0	16.00 (2.00, 24.00)	123 ± 108
26 weeks	0.4	1	Male	0.362 ± 0.121	1.00 (0.50, 1.00)	2.09 ± 0.20
			Female	0.603 ± 0.108	0.25 (0.25, 0.50)	2.32 ± 0.26
		181	Male	0.505 ± 0.146	1.25 (0.50, 4.00)	3.21 ± 0.26
			Female	0.950 ± 0.175	0.25 (0.25, 0.50)	3.55 ± 0.70
	2	1	Male	2.66 ± 0.58	0.25 (0.25, 0.50)	12.4 ± 1.5
			Female	3.32 ± 0.72	0.38 (0.25, 1.00)	13.2 ± 1.1
		181	Male	4.01 ± 0.87	0.50 (0.25, 0.50)	18.2 ± 0.7
			Female	3.97 ± 1.54	0.50 (0.25, 0.50)	17.0 ± 2.3
	10	1	Male	7.65 ± 1.47	3.00 (1.00, 8.00)	62.2 ± 19.2
			Female	14.7 ± 2.2	0.38 (0.25, 4.00)	85.2 ± 9.7
		149	Male*2	10.2 ± 2.1	1.00 (0.50, 2.00)	55.6 ± 13.5
		181	Female	19.3 ± 4.1	0.38 (0.25, 1.00)	71.2 ± 8.8

Arithmetic mean ± SD; n = 4; *1, Median (range); *2, n = 3

Lenvatinib was administered orally once daily at 0.1 to 30 mg/kg for 4 weeks to male and female dogs to determine plasma lenvatinib concentrations (the table below). There were no clear gender-related differences in the PK parameters of lenvatinib. In the investigated dose range, C_{max} and AUC_{0-24h} of lenvatinib on Day 1 showed dose proportionality. C_{max} in the 30 mg/kg group (males, females) and AUC_{0-24h} in the 0.1 mg/kg group (females), the 0.5 mg/kg group (females), and the 30 mg/kg group (males) tended to decrease following repeated administration, but in most of the groups, C_{max} and AUC_{0-24h} were not affected by repeated administration.

PK parameters of lenvatinib (male and female dogs, 4-week repeated oral administration)

Dose (mg/kg)	Day of measurement (Day)	Sex	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{0-24h} (μg·h/mL)
0.1	1	Male	3	0.0234 ± 0.0072	2.00 (2.00, 2.00)	0.142 ± 0.009
		Female	3	0.0294 ± 0.0067	2.00 (2.00, 2.00)	0.198 ± 0.053
	28	Male	3	0.0191 ± 0.0021	2.00 (2.00, 2.00)	0.141 ± 0.026
		Female	3	0.0208 ± 0.0059	2.00 (2.00, 2.00)	0.133 ± 0.054
0.5	1	Male	5	0.101 ± 0.035	2.00 (1.00, 2.00)	0.615 ± 0.165
		Female	5	0.123 ± 0.033	2.00 (2.00, 4.00)	0.817 ± 0.183
	28	Male	5	0.105 ± 0.044	2.00 (2.00, 2.00)	0.558 ± 0.162
		Female	5	0.102 ± 0.018	2.00 (2.00, 2.00)	0.568 ± 0.103
2	1	Male	3	0.375 ± 0.027	2.00 (2.00, 4.00)	2.37 ± 0.86
		Female	3	0.277 ± 0.095	2.00 (1.00, 4.00)	1.61 ± 0.11
	8	Male	3	0.367 ± 0.079	4.00 (2.00, 4.00)	2.63 ± 0.65
		Female	3	0.377 ± 0.170	4.00 (4.00, 4.00)	2.78 ± 0.89
6	1	Male	3	0.893 ± 0.114	4.00 (2.00, 4.00)	6.55 ± 1.83
		Female	3	1.31 ± 0.22	2.00 (2.00, 4.00)	7.52 ± 1.38
	8	Male	3	0.524 ± 0.437	8.00 (4.00, 8.00)	7.18 ± 6.30
		Female	3	0.947 ± 0.768	2.00 (0, 4.00)	7.02 ± 5.58
30	1	Male	3	3.97 ± 1.55	4.00 (2.00, 8.00)	44.1 ± 23.6
		Female	3	4.14 ± 2.23	4.00 (4.00, 4.00)	38.6 ± 24.0
	8	Male	3	1.25 ± 0.54	4.00 (4.00, 4.00)	15.4 ± 5.2
		Female	3	2.44 ± 0.26	8.00 (4.00, 8.00)	39.3 ± 3.4

Arithmetic mean ± SD; *, Median (range)

Lenvatinib (in capsules) was administered orally once daily at 0.3 to 30 mg/kg for 4 weeks to male and female cynomolgus monkeys to determine plasma lenvatinib concentrations (the table below). There were no clear gender-related differences in the PK parameters of lenvatinib. In the investigated dose range, C_{max} and AUC_{0-24h} of lenvatinib on Day 1 showed dose proportionality. In almost all groups, the repeated administration did not affect C_{max} or AUC_{0-24h} of lenvatinib, while, in the 30 mg/kg group (males), AUC_{0-24h} tended to increase following repeated administration.

PK parameters of lenvatinib (male and female cynomolgus monkeys, 4-week repeated oral administration)

Dose (mg/kg)	Day of measurement (Day)	Sex	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{0-24h} (μg·h/mL)
0.3	1	Male	3	0.0342 ± 0.0215	4.00 (4.00, 4.00)	0.194 ± 0.165
		Female	3	0.0188 ± 0.0194	3.00 (2.00, 4.00)	0.0962 ± 0.0992
	28	Male	3	0.0422 ± 0.0055	4.00 (4.00, 4.00)	0.328 ± 0.030
		Female	3	0.0538 ± 0.0422	2.00 (2.00, 4.00)	0.292 ± 0.162
3	1	Male	5	0.400 ± 0.221	2.00 (1.00, 4.00)	2.27 ± 1.07
		Female	5	0.248 ± 0.070	2.00 (2.00, 4.00)	1.66 ± 0.26
	28	Male	5	0.388 ± 0.087	2.00 (2.00, 4.00)	2.34 ± 0.52
		Female	5	0.275 ± 0.108	4.00 (2.00, 4.00)	2.05 ± 0.55
30	1	Male	5	3.32 ± 4.16	4.00 (2.00, 4.00)	16.4 ± 16.2
		Female	5	2.62 ± 1.52	4.00 (2.00, 4.00)	15.9 ± 7.7
	28	Male	5	3.34 ± 1.71	4.00 (2.00, 8.00)	30.0 ± 19.0
		Female	4	1.98 ± 1.30	4.00 (4.00, 4.00)	18.8 ± 13.2

Arithmetic mean ± SD; *, Median (range)

Lenvatinib (solution) was administered orally once daily at 0.1 to 3 mg/kg for 13 or 39 weeks to male and female cynomolgus monkeys to determine plasma lenvatinib concentrations. The PK parameters of lenvatinib following repeated administration for 39 weeks were as shown in the table below and did not show any clear gender-related difference. In the investigated dose range, a trend of more than dose-proportional increase was observed in C_{max} and AUC_{0-24h} of lenvatinib on Day 1, but the deviation from linearity was not large. The applicant explained that such a non-linear increase was considered attributable to inter-animal variability. The repeated administration did not affect C_{max} or AUC_{0-24h} of lenvatinib. The PK of lenvatinib in the 13-week repeat-dose study tended to be similar to that in the 39-week repeat-dose study.

PK parameters of lenvatinib
(male and female cynomolgus monkeys, 39-week repeated oral administration)

Dose (mg/kg)	Day of measurement (Day)	Sex	C_{max} (μg/mL)	t_{max}*1 (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)
0.1	1	Male	0.0125 ± 0.0023	4.00 (2.00, 4.00)	0.0884 ± 0.0343
		Female	0.0204 ± 0.0111	2.00 (2.00, 4.00)	0.150 ± 0.094
	273	Male	0.0332 ± 0.0133	2.00 (2.00, 2.00)	0.205 ± 0.095
		Female	0.0388 ± 0.0096	2.00 (1.00, 2.00)	0.265 ± 0.040
0.5	1	Male	0.173 ± 0.049	2.00 (1.00, 4.00)	1.05 ± 0.21
		Female	0.163 ± 0.065	1.50 (1.00, 2.00)	0.973 ± 0.257
	273	Male	0.290 ± 0.037	1.00 (1.00, 2.00)	1.54 ± 0.36
		Female	0.231 ± 0.033	1.50 (1.00, 2.00)	1.29 ± 0.09
3.0	1	Male	1.33 ± 0.34	1.50 (1.00, 2.00)	7.61 ± 1.66
		Female	1.92 ± 0.58	1.00 (1.00, 2.00)	8.22 ± 2.75
	273	Male*2	1.89 ± 0.22	2.00 (1.00, 4.00)	11.2 ± 1.9
		Female	1.74 ± 0.12	1.50 (1.00, 4.00)	8.37 ± 1.65

Arithmetic mean ± SD; n = 4; *1, Median (range); *2, n = 3

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

Membrane permeability of ^{14}C-lenvatinib was investigated in a pig kidney LLC-PK1 cell line. The permeability coefficient of ^{14}C-lenvatinib from the apical surface to the basolateral surface ($P_{app\ A\rightarrow B}$) at 1 μmol/L was 39.7×10^{-6}cm/s, which was comparable to the $P_{app\ A\rightarrow B}$ of ^{3}H-labeled prazosin (41.3×10^{-6}cm/s), used as the control in this investigation. The applicant explained that the membrane permeability of lenvatinib was considered to be high, because it has been reported that the $P_{app\ A\rightarrow B}$ of prazosin in a human colon cancer Caco-2 cell line is comparable to those of highly membrane-permeable metoprolol and drugs classified in Class 1 or 2 under Biopharmaceutics Classification System (BCS) *(Eur J Med Chem.* 2002;37:399-407, *J Pharm Sci.* 2008;97:4557-74).

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

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

Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib to male albino rats, the tissue distribution of the radioactivity was investigated. At 30 minutes after dosing (the first timepoint to measure tissue radioactivity concentrations), the radioactivity concentration peaked in most of the tissues. Compared with the plasma radioactivity concentration (6.28 μg eq./mL), the radioactivity concentration was higher in the small intestine, liver, adrenal glands, and stomach (2.59, 1.50, 1.32, and 1.19 times, respectively, the plasma radioactivity concentration). The cerebral and spinal radioactivity concentrations were, on the other hand, as low as 1.4% to 1.8% of the plasma radioactivity concentration. The radioactivity concentrations in most of the tissues decreased over time in the same nammer as the blood radioactivity concentration did. The radioactivity was slowly eliminated from the trachea, artery, submandibular lymph node, sciatic nerve, and urinary bladder, but at 336 hours after dosing, the radioactivity decreased to ≤0.15% of the administered radioactivity in all of the investigated tissues.

Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib or CB-^{14}C-lenvatinib to male cynomolgus monkeys, the tissue distribution of the radioactivity was investigated.

In the study using ^{14}C-lenvatinib, the radioactivity concentration peaked in most of the tissues at 4 hours after dosing (the first timepoint to measure tissue radioactivity concentrations), but those in the choroid, irises, large intestine, sclera, corneas, and lenses peaked at 24 hours. At 4 hours after dosing, the radioactivity concentrations in most of the tissues were higher than the plasma radioactivity concentration, and the radioactivity detected in the liver and gallbladder bile accounted for 10.77% and 9.04%, respectively, of the administered radioactivity. The cerebral and spinal radioactivity concentrations were, on the other hand, as low as 10% to 14% of the plasma radioactivity concentration. The radioactivity concentrations in most of the tissues decreased over time in the same manner as the plasma radioactivity concentration did. The radioactivity was slowly eliminated from melanin-containing eye tissues (choroid, ciliary body, irises), skin, fat, and sclera, but at 168 hours after dosing, the radioactivity decreased to ≤0.74% of the administered radioactivity in all of the investigated tissues.

In the study using CB-^{14}C-lenvatinib, the radioactivity concentration peaked in most of the tissues at 2 hours after dosing (the first timepoint to measure tissue radioactivity concentrations). High radioactivity distributions were found in the liver, gallbladder, kidneys, and eye tissues (choroid, ciliary body, irises). The mean radioactivity concentration in the central nervous system was 10% of the plasma radioactivity concentration. The radioactivity was eliminated from all the investigated tissues except for eye tissues by 168 hours after dosing.

The applicant explained that the above data showed high melanin affinity of lenvatinib and its metabolites.

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

Lenvatinib at 0.3 to 30 μg/mL was incubated with mouse, rat, dog, monkey, and human plasma specimens, and the plasma protein binding of lenvatinib was investigated by the equilibrium dialysis method. The highest plasma protein binding rate of lenvatinib (mean at each concentration) was found in humans (97.87%-98.62%) followed in descending order by rats (97.70%-98.20%), mice (96.28%-96.92%), monkeys (95.90%-96.17%), and dogs (89.71%-91.75%). In any of the animal species, the plasma protein binding rate of lenvatinib was not clearly concentration-dependent in the investigated concentration range.

Lenvatinib at 0.3 to 30 μg/mL was incubated with human serum albumin, α1-acid glycoprotein, and γ-globulin, and the binding rate of lenvatinib (mean at each concentration) was 96.62% to 97.05%, 46.37% to 69.90%, and 19.11% to 23.86%, respectively. The applicant thus explained that in human plasma, the main binding protein for lenvatinib was albumin.

^{14}C-lenvatinib at 0.1 to 10 μg/mL was incubated with mouse, rat, dog, monkey, and human blood specimens, and the distribution of lenvatinib in blood cells was investigated. The highest blood/plasma concentration ratio of the radioactivity (mean at each concentration) was found in dogs (0.893-1.06) followed in descending order by monkeys (0.699-0.813), mice (0.686-0.724), rats (0.627-0.660), and humans (0.589-0.608). The applicant explained that the differences in blood/plasma concentration ratio of the radioactivity among the animal species were considered to reflect the differences in plasma protein binding rate. In the investigated concentration range, the blood/plasma concentration ratio of the radioactivity was almost constant in the human blood specimens. However, in other animal species, the ratio tended to decrease with the increasing lenvatinib concentration. The applicant explained that blood cell binding capacity of lenvatinib was possibly saturated at increased lenvatinib concentrations.

3.(ii).A.(2).3) Placental transfer

^{14}C-lenvatinib at 3 mg/kg was administered orally in a single dose to pregnant rats (Gestation Day 13, Gestation Day 18), and the placental transfer of lenvatinib were investigated. At 0.5 hours after dosing (the first timepoint to measure radioactivity concentrations), the radioactivity concentrations in fetuses were ≤2% of the radioactivity concentrations in maternal plasma, and the distribution of radioactivity in each fetus was ≤0.02% of the administered radioactivity at any timepoint (0.5, 6, and 24 hours after dosing).

The applicant explained that the above findings indicated low placental transfer of lenvatinib or its metabolites.

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

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

Lenvatinib at 10 μg/mL was incubated with mouse, rat, dog, monkey, and human liver microsomes in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH), and the metabolites of lenvatinib were investigated. In the study using human liver microsomes, me114 (demethylated form) was detected as a major metabolite of lenvatinib, and the other metabolites detected included me88 (decyclopropylated form), me107 (*N*-oxidated form), me105 (hydroxylated form at cyclopropyl group), me37 (quinoline form, formed by *O*-dearylation), me103 (form hydroxylated at cyclopropyl group of me114), me110 (form hydroxylated at cyclopropyl group of me105), and me119 (*N*-oxidated form of me114). Each of the 8 metabolites detected in the human liver microsomes was detected in

liver microsomes of at least 1 animal species investigated.

To identify cytochrome P450 (CYP) isoforms involved in human metabolism of lenvatinib, the following studies were conducted. The applicant explained that the results of the studies identified CYP3A4 as a possible major isoform involved in human metabolism of lenvatinib.

- Lenvatinib at 0.005 to 10 μg/mL was incubated with recombinant human CYP (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4). As a result, the highest contribution to CYP-dependent metabolism of lenvatinib (results at each concentration) was found with CYP3A4 (80.0%-90.0%) followed by CYP1A2 (2.4%-7.6%) and CYP2B6 (3.0%-6.7%).

- ^{14}C-lenvatinib at 5 to 20 ng/mL was incubated with human liver microsomes in the presence of CYP3A inhibitor (ketoconazole), CYP2C19 and 2B6 inhibitor (ticlopidine), CYP1A2 inhibitor (α-naphthoflavone), and anti-CYP3A4 or 2C19 monoclonal antibody. As a result, the metabolism of lenvatinib was inhibited by 48.0% to 52.4% and 23.3% to 48.2% in the presence of CYP3A inhibitor and anti-CYP3A4 monoclonal antibody, respectively. The other inhibitors and anti-CYP2C19 monoclonal antibody did not show any clear inhibitory effect against the metabolism of lenvatinib.

To identify metabolizing enzymes involved in formation of me115 (quinolone form) and me118 (quinolone form of me114), major fecal metabolites in humans [see "4.(ii).A.(1).1) Foreign phase I study"], as well as me88, me114, and me107, which were suggested to be formed through CYP-mediated metabolism, the following studies using human liver S9 fraction were conducted. The applicant explained that the results of the studies suggested that (a) CYP is mainly involved in formation of me88, me114, and me107, (b) aldehyde oxidase (AO) is mainly involved in formation of me115, and (c) me118 is formed as a consequence of AO-mediated metabolism on me114, which is previously formed from lenvatinib by CYP.

- A CYP inhibitor (ketoconazole) suppressed the formation of me88, me114, and me107 to 0%, 32%, and 12%, respectively, of levels of these metabolites formed without the inhibitor.

- From lenvatinib, me115 was formed independently of NADPH, and raloxifene and menadione (AO inhibitors) suppressed the formation of me115 to 0% and 35%, respectively, of a level of the metabolite formed without an AO inhibitor. On the other hand, addition of either xanthine oxidase inhibitor (allopurinol) or flavin-containing monooxygenase inhibitor (methimazole) hardly affected formation of me115.

- From me114, me118 was formed, but not from me107 or me115. AO inhibitors (raloxifene, menadione) suppressed formation of me118.

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

Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib to male rats, its metabolites in the plasma, liver, kidneys, urine, feces, and bile were investigated.

- At 4 hours after dosing, only unchanged lenvatinib was identified in the plasma, and the unchanged lenvatinib was also the main compound detected in the liver and kidneys (72.08% and 75.16%, respectively, of the radioactivity in the sample). As major metabolites in the liver and kidneys, me40 (glutathione conjugate at the 4-position on the quinoline ring of lenvatinib) and me41 (mercapturic acid conjugate at the 4-position on the quinoline ring of lenvatinib) were detected (14.14% and 6.70%, respectively, of the radioactivity in the sample).

- In the urine sample until 48 hours after dosing, me41 was mainly detected (9.15% of the administered radioactivity), but unchanged lenvatinib was hardly detected. In the fecal sample until 48 hours after dosing, unchanged lenvatinib was mainly detected (31.01% of the administered radioactivity), and as the major fecal metabolites, me25 and m11 (both oxidized forms of me36 [cysteine conjugate at the 4-position on the quinoline ring of lenvatinib]) were detected (the radioactivity sum of me25 and m11 accounts for 8.56% of the administered radioactivity).

- In the bile until 24 hours after dosing, me40 and unchanged lenvatinib were mainly detected (10.00% and 4.65%, respectively, of the administered radioactivity).

Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib to male monkeys, the following studies of the metabolites in the plasma, liver, kidneys, urine, feces, and bile were conducted.

- Unchanged lenvatinib was the main compound detected in the plasma at any timepoint (1-48 hours after dosing).

- At 4 hours after dosing, the main metabolites detected in the liver were me10 (with disulfide bonds linking between 2 cysteine residues of lenvatinib through the C-N bound formation in the quinoline ring) and me40 (9.86% and 10.05%, respectively, of the radioactivity in the sample). As the major metabolites in the kidneys, me104 and me105 mixture and me10 were detected (2.37% and 3.74%, respectively, of the radioactivity in the sample).

- In the urine until 48 hours after dosing, me10, m11, and m16 (disulfide form) were mainly detected (11.80%, 10.73%, and 18.23%, respectively, of the radioactivity in the sample). In the gallbladder bile at 4 hours after dosing, m16 was mainly detected (38.42% of the radioactivity in the sample).

- In the feces until 72 hours after dosing, unchanged lenvatinib was mainly detected (8.38% of the radioactivity in the sample). As the major fecal metabolite, me19 (oxidized me36) was detected (6.24% of the radioactivity in the sample). In addition, 14.60% of the fecal radioactivity was further extracted by treatment with 2-mercaptoethanol. The applicant explained that the presence of the fecal metabolites having disulfide or thioether bond was suggested.

The main metabolic pathway of lenvatinib was presumed to involve cleavage of *O*-aryl bond at the 4-position of the quinoline ring formed through glutathione conjugation. CB-^{14}C-lenvatinib at 3 mg/kg was administered orally in a single dose to male monkeys to investigate the metabolism profile of the chlorobenzene moiety of lenvatinib, and the following studies of the metabolites in the plasma, liver, kidneys, urine, feces, and gallbladder bile were conducted.

- Unchanged lenvatinib was mainly detected in the plasma at any timepoint (1-24 hours after dosing). As the major metabolite in the plasma, me50 (glucuronate conjugate of me92 [chlorophenol form resulted from cleavage at the 4-position of the quinoline ring of lenvatinib]) was detected, and me50 accounted for 38.93% of the radioactivity in the plasma at 24 hours after dosing.

- At 2 hours after dosing, as the major metabolites in the liver and kidneys, me92 (39.05% and 11.93%, respectively, of the radioactivity in the sample) and me50 (8.53% and 16.51%, respectively, of the radioactivity in the sample) were detected.

- In the gallbladder bile at 2 hours after dosing, a mixture of me117 (2-oxygen and 2-hydrogen adduct) and unchanged lenvatinib, which were eluted in one peak, was mainly detected (17.86% of the radioactivity in the sample), and as the major metabolite, me61 (cysteine conjugate of me92) was detected (12.52% of the radioactivity in the sample).

- In the urine until 72 hours after dosing, unchanged lenvatinib was not detected, and me50 and me79 (sulfate conjugate of me92) were mainly detected (71.92% and 8.42%, respectively, of the radioactivity in the sample). The radioactivity of unchanged lenvatinib in the feces until 72 hours after dosing accounted for 10.84% in the fecal radioactivity, and as the major fecal metabolites, me92 and me94 (carboxylate form) mixture and me115 were detected (29.85% and 21.28%, respectively, of the radioactivity in the sample).

The applicant explained that based on the results from the above studies of *in vitro* and *in vivo* metabolism, the main metabolic pathway of lenvatinib is presumed to be oxidation metabolism by CYPs and AO as well as glutathione conjugation.

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

3.(ii).A.(4).1) Excretion in urine, feces, and bile

Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib to male rats, urinary and fecal excretion rates of the radioactivity up to 168 hours after dosing (% of the dosed radioactivity) were 12.2% and 87.2%, respectively. Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib to biliary cannulated male rats, the biliary, urinary, and fecal excretion rates of the radioactivity up to 48 hours after dosing were 41.6%, 18.1%, and 27.2%, respectively.

The applicant explained that the above findings indicated that lenvatinib is mainly excreted in feces through bile in rats.

Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib or CB-^{14}C-lenvatinib to male cynomolgus monkeys, urinary and fecal excretion rates of the radioactivity were determined. The urinary and fecal excretion rates up to 168 hours after dosing were 17.2% and 72.8%, respectively, in the ^{14}C-lenvatinib group and 79.9% and 13.6%, respectively, in the CB-^{14}C-lenvatinib group.

The applicant explained that the above findings suggested that after cleavage of *O*-aryl bond at the 4-position of the quinoline ring of lenvatinib, its metabolites with the quinoline moiety are mainly excreted in feces, and those with the chlorobenzene moiety are mainly excreted in urine.

Following oral administration of ^{14}C-lenvatinib to rats and monkeys, the radioactivity concentration did not show biphasic changes, suggestive of enterohepatic circulation. The applicant therefore explained that the enterohepatic circulation is not largely involved in the PK of lenvatinib.

3.(ii).A.(4).2) Excretion in milk

Following a single oral dose of 3 mg/kg of ^{14}C-lenvatinib to lactating female rats (9 or 10 days after the delivery), the excretion of the radioactivity in milk was investigated. The radioactivity concentration in the milk peaked (5.28 μg eq./mL) at 1 hour after dosing. $t_{1/2}$ of the radioactivity in milk (4.34 hours) was close to that in plasma (4.02 hours), indicating rapid elimination of the radioactivity from milk. On the other hand, $AUC_{0\text{-inf}}$ of the radioactivity in milk (37.50 μg eq.·h/mL) was approximately 2 times $AUC_{0\text{-inf}}$ in the plasma (17.85 μg eq.·h/mL). At any timepoint (1-12 hours after dosing), unchanged lenvatinib was the main compound detected in milk (94.69%-98.45% of the radioactivity in milk).

The applicant explained that the above findings indicated that lenvatinib is readily transferred to milk and excreted mainly as unchanged lenvatinib in milk.

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

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

The applicant explained that the possible occurrence of pharmacokinetic interaction between lenvatinib and a substrate of CYP3A or CYP2C8 following their concomitant use was suggested, based on C_{max} (2.34 μmol/L, total concentration) and gastrointestinal concentration (225 μmol/L) of lenvatinib at steady state during the treatment under the proposed dosage and administration in addition to the study described below.

- Substrates of the CYP isoforms (1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A) were incubated with human liver microsomes in the presence of lenvatinib (100 μmol/L) and the inhibitory effect of lenvatinib against CYP isoforms was investigated. As a result, lenvatinib inhibited metabolism of a substrate of CYP3A (midazolam) by 56.6%. On the other hand, the inhibitory effect of lenvatinib against metabolism of substrates of CYP1A2, 2B6, 2C9, 2C19, and 2D6 was weak (inhibitory rate, 21.4%-42.2%), and lenvatinib did not clearly inhibit metabolism of the substrates of CYP2A6 or 2E1.

- Substrates of CYP2C8 and 3A were incubated with human liver microsomes in the presence of lenvatinib (3-100 μmol/L). As a result, lenvatinib inhibited metabolism of the substrate of CYP2C8 with an IC_{50} value of 10.1 μmol/L. However, lenvatinib only weakly inhibited metabolism of a substrate of CYP3A even at a concentration of 100 μmol/L (inhibitory rate, 49.3%).

- The time-dependent inhibitory effect of lenvatinib (3-100 μmol/L) against CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A was investigated using human liver microsomes. As a result, lenvatinib inhibited metabolism of a substrate of CYP3A in a time-dependent manner. The maximum inactivation rate constant (k_{inact}) and IC_{50} at the k_{inact} (K_I) were 0.0835 min^{-1} and 72.266 μmol/L, respectively. On the other hand, lenvatinib did not inhibit the other CYP isoforms in a time-dependent manner.

Substrates of UDP-glucuronosyltransferase (UGT) isoforms (1A1, 1A4, 1A6, 1A9, 2B7) were incubated with human liver microsomes in the presence of lenvatinib (0.03-30 μmol/L). As a result, lenvatinib inhibited metabolism of substrates of UGT1A1 and 1A4 with IC_{50} values of 10.6 and 14.0 μmol/L, respectively. However, the inhibitory effect of lenvatinib at 30 μmol/L against metabolism of a substrate of UGT1A9 was weak (inhibitory rate, 31.9%), and lenvatinib did not clearly inhibit metabolism of the substrates of UGT1A6 or 2B7.

The above findings showed that lenvatinib inhibited UGT1A1 and 1A4. The applicant accordingly explained that the possible occurrence of pharmacokinetic interaction between lenvatinib and a drug which was metabolized only by UGT1A1 and was mostly metabolized in the gastrointestinal tract cannot be ruled out, in consideration of the IC_{50} values against UGT1A1 and 1A4 and C_{max} of lenvatinib (concentration of free form, 0.047 μmol/L) at steady state during the treatment under the proposed dosage and administration.

The inhibitory effect of lenvatinib against AO was investigated using human liver cytosol fraction in the presence of lenvatinib (10, 100 μmol/L) as well as its metabolites of me88 (10, 100 μmol/L), me114 (1-100 μmol/L), me107 (1-100 μmol/L), me118 (10, 100 μmol/L), me115 (10, 50 μmol/L), and me37 (10, 100 μmol/L). As a result, me114 and me107 inhibited metabolism of a substrate of AO with IC_{50} values of 11.57 and 30.78 μmol/L, respectively. On the other hand, lenvatinib, me88, me118, me115, and me37 only weakly inhibited AO even at the maximum concentrations investigated, and the AO enzyme activity in their presence was 63.8% to 109.5% of that in the vehicle.

As described above, me114 and me107 inhibited AO, but their plasma concentrations following a single oral dose of 24 mg of lenvatinib were mostly below the lower limit of quantification (0.25 ng/mL) [see "4.(ii).A.(1).1) Foreign phase I study"]. The applicant therefore explained that the pharmacokinetic interaction mediated by the inhibition against AO is unlikely to occur during the treatment of lenvatinib.

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

The applicant explained that based on the results from the following studies, lenvatinib is unlikely to cause pharmacokinetic interaction mediated by induction of CYP and UGT isoforms.

- Human hepatocytes were treated with lenvatinib (0.3-3 μmol/L) for 72 hours, and enzyme activities of CYP1A2, 2C9, and 3A as well as mRNA expression levels of CYP1A1, 1A2, 2B6, 2C9, and 3A4 were investigated. Following treatment with lenvatinib at 3 μmol/L, the enzyme activity of CYP3A and mRNA expression level of CYP3A4 increased to 1.54 and 1.65 times, respectively, those in the vehicle (0.1% DMSO solution). However, they did not increase in a lenvatinib-concentration dependent manner, and the extents of their increases following treatment with lenvatinib were <20% of those with rifampicin, the positive control. The applicant explained that the above findings suggest that lenvatinib only weakly induces the enzyme activity of CYP3A. Lenvatinib did not increase enzyme activities or mRNA expression levels of the other CYP isoforms investigated.

- Human hepatocytes were treated with lenvatinib (0.3-3 μmol/L) for 72 hours, and enzyme activities as well as mRNA expression levels of UGT1A1, 1A4, 1A6, 1A9, and 2B7 were investigated. As a result, lenvatinib did not increase enzyme activities or mRNA expression levels of any UGT isoform investigated.

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

The applicant explained that the results from the following studies indicated that lenvatinib was a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

- P-gp-mediated transport of ^{14}C-lenvatinib (1, 3, 10 μmol/L) was investigated using a pig kidney LLC-PK1 cell line expressing human P-gp (P-gp-expressing LLC-PK1 cell line). As a result, the membrane permeability clearance ratio of ^{14}C-lenvatinib at 1, 3, and 10 μmol/L (clearance from the basolateral surface to the apical surface/clearance from the apical surface to the basolateral surface) was 1.28, 1.31, and 1.33, respectively, in the LLC-PK1 cell line and 10.91, 10.18, and 7.95, respectively, in the P-gp-expressing LLC-PK1 cell line. The membrane permeability clearance ratio of digoxin, a P-gp substrate, at 1 μmol/L in the P-gp-expressing LLC-PK1 cell line was 12.21.

- BCRP-mediated transport of ^{14}C-lenvatinib (1 μmol/L) was investigated using a LLC-PK1 cell line expressing human BCRP (BCRP-expressing LLC-PK1 cell line). As a result, the efflux ratio of ^{14}C-lenvatinib was 1.4 and 8.4 in the LLC-PK1 cell line and BCRP-expressing LLC-PK1 cell line, respectively.

- Transport of ^{14}C-lenvatinib (1 μmol/L) mediated by each transporter was investigated using a mouse proximal tubule S_2 cell line expressing human organic anion transporter (OAT) 1 or 3, or organic cation transporter (OCT) 2 or a human embryonic kidney 293 (HEK293) cell line expressing human organic anion transport polypeptide (OATP) 1B1 or 1B3 or OCT1. As a result, the uptake of ^{14}C-lenvatinib into either cell line expressing any one of the transporters was comparable to that into the cell lines not expressing any one of them.

- Human bile salt export pump (BSEP)-mediated transport of ^{14}C-lenvatinib (10 μmol/L) was investigated using membrane vesicles expressing BSEP. As a result, the uptake activity of ^{14}C-lenvatinib into the membrane vesicles was comparable to that into the membrane vesicles not expressing BSEP.

The applicant explained that lenvatinib is unlikely to cause pharmacokinetic interactions mediated by inhibition against OAT1 and 3, OCT1 and 2, and OATP1B1 as well as BSEP, in consideration of the IC_{50} value of lenvatinib against each transporter and C_{max} of lenvatinib at steady state (total concentration and concentration of the free form was 2.34 and 0.047 μmol/L, respectively) during the treatment under the proposed dosage and administration although lenvatinib inhibits OAT1 and 3, OCT1 and 2, and OATP1B1 as well as BSEP as a result of the following studies.

- The inhibitory effect of lenvatinib (1-10 μmol/L) against P-gp-mediated transport of ^{3}H-labeled digoxin (^{3}H-digoxin) (1 μmol/L) was investigated using a P-gp-expressing LLC-PK1 cell line. As a result, lenvatinib did not clearly inhibit the P-gp-mediated transport of ^{3}H-digoxin even at the maximum concentration investigated.

- The inhibitory effect of lenvatinib (0.1-30 μmol/L) against BCRP-mediated transport of ^{3}H-labeled prazosin (^{3}H-prazosin) (0.01 μmol/L) was investigated using a BCRP-expressing LLC-PK1 cell line. As a result, lenvatinib did not clearly inhibit the BCRP-mediated transport of ^{3}H-prazosin even at the maximum concentration investigated.

- Using an S_2 cell line expressing human OAT1 or 3, or OCT2 or a HEK293 cell line expressing human OATP1B1 or 1B3 or OCT1, the inhibitory effect of lenvatinib (0.1-30 μmol/L) against OAT-, OCT-, and OATP-mediated transport of the corresponding substrates* was investigated. As a result, lenvatinib inhibited transport of the corresponding substrates mediated by OAT1- and OAT 3-, OCT1- and OCT 2- as well as OATP1B1 in a concentration-dependent manner with IC_{50} values of 7.36, 4.11, 14.9, 10.8, and 7.29 μmol/L, respectively. However, lenvatinib did not clearly inhibit OATP1B3-mediated transport of the corresponding substrate even at the maximum concentration investigated.

- The inhibitory effect of lenvatinib (0.1-25 μmol/L) against BSEP-mediated uptake of ^{3}H-labeled taurocholic acid (^{3}H-taurocholic acid) was investigated using membrane vesicles expressing human

BSEP. As a result, lenvatinib inhibited uptake of ^{3}H-taurocholic acid into the membrane vesicles with an IC_{50} value of 14.2 μmol/L.

*: Substrates of the transporters used include *p*-aminohippuric acid for OAT1, estrone sulfate for OAT3, tetraethylammonium for OCT1, metformin for OCT2, and estradiol-17β-glucuronide for OATP1B1 and 1B3.

Human hepatocytes were treated with lenvatinib (0.3-3 μmol/L) for 72 hours. As a result, the mRNA expression level of P-gp did not increase even at the maximum concentration investigated, indicating that lenvatinib does not clearly induce P-gp expression.

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 lenvatinib is acceptable.

3.(ii).B.(1) Tissue distribution

The results from tissue distribution studies in cynomolgus monkeys have shown that lenvatinib and its metabolites have high affinity to melanin-containing tissues [see "3.(ii).A.(2).1) Tissue distribution"]. PMDA therefore asked the applicant to explain the possibility that distribution of lenvatinib and its metabolites in melanin-containing tissues raises safety issues in clinical use.

The applicant responded as follows:
In consideration of the above results in cynomolgus monkeys, lenvatinib or its metabolites may accumulate in melanin-containing tissues during the treatment under the proposed dosage and administration. However, the 39-week repeat-dose study in monkeys [see "3.(iii).A.(2).9) Thirty-nine-week repeated oral dose toxicity study in monkeys"] did not show toxicity findings in the eyes or skin at up to the highest dose (3 mg/kg) investigated.

Based on the results from the global phase III study (Study E7080-G000-303) as well as Japanese and foreign phase II studies (Study E7080-J081-208 and Study E7080-G000-201, respectively) in patients with thyroid cancer, adverse events related to melanin-containing tissues (eyes, skin) were investigated by race (Caucasian, Black, Asian). As a result, the incidences of palmar-plantar erythrodysaesthesia syndrome, an adverse event related to the skin, in Black and Asian patients (50.0% [6 of 12 patients] and 60.7% [67 of 107 patients], respectively) tended to be higher than that in Caucasian patients (23.8% [94 of 395 patients]). However, the incidence of Grade 3 palmar-plantar erythrodysaesthesia syndrome was 2.53% (10 of 395 patients) in Caucasian patients, 0% (0 of 12 patients) in Black patients, and 4.67% (5 of 107 patients) in Asian patients, indicating that the incidences in Black and Asian patients did not tend to be remarkably higher than that in Caucasian patients. Furthermore, the incidence of adverse events related to the eyes in Caucasian patients was not clearly different from that in Asian patients.

Based on the above, the distribution of lenvatinib and its metabolites in melanin-containing tissues is considered unlikely to raise safety issues in clinical use of lenvatinib.

PMDA considers as follows:
In clinical use of lenvatinib, attention should be paid to adverse events potentially related to the distribution of lenvatinib or its metabolites in melanin-containing tissues, taking into account that the non-clinical studies suggested lenvatinib or its metabolites remain in melanin-containing tissues for a long period, that the incidence of palmar-plantar erythrodysaesthesia syndrome in Black and Asian patients tended to be higher than that in Caucasian patients, and that the incidence of palmar-plantar erythrodysaesthesia syndrome in Japanese patients was higher than that in foreign patients in Study E7080-G000-303 [see "4.(iii).B.(3).1) Safety profile and its differences between Japanese and non-Japanese patients"].

3.(ii).B.(2) Pharmacokinetic interactions

Lenvatinib has been demonstrated to inhibit CYP3A and 2C8 *in vitro* [see "3.(ii).A.(5).1) Enzyme

inhibition"]. The applicant explained whether or not the clinical studies to investigate pharmacokinetic interactions of lenvatinib with CYP3A and 2C8 substrates are necessary as follows:
Regarding the effect of lenvatinib on the PK of a CYP3A substrate (midazolam) or CYP2C8 substrate (repaglinide) during their concomitant use, a simulation was performed using physiologically-based pharmacokinetic models by Simcyp (ver.13.1, SimCYP). As a result, the ratios [95% CI] of the geometric mean AUC of midazolam monotherapy to that of concomitant use of midazolam and lenvatinib at 24 and 32 mg were 1.18 [1.16, 1.20] and 1.22 [1.20, 1.24], respectively; the corresponding ratios [95% CI] of repaglinide were 1.004 [1.003, 1.004] and 1.005 [1.005, 1.006], suggesting that the concomitant use with lenvatinib slightly increased AUC of midazolam, but 95% CIs of the ratios of the geometric mean AUC were all estimated to be <1.25. The sensitivity analysis indicated that AUC of repaglinide during concomitant use with lenvatinib was estimated to increase only by <1% from that of repaglinide monotherapy on the assumption that the K_i value of lenvatinib against CYP2C8 was 1.01 μmol/L, which was smaller than the IC_{50} value (10.1 μmol/L) calculated based on the *in vitro* study results [see "3.(ii).A.(5).1) Enzyme inhibition"]. In Study E7080-G000-303, 251 of 261 subjects (96.2%) in the lenvatinib group concomitantly received a CYP3A substrate and lenvatinib, and the tolerability of lenvatinib under the proposed dosage and administration was confirmed [see "4.(iii).B.(3) Safety"].

Based on the above, the pharmacokinetic interactions mediated by inhibitory effect of lenvatinib against CYP3A and 2C8 are considered unlikely to raise issues in clinical use, and it is therefore considered almost unnecessary to conduct clinical studies for the pharmacokinetic interactions.

PMDA considers as follows:
PMDA largely accepted the applicant's explanation. In consideration of the following matters, it is necessary to continue to collect information on the pharmacokinetic interactions mediated by inhibitory effect of lenvatinib against CYP3A and to appropriately provide the information to healthcare providers in clinical settings when new useful information becomes available.

- It is suggested that AUC of midazolam, a CYP3A substrate, increases when it is administered concomitantly with lenvatinib, and based on the results from Study E7080-G000-303, lenvatinib is likely to be used concomitantly with CYP3A substrates in clinical practices.

3.(iii) Summary of toxicology studies

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

In the *in vivo* studies, unless otherwise specified, lenvatinib suspended in water for injection was administered.

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Single oral dose toxicity study in rats

Lenvatinib at 0 (vehicle control, 75% PEG400 solution), 500, 1000, or 2000 mg/kg was administered orally in a single dose to male and female SD rats (n = 5/sex/group) followed by a 4-week observation period. One animal in the 1000 mg/kg group and 2 animals in the 2000 mg/kg group died 14 days after administration or later. In these animals, decreased activity, decreased body temperature, red urine, discoloration of the eyes, dilatation of the stomach and doudenum, mucosal hypertrophy, etc., were observed. In addition, in the surviving animals in the ≥1000 mg/kg groups, decreased food consumption, reduced body weight gain, white incisors, etc., were observed.

Based on the above, the approximate lethal dose of lenvatinib in this study was determined to be 1000 mg/kg.

3.(iii).A.(1).2) Single oral dose toxicity study in dogs (Reference data, non-GLP study)

Lenvatinib, mixed with lactose and encapsulated, was administered orally at 100, 300, or 1000 mg/kg to the same dogs (beagles, n = 1/sex) in a dose escalation manner with 1 week interval between doses. No deaths were observed and vomiting was observed immediately after administration at 1000 mg/kg. C_{max} and $AUC_{0\text{-}24h}$ at 1000 mg/kg were lower than those at 300 mg/kg.

Based on the above, the approximate lethal dose of lenvatinib in this study was determined to be >1000 mg/kg.

3.(iii).A.(1).3) Single oral dose toxicity study in monkeys (Reference data, non-GLP study)

Lenvatinib was administered orally at 0 mg/kg/day (vehicle control, 75% PEG400 solution) to male cynomolgus monkeys (n = 2/group) as the control group, and to the same animals, lenvatinib at 30, 100, 300, and 1000 mg/kg/day was administered orally as the lenvatinib group at an interval of 1 day between each dose in a dose escalation manner. No deaths were observed. Decreased food consumption was observed after administration of ≥300 mg/kg. The necropsy performed on the following day of administration at 1000 mg/kg revealed abnormal materials in the stomach, red spots on the stomach, and watery contents in the small and large intestines. The blood lenvatinib concentrations at 2 hours after administration at 300 and 1000 mg/kg/day were lower than that at 100 mg/kg/day.

Based on the above, the approximate lethal dose of lenvatinib in this study was determined to be >1000 mg/kg.

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

3.(iii).A.(2).1) Four-week repeated oral dose toxicity study in rats

Lenvatinib was administered orally at 0 (vehicle control, 75% PEG400 solution), 10, 30, or 100 mg/kg/day to male and female SD rats (n = 10/sex/group) for 4 weeks. In the 100 mg/kg/day group, 6 of 20 animals died or were sacrificed due to the moribund condition. The major cause of the deaths was determined to be uremia based on the laboratory findings (increases in blood urea nitrogen [BUN] and creatinine, decreased serum protein, proteinuria, urine occult blood) and histopathological findings in the kidneys (hyalinization and hyperplasia of the glomerular, dilatation of the renal tubule).

The findings observed included decreased reticulocyte count, proteinuria, glomerular hyaline droplet in the kidney, white and dysplastic incisors, decreased seminiferous epithelial cells in the testis, desquamated seminiferous epithelial cells in the epididymis, follicular atresia, myeloid cell loss, hypertrophy of epiphyseal growth plate and cartilaginous, cystic hyperplasia in the spleen in the ≥10 mg/kg/day groups; decreased platelet count, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total cholesterol, occult blood and epithelial cell in the urine, decreased testis weight, oedema in the doudenum and glandular stomach, increased mucous cells and internal haemorrhage in the stomach, inflammation in the doudenum and ileum, accumulation of foam cells and neutrophils in the jejunum, cecal submucosal tissue oedema, basophilic cell vacuolation in the pituitary gland, sinusoid dilatation and cortical necrosis in the adrenal glands, and glomerular lesion in the kidneys in the ≥30 mg/kg/day groups; and decreases in erythrocyte count, hemoglobin concentration, hematocrit level, total protein, albumin, globulin, and albumin/globulin ratio (A/G ratio), increases in BUN and creatinine, decreased ovary weight, increases in kidney weight and adrenal gland weight, adrenal gland hypertrophy, small thymus, myocardial fibril formation, bacterial myocarditis, centrilobular hepatic necrosis, extramedullary haematopoiesis in the liver, dilated renal tubule, thrombosis in the kidneys, acinus atrophy in the mandibular gland, epidermal atrophy and ulcer in the tongue, erosion in the glandular stomach and ileum, mucosal oedema in the rectum, acinus cell atrophy, oedema and fat necrosis in the pancreas, and epidermal atrophy in the vagina in the 100 mg/kg/day group.

Based on the above, the no observed adverse effect level (NOAEL) of lenvatinib in this study was determined to be <10 mg/kg/day.

3.(iii).A.(2).2) Four-week repeated oral dose toxicity study with a 4-week recovery period in rats

Lenvatinib was administered orally at 0 (vehicle control, 75% PEG400 solution), 1, or 15 mg/kg/day to male and female SD rats (n = 10-16/sex/group) for 4 weeks. The treatement period was followed by a 4-week recovery period for 6 males and 6 females each in the 0 and 15 mg/kg/day groups to investigate the reversibility.

During the recovery period, 1 animal in the 15 mg/kg/day group was found in a moribund condition due to decreased food consumption attributable to the fragile incisors. Then, the feed was changed from solid to powder, and after the recovery period, the food consumption and body weight in the 15 mg/kg/day group were found comparable to those in the 0 mg/kg/day group.

The findings included dysplasia in incisors in the ≥1 mg/kg/day groups; decreases in reticulocyte and platelet counts, increases in ALT, total cholesterol, and alkaline phosphatase (ALP), proteinuria, glomerular hyaline droplet and glomerular lesion in the kidneys, decreased testis weight, decreased seminiferous epithelial cells, desquamated seminiferous epithelial cells in the epididymis, follicular atresia, hypertrophy of epiphyseal growth plate and cartilaginous, mucosal mineralization in the stomach, basophilic cell vacuolation in the pituitary gland, myeloid cell loss, and cystic hyperplasia in the spleen in the 15 mg/kg/day group. After recovery period, the findings after the end of administration seemed reversible, although findings similar or related to the initial histopathological findings remained in the kidneys, incisors, testis, epididymides, ovaries, and bones. The findings in the tissues other than the above completely resolved.

Based on the above, the NOAEL of lenvatinib in this study was determined to be <1 mg/kg/day.

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

Lenvatinib was administered orally at 0 (vehicle control), 0.4, 2, or 10 mg/kg/day to male and female SD rats (n = 10/sex/group) for 13 weeks.

The findings included white discoloration, fracture, and dysplasia of incisors, loose stool, decreases in body weight and food consumption, decreases in erythrocyte count, platelet count, and eosinophil count, increases in mean cell volume (MCV), mean corpuscular hemoglobin (MCH), neutrophil count, monocyte count, AST, total cholesterol, glucose, and BUN, decreases in total protein, albumin, globulin, and A/G ratio, follicular atresia, acinus hyperplasia in the submandibular gland in the ≥2 mg/kg/day groups; and proteinuria and increased phosphate crystals in the urine, hypertrophy of epiphyseal plate and cartilages, glomerular lesion in the kidneys, sinusoid dilatation and pigmentation of Kupffer cells in the liver, artery fibrinoid necrosis and eosinophilic exudates in the brain choroid plexus, decreased seminiferous epithelial cells in the testis, increased mucus secretion in the vagina, sinusoid dilatation, cortical necrosis, and cortical vacuolation in the adrenal glands, mucosal hyperplasia in the glandular stomach and doudenum, mucosal mineralization in the stomach, inflammation in the duodenum gland, inflammatory cell infiltration in the glandular stomach, jejunum mucosa, and ileum mucosa, cecal submucosal tissue oedema, atrophy of the thymus, foam cell accumulation in the pulmonary alveoli, decreased zymogen granules in the pancreas, basophilic cell vacuolation in the pituitary gland, extramedullary haematopoiesis in the spleen, and myeloid cell loss in the 10 mg/kg/day group.

Based on the above, the NOAEL of lenvatinib in this study was determined to be 0.4 mg/kg/day.

3.(iii).A.(2).4) Twenty-six-week repeated oral dose toxicity study in rats (treatment period of 150 days)

Lenvatinib was administered orally at 0 (vehicle control), 0.4, 2, or 10 mg/kg/day to male and female SD rats (n = 15/sex/group) for 26 weeks. In the 10 mg/kg/day group, 8 males died by Day 147, and thus all surviving animals on Day 150 were subjected to necropsy.

In the 10 mg/kg/day group, 8 males and 3 females died or were found in a moribund condition between Day 84 and Day 147. The cause of any of the moribund conditions and deaths was determined to be the effect on the doudenum and kidneys.

The findings included decreases in total protein and albumin, increases in leukocyte count, neutrophil count, lymphocyte count, and BUN, decreased A/G ratio, white discoloration, fracture, and dysplasia of incisors, glomerular lesion in the kidneys, sinusoid dilatation in the adrenal glands, mineralization in the trabeculae lienis in the ≥2 mg/kg/day groups; and decreased erythrocyte count, increases in MCH and MCV, increases in monocyte count and ALT, decreased glucose, increased total cholesterol, hypertrophy of epiphyseal growth plate and cartilaginous, glomerulonephropathy, inflammation and

cystoid dilation in the doudenum gland, arteriolar media necrosis in the doudenum, perivascular eosinophilic exudates in the brain choroid plexus, decreased seminiferous epithelial cells in the testis, desquamated seminiferous epithelial cells in the epididymis, follicular atresia, mucosal hyperplasia and inflammation cell infiltration in the glandular stomach, accumulation of foam cell and neutrophil in the jejunum, lacunar hyperplasia in the ileum and large intestine, cecal submucosal tissue oedema, basophilic cell vacuolation in the pituitary gland, myeloid cell loss, Kupffer cell hyperplasia/hyperplasia in the liver, periportal hepatocyte pigmentation, cholangitis in the common bile duct, decreased lymphocyte in the spleen, and decreased zymogen granules in the pancreas in the 10 mg/kg/day group.

Based on the above, the NOAEL of lenvatinib in this study was determined to be 0.4 mg/kg/day.

$AUC_{0\text{-}24h}$ (3.2102-3.5546 μg·h/mL) at 0.4 mg/kg/day was, in terms of the unbound drug plasma concentrations[*1], approximately 0.8 to 0.9 times the exposure at the clinical dose[*2].

*1: The plasma protein binding rate was 97.70% to 98.20% in rats and 97.87% to 98.62% in humans.
*2: In the Japanese phase I study (Study E7080-J081-105), $AUC_{0\text{-}\tau}$ on Day 15 in Cycle 1 was 4.140 μg·h/mL in patients with solid cancer who received multiple doses of lenvatinib 24 mg once daily (QD).

3.(iii).A.(2).5) Four-week repeated oral dose toxicity study in dogs (treatment period of 15 days)

Lenvatinib was administered orally at 0 (lactose[*]), 2, or 6 mg/kg/day for 15 days, or at 30 mg/kg/day for 8 days to male and female dogs (beagles, n = 3/sex/group). In all the dose groups, the treatment period, which was initially planned to be 4 weeks, was reduced due to deterioration of the general conditions. After the end of administration, animals in the 30 mg/kg/day group were followed up for reversibility during the subsequent 20-day recovery period, and those in the other groups were subjected to necropsy after 15 days of administration.

*: In the lenvatinib groups, encapsulated mixture of lenvatinib and lactose was administered, while in the control group, only encapsulated lactose was administered. The same method was applied in the following studies.

In the 30 mg/kg/day group, 1 of 6 animals exhibited remarkably decreased food consumption even during the recovery period and became moribund due to haemoconcentration and azotemia. It was thus subjected to necropsy on Day 13 of the recovery period.

In all the lenvatinib groups, findings suggesting gastrointestinal toxicity such as watery stool, bloody stool, blackish feces, and vomiting, decreases in body weight and food consumption, and decreased reticulocyte rate as well as increases in fibrinogen, AST, ALP, and total cholesterol were observed during the treatment period. In the 30 mg/kg/day group, increased BUN was additionally observed. These findings in the 30 mg/kg/day group tended to resolve during the recovery period. At the histopathological examination of the surviving animals, arterial fibrinoid necrosis was observed in the stomach, small intestine, large intestine, liver, heart, ovaries, etc., in the 2 and 6 mg/kg/day groups, and mononuclear cell infiltration was observed in the brain choroid plexus, meninges, etc. In addition, basophilic renal tubule and glomerular lesion in the kidneys, decreased seminiferous epithelial cells in the testes, increased atretic follicle in the ovaries, and vacuolation in the adrenal fasciculata, which were considered to be changes attributable to the pharmacological effect of lenvatinib, were observed. In the 30 mg/kg/day group, in which the recovery period was included, decreased seminiferous epithelial cells in the testes, mononuclear cell infiltration in the brain choroid plexus, and oral mucosal ulcer were observed, but no vascular lesions were observed. Thus, the fibrinoid necrosis in the artery observed in the 2 and 6 mg/kg/day groups were considered to be reversible.

Based on the above, the NOAEL of lenvatinib in this study was determined to be <2 mg/kg/day.

3.(iii).A.(2).6) Four-week repeated oral dose toxicity study with a 4-week recovery period in dogs

Lenvatinib was administered orally at 0 (lactose), 0.1, or 0.5 mg/kg/day to male and female dogs (beagles, n = 3-5/sex/group) for 4 weeks. For 2 males and 2 females each in the 0 and 0.5 mg/kg/day

groups, a 4-week recovery period was included after the end of the administration to investigate the reversibility.

The findings included decreased seminiferous epithelial cells in the testis in the ≥0.1 mg/kg/day groups; and watery stool, glomerular lesion in the kidneys, arterial fibrinoid necrosis in the gallbladder, and decreases in lymphocytes and necrosis in the jejunum and ileum in the 0.5 mg/kg/day group. All the changes were reversible.

Based on the above, the NOAEL of lenvatinib in this study was determined to be <0.1 mg/kg/day.

$AUC_{0\text{-}24h}$ (0.1329-0.1413 μg·h/mL) at 0.1 mg/kg/day was, in terms of the unbound drug plasma concentrations[*1], approximately 0.2 times the exposure at the clinical dose[*2].

*1: The plasma protein binding rate was 89.71% to 91.75% in dogs and 97.87% to 98.62% in humans.
*2: In the Japanese phase I study (Study E7080-J081-105), $AUC_{0\text{-}\tau}$ on Day 15 in Cycle 1 was 4.140 μg·h/mL in patients with solid cancer who received multiple doses of lenvatinib 24 mg QD.

3.(iii).A.(2).7) Four-week repeated oral dose toxicity study with a 4-week recovery period in monkeys

Lenvatinib was administered orally at 0 (lactose), 0.3, 3, or 30 mg/kg/day to male and female cynomolgus monkeys (n = 3-5/sex/group) for 4 weeks. For 2 males and 2 females each in 0, 3, and 30 mg/kg/day groups, a 4-week recovery period was included after the end of administration to investigate the reversibility.

In the 30 mg/kg/day group, 1 of 10 animals exhibited remarkably decreased food consumption and died on Day 21. The histopathological findings in this animal included hepatocyte vacuolation, erosion in the gallbladder, basophilic renal tubule, inflammation in the duodenal gland, and degenerative changes in the uterine artery in a ddition to the histopathological findings observed also in the surviving animals.

The findings observed included loose stool, increased total bilirubin, submucosal oedema in the gallbladder, and haemorrhage in the brain choroid plexus in the 3 mg/kg/day group; and decreases in food consumption and body weight, watery stool, decreased activity, increases in total cholesterol, AST, ALT, BUN, and creatinine, increased urine protein, glomerular lesion in the kidneys, arterial fibrinoid necrosis in the gallbladder, localized arterial media degeneration in the stomach, cecum, and uterus, submucosal tissue oedema and haemorrhage in the intestine, gallbladder, and brain choroid plexus, decreased mucus in the duodenal gland, acinus atrophy in the submandibular gland, sublingual gland, and parotid gland, and decreased seminiferous epithelial cells in the testis in the surviving animals in the 30 mg/kg/day group. All the changes were reversible. In the recovery group, soft testis and desquamated seminiferous epithelial cells in the epididymis were observed.

Based on the above, the NOAEL of lenvatinib in this study was determined to be 0.3 mg/kg/day.

3.(iii).A.(2).8) Thirteen-week repeated oral dose toxicity study in monkeys

Lenvatinib was administered orally at 0 (vehicle control), 0.1, 0.5, or 3 mg/kg/day to male and female cynomolgus monkeys (n = 3/sex/group) for 13 weeks.

In the 3 mg/kg/day group, 1 of 6 animals exhibited decreases in food consumption and body weight from Week 7 and then deterioration of the general condition from Day 63. On Day 75, the animal was found in a moribund condition and therefore euthanized. In this animal, clinical chemistry changes (increases in AST, ALT, total bilirubin, and BUN, decreases in serum sodium and chlorine, etc.,) as well as histopathological changes in the kidneys, doudenum, ovaries, gallbladder, vagina, stomach, and small intestine were observed. The cause of moribund condition was considered to be the deterioration of the general condition mainly attributable to gastrointestinal changes.

In the surviving animals, basophilic cell vacuolation in the pituitary gland and follicular atresia were observed in the ≥0.5 mg/kg/day groups; and glomerular lesion in the kidneys and duodenal gland atrophy were observed in the 3 mg/kg/day group.

Based on the above, the NOAEL of lenvatinib in this study was determined to be 0.1 mg/kg/day.

3.(iii).A.(2).9) Thirty-nine-week repeated oral dose toxicity study in monkeys

Lenvatinib was administered orally at 0 (vehicle control), 0.1, 0.5, or 3 mg/kg/day to male and female cynomolgus monkeys (n = 4/sex/group) for 39 weeks.

In the 3 mg/kg/day group, 1 of 8 animals exhibited decreases in food consumption and body weight from Week 4 and then deterioration of the general condition including loose stool and watery stool from Day 37. On Day 51, the animal was found in a moribund condition and therefore euthanized. In this animal, clinical chemistry changes such as increases in BUN and potassium and decreases in sodium and chlorine as well as histopathological changes in the kidneys, gallbladder, brain choroid plexus, femur, doudenum, colon, and rectum, which were also observed in the surviving animals in the 3 mg/kg/day group, were observed. The cause of deterioration of the general condition was consideredt mainly attributable to gastrointestinal disorders.

The findings in the surviving animals included decreased frequency of menstruations, glomerular lesion in the kidneys, epiphyseal growth plate hypertrophy in the femur, and follicular atresia in the ≥0.5 mg/kg/day groups; and decreased body weight, increased urine protein, localized arterial degeneration, fibrinoid necrosis, and submucosal inflammatory cell infiltration in the gallbladder, eosinophilic exudate and arterial fibrinoid necrosis in the brain choroid plexus, duodenal gland atrophy, lacunar hyperplasia in the duodenum, epidermal atrophy in the vagina, basophilic cell vacuolation in the pituitary gland, and decreased zymogen granules in the pancreas in the 3 mg/kg/day group.

Based on the above, the NOAEL of lenvatinib in this study was determined to be 0.1 mg/kg/day.

$AUC_{0\text{-}24h}$ (0.2051-0.2649 μg·h/mL) at 0.1 mg/kg/day was, in terms of the unbound drug plasma concentrations[*1], approximately 0.1 times the exposure at the clinical dose[*2].

*1: The plasma protein binding rate was 95.90% to 96.17% in monkeys and 97.87% to 98.62% in humans.
*2: In the Japanese phase I study (Study E7080-J081-105), $AUC_{0\text{-}\tau}$ on Day 15 in Cycle 1 was 4.140 μg·h/mL in patients with solid cancer who received multiple doses of lenvatinib 24 mg QD.

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

A bacterial reverse mutation assay, a mouse lymphoma TK assay, and a micronucleus assay in rats did not indicate genotoxicity.

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

Since lenvatinib is intended to be used for treatment of advanced cancer as an antineoplastic drug, no carcinogenicity study was conducted.

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

Since lenvatinib is intended to be used for treatment of advanced cancer as an antineoplastic drug, the study of fertility and early embryonic development to implantation and the study for effect on pre- and postnatal development, including maternal function were not conducted.

Lenvatinib was considered to possibly affect male and female fertility, because (a) repeat-dose toxicity studies showed ovarian changes such as follicular atresia, decreased frequency of menstruations, and decreased seminiferous epithelial cells in the testis [see "3.(iii).A.(2) Repeat-dose toxicity"], and (b) VEGFR has been reported to play important roles in microvascular function in the testis, initial proliferation stage of spermatogonia, and spermatogenesis (*Mol Cell Endocrinol.* 1997;131:9-20, *Biol Reprod.* 2003;69:985-94.).

3.(iii).A.(5).1) Embryo-fetal development in rats

Lenvatinib was administered orally at 0 (vehicle control), 0.1, 0.3, or 1.0 mg/kg/day to pregnant SD rats (n = 18-19/group) from Gestation Day 6 to Gestation Day 17. On Gestation Day 20, the animals underwent caesarean section, and an external inspection and visceral and skeletal examinations of fetuses were performed.

The effects on the maternal animals in the 1.0 mg/kg/day group included decreased body weight, reduction in body weight gain, decreased food consumption, furthermore increased post-implantation mortality due to increased resorbed embryos after early death, decreased number of live fetuses per dam, and increased number of dams without live fetuses.

The effects on the embryo-fetal development included mandibular macrognathia, thoracic cartilage separations and increased vertebral separations in the ≥0.1 mg/kg/day groups; and decreased fetal body weight, cryptophthalmos, abnormal tail, calvarial oedema, discontinued costicartilage, increased thoracic hemicentrum, dumbbell spine, and increased 14-rib in the ≥0.3 mg/kg/day groups.

Based on the above, the NOAELs of lenvatinib for the maternal animals and the embryo-fetal development in this study were determined to be <0.3 and <0.1 mg/kg/day, respectively. The estimated AUC (0.7081 μg·h/mL)[*1] at 0.1 mg/kg/day was, in terms of the unbound drug plasma concentrations[*2], approximately 0.2 times the exposure at the clinical dose[*3].

*1: Value estimated from AUC on Day 90 in females in the 0.4 mg/kg/day group in the rat 13-week repeat-dose toxicity study
*2: The plasma protein binding rate was 97.70% to 98.20% in rats and 97.87% to 98.62% in humans.
*3: In the Japanese phase I study (Study E7080-J081-105), $AUC_{0-\tau}$ on Day 15 in Cycle 1 was 4.14 μg·h/mL in patients with solid cancer who received multiple doses of lenvatinib 24 mg QD.

3.(iii).A.(5).2) Embryo-fetal development in rabbits

Lenvatinib was administered orally at 0 (vehicle control), 0.03, 0.1, or 0.5 mg/kg/day to pregnant NZW rabbits (n = 17-20/group) from Gestation Day 6 to Gestation Day 18. On Gestation Day 29, the animals underwent caesarean section, and an external inspection and visceral and skeletal examinations of fetuses were performed.

The effects on the maternal animals included decreases in body weight and food consumption in the 0.5 mg/kg/day group. In this group, 7 of 18 animals experienced spontaneous abortion, and of the remaining 11 animals without spontaneous abortion, 10 animals were all found to have embryonic resorptions, resulting in a marked increase in post-implantation mortality.

The effects on the fetuses included rib fusion in the 0.1 mg/kg/day group; and malformation complex associated with dorsal esophagus subclavian artery, rib fusion, thoracic hemivertebra, and morphological abnormality of the lumbar arch in 1 fetus as well as short tail or dorsal esophagus subclavian artery in 2 futuses in the 0.5 mg/kg/day group.

Based on the above, the NOAELs of lenvatinib for the maternal animals and the embryo-fetal development in this study were determined to be 0.1 and 0.03 mg/kg/day, respectively.

The applicant explained that caution should be paid to the possibile occurrences of embryonic lethality and teratogenicity in clinical use of lenvatinib and that the package insert etc., will advise that lenvatinib should not be administered to pregnant women for the following reasons: (a) teratogenicity observed in the above rat and rabbit embryo-fetal development studies is considered attributable to the pharmacological effect of lenvatinib; and (b) in the rat embryo-fetal development study, embryonic lethality and teratogenicity were observed following the exposure lower than that at the clinical dose.

3.(iii).A.(5).3) Two-week repeated dose finding study in juvenile rats (Reference data, non-GLP study)

A dose-finding study consisting of Arm 1 (7 days of age on Day 1) and Arm 2 (21 days of age on Day 1) was conducted to evaluate the toxicity of lenvatinib in juvenile rats.

In Arm 1, lenvatinib was administered orally at 0 (vehicle control), 0.2, 0.4, 1, or 5 mg/kg/day to male and female SD rats at 7 days of age (n = 5-8/sex/group) for 2 weeks followed by a 2-week recovery period, in which 3 males and 3 females each in the 0, 0.4, and 1 mg/kg/day groups were to be investigated for the reversibility.

In the 1 mg/kg/day group, 14 of 16 animals died by Day 13, and in the 5 mg/kg/day group, all the animals died by Day 12. In these animals, decreased body weight, delayed eyelid opening, peritonitis, etc., were observed. The cause of death is considered to be serious gastrointestinal toxicity.

The findings included decreased body weight, increased BUN, and short and small bones at the osteometry in the ≥0.2 mg/kg/day groups; increased total cholesterol, dysplasia in incisors, glomerular lesion in the kidneys, and sinusoid dilatation, cortical necrosis in the adrenal glands, and thrombus in the heart in the 0.4 mg/kg/day group; and epiphyseal growth plate hypertrophy and inflammation cell infiltration in the gastrointestinal mucosa in the ≥1 mg/kg/day groups. All of these histopathological findings except for glomerular lesion in the kidneys and thrombus in the heart were reversible.

In Arm 2, lenvatinib was administered orally at 0 (vehicle control), 0.4, 1, 5, or 25 mg/kg/day to male and female SD rats at 21 days of age (n = 5-8/sex/group) for 2 weeks followed by a 2-week recovery period, in which 3 males and 3 females each in the 0, 0.4, and 1 mg/kg/day groups were to be investigated for the reversibility.

In the 25 mg/kg/day group, 2 animals were found in a moribund condition. The findings observed in the Arm 2 included reduction in body weight gain, decreased food consumption, dysplasia in incisors, sinusoid dilatation in the adrenal glands, and epiphyseal growth plate hypertrophy in the ≥5 mg/kg/day groups; and delayed vaginal opening, increases in ALT, AST, BUN, total bilirubin, and total cholesterol, decreases in glucose and calcium, glomerular lesion in the kidneys, cortical necrosis in the adrenal glands, inflammation and cystoid dilation in the duodenal gland, decreased seminiferous epithelial cells in the testis, and arterial fibrinoid necrosis and eosinophilic exudates in the brain choroid plexus in the 25 mg/kg/day group. In the recovery groups, no toxicological findings due to lenvatinib were observed.

Based on the above, the dose of lenvatinib causing no toxicologically significant changes in rats at 7 and 21 days of age was determined to be 0.2 and 1 mg/kg/day, respectively.

3.(iii).A.(5).4) Eight-week repeat-dose toxicity study with a 4-week recovery period in juvenile rats

Lenvatinib was administered orally at 0 (vehicle control), 0.4, 2, or 10 mg/kg/day to male and female SD rats at 21 days of age (n = 10-16/sex/group) for 8 weeks. For 6 males and 6 females each in the 0, 2, and 10 mg/kg/day groups, a 4-week recovery period was included after the end of administration to investigate the reversibility.

In the 10 mg/kg group, 13 of 32 animals were found in a moribund condition or dead between Day 26 and Day 51. The main cause leading to death or a moribund condition was considered to be duodenal lesion and changes related to the concerned lesion, and secondary changes due to bacterial infection were also observed in some animals.

The findings included decreased food consumption, reductions in body weight gain, decrease in rearing in the open field test, increases in neutrophil count and ALT, short and thin bones at the osteometry, fracture and dysplasia of incisors, hypertrophy of epiphyseal growth plate and cartilaginous in the femur, glomerular lesion in the kidneys in the ≥2 mg/kg/day groups; and watery stool, blackish feces, preputial separation and delayed vaginal opening, prolonged response latency and decreased number of ambulation in the open field test, decreases in erythrocyte parameters, leukocyte count, glucose, total protein, albumin, globulin, and calcium and increases in AST, ALP, BUN, and total cholesterol, and proteinuria at the laboratory test, sinusoid dilatation and cortical necrosis in the adrenal glands, and inflammation and cystoid dilation in the doudenum, and arterial fibrinoid necrosis and eosinophilic exudates in the brain choroid plexus in the histopathological examination in the 10 mg/kg/day group.

The findings in the recovery group included fracture of incisors, proteinuria, and short and small bones in the ≥2 mg/kg/day groups; and watery stool and histopathological changes in the incisors, bones, kidneys, adrenal glands, liver, stomach, and duodenum in the 10 mg/kg/day group. The small diameter of the femur resolved to a normal level, and the body weight, food consumption, and histopathological changes tended to resolve. The other changes observed at the end of the administration were confirmed to be reversible.

As described above, growth retardation and its associated secondary change of delayed physical development were observed in juvenile rats following administration of lenvatinib. However, the target organs of lenvatinib in these rats were the same as those in the adult rats and the applicant discussed that there were no additional toxicological changes specific to juvenile animals.

In addition, rats at 7 days and 21 days of age are generally considered to correspond to human newborns and children at 2 years of age, respectively (Beck, M.J. Nonclinical Juvenile Toxicity Testing In: Hood RD, ed. *Developmental and Reproductive Toxicology: A Practical Approach.* 3rd ed. Informa Healthcare, 2012:309-311). Based on the results from the Arm 1 (rats at 7 days of age) in the dose- finding study [see "3.(iii).A.(5).3) Two-week repeated dose finding study in juvenile rats"], it was considered that administration to children aged <2 years should be avoided in clinical practices. Since the rats used in this study were 21 days of age at the initiation of study, the toxicity in children roughly at ≥2 years of age was adequately investigated.

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

3.(iii).A.(6).1) 3T3 NRU phototoxicity

Phototoxicity of lenvatinib at the concentrations of 1.17 to 20 μg/mL was investigated in BALB/c 3T3 fibroblast. As a result, lenvatinib did not exhibit phototoxicity.

3.(iii).A.(6).2) Safety evaluation of impurities

i) Impurity C and Impurity D

General toxicity and genotoxicity were evaluated for Impurity C[*1] (acceptance criterion, ≤[redacted]%) and Impurity D[*2] (acceptance criterion, ≤[redacted]%), which were contained in the drug substance at a concentration exceeding the qualification threshold.

*1: [redacted]
*2: [redacted]

(a) General toxicity of impurities

In the repeat-dose toxicity studies such as the rat 26-week and monkey 39-week repeated oral dose toxicity studies [see "3.(iii).A.(2).4) Twenty-six-week repeated oral dose toxicity study in rats" and "3.(iii).A.(2).9) Thirty-nine-week repeated oral dose toxicity study in monkeys"] and embryo-fetal development studies [see "3.(iii).A.(5).1) Embryo-fetal development in rats" and "3.(iii).A.(5).2) Embryo-fetal development in rabbits"], animals in the high dose group received Impurity C and Impurity D at the doses equivalent to the human maximum daily dose or higher to evaluate the toxicity. The applicant determined that the safety of these 2 impurities was qualified.

(b) Genotoxicity of impurities

- Impurity C:
  The drug substance used in the bacterial reverse mutation assay, mouse lymphoma TK assay, and micronucleus assay in rats [see "3.(iii).A.(3) Genotoxicity"] contained Impurity C at a concentration not less than the acceptance criterion. Impurity C was therefore considered unlikely to raise concern about genotoxicity in clinical practices.

- Impurity D:
  The bacterial reverse mutation assay and mouse lymphoma TK assay using the drug substance containing Impurity D at a concentration not less than the acceptance criterion did not exhibit genotoxicity. In addition, the drug substance used in the micronucleus assay in rats [see

"3.(iii).A.(3) Genotoxicity"] contained Impurity D at a concentration equivalent to the upper limit of acceptance criterion for this impurity. Based on the above, Impurity D was considered unlikely to raise concern about genotoxicity in clinical practices.

ii) Impurity A and Impurity B

Impurity A[*1] and Impurity B[*2] were suggested to be mutagenic. The genotoxicity risk of these impurities was explained as shown below.

*1: [redacted]
*2: [redacted]

- Impurity A:
  The results from the bacterial reverse mutation assay suggest that Impurity A is mutagenic. The concentration of Impurity A in the drug substance will be controlled so that the daily intake (ICH, 2014. M7. ICH Harmonized Tripartite Guideline) is <1.5 µg/day, threshold of toxicological concern (TTC) in clinical practices. This impurity was therefore considered unlikely to raise concern about genotoxicity in clinical practices.

- Impurity B:
  The results from the bacterial reverse mutation assay suggest that Impurity B is mutagenic. It is difficult to control the concentration of the maximum daily intake of Impurity B within <1.5 µg/day equivalent to the TTC level (ICH, 2014. M7. ICH Harmonized Tripartite Guideline) because this impurity is also detected as a degradation product and the content of this inpurity in the drug product possibly increases depending on the storage status. However, lenvatinib is a drug used for treatment of advanced cancer and it was considered allowable to control the content of the impurity at a level as low as possible.

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

Based on the submitted data and the following review, PMDA has concluded that the non-clinical toxicity evaluation of lenvatinib does not raise concerns about the clinical use of the drug.

Genotoxicity risk of Impurity B, mutagenic impurity

As Impurity B is mutagenic, PMDA asked the applicant to reexamine the acceptance criterion for this impurity to reduce the risk of genotoxicity.

The applicant responded as follows:

Although it is difficult to establish the acceptance criterion to control Impurity B at the TTC level, the acceptance criteria in the drug product is changed to ≤[redacted]% [see "2.B. Acceptance criteria for mutagenic impurities"]. This change is considered appropriate in light of the following points.

- The treatment period of lenvatinib in clinical settings is expected to be up to 10 years, and the acceptable intake of a mutagenic impurity at a carcinogenic risk of $\leq 10^{-5}$ is 10 µg/day (ICH, 2014. M7. ICH Harmonized Tripartite Guideline). In the case where the acceptance criterion of Impurity B is set at ≤[redacted]%, the maximum intake of the impurity in humans at the clinical dose of lenvatinib (24 mg/day) is calculated to be [redacted] µg/day, which is below 10 µg/day, the acceptable intake.

- In the bacterial reverse mutation assay, Impurity B presented the maximum number of revertants, 3.5 and 4.1 times those of the negative control in TA98 strain and TA100 strain, respectively, at a concentration of 156 µg/plate. Impurity B is therefore considered to be a relatively weak mutagen.

- In the rat 26-week and monkey 39-week repeat-dose toxicity studies using the lenvatinib, which contained Impurity B at [redacted] ppm, no changes indicating precancerous lesion were observed in any organ or tissue.

PMDA accepted the applicant's explanation.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

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

The major formulations used in clinical studies of lenvatinib mesilate (hereinafter referred to as lenvatinib) include 0.1, 1, 4, and 10 mg film-coated tablets as well as 1, 4, and 10 mg capsules.

Of the clinical studies submitted as the evaluation data, the film-coated tablet was used in foreign and Japanese phase I studies at the early development stage (Study E7080-E044-101 [Study 101], Study E7080-J081-103 [Study 103], Study E7080-E044-104 [Study 104]) as well as foreign phase II study (Study E7080-G000-201 [Study 201]), while the capsule was used in subsequently conducted clinical studies such as a Japanese phase I study (Study E7080-J081-105 [Study 105]), a Japanese phase II study (Study E7080-J081-208 [Study 208]), and the global phase III study (Study E7080-G000-303 [Study 303]). In Japan, the to-be-marketed formulations are 4 and 10 mg capsules and all of the 1, 4, and 10 mg capsules have been demonstrated to be biologically equivalent by dissolution test.

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

Lenvatinib in human plasma, whole blood, serum, urine, and feces as well as its metabolites in human plasma, urine, and feces (me88 [decyclopropylated form], me114 [demethylated form], me107 [*N*-oxidated form], me37 [quinoline form, formed by *O*-dearylation]) were quantified by LC-MS/MS.

4.(i).A.(2) Relative bioavailability and bioequivalence

4.(i).A.(2).1) Foreign phase I study (5.3.1.2.1; Study E7080-A001-001 [[redacted] to [redacted] 20[redacted]])

A crossover study was conducted to compare the bioavailability between 10 mg film-coated tablets and 10 mg capsules following a single oral dose of each formulation to 20 healthy adult subjects under fasted conditions.

The ratios [90% CI] of the geometric mean C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ of lenvatinib capsules to those of lenvatinib film-coated tablets were 0.864 [0.798, 0.934], 0.903 [0.864, 0.945], and 0.903 [0.863, 0.945], respectively.

Although the above data indicated that C_{max} of lenvatinib capsules tended to be slightly lower than that of lenvatinib film-coated tablets, AUC was similar between these 2 formulations. The applicant explained that they had considered it allowable to change the formulation employed in clinical studies at the late development stage from the film-coated tablets to the capsules.

4.(i).A.(2).2) Foreign phase I study (5.3.1.2.2; Study E7080-A001-008 [[redacted] to [redacted] 20[redacted]])

The crystal content in the capsules used in clinical studies of lenvatinib was [redacted]%. A crossover study was thus conducted to investigate the bioequivalence (BE) among the formulations with different crystal content. Using 3 types of the 10 mg capsules with different crystal content, lenvatinib at 10 mg was administered orally in a single dose to 60 healthy adult subjects (59 subjects included in PK analysis) under fasted conditions. [redacted].

The ratios of the geometric mean C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ of each lenvatinib test formulation to those of the lenvatinib standard formulation were as shown in the table below. All the 90% CIs of the ratio of the geometric mean fell within the acceptance criteria for BE (0.8-1.25), indicating that either test formulation was biologically equivalent to the standard formulation.

Comparison of PK parameters of lenvatinib between each test formulation and the standard formulation

Comparison	n	Ratio of geometric mean [90% CI]		
		C_{max}	AUC_{0-t}	AUC_{0-inf}
Test formulation with a low crystal content/standard formulation	58	0.987 [0.886, 1.10]	1.01 [0.948, 1.07]	1.01 [0.953, 1.07]
Test formulation with a high crystal content/standard formulation	59	0.906 [0.835, 0.984]	0.960 [0.921, 1.00]	0.965 [0.925, 1.01]*

*, n = 57

4.(i).A.(3) Food effect

4.(i).A.(3).1) Foreign phase I study (5.3.3.2.4; Study E7080-E044-101 [ongoing since [redacted] 20[redacted]; data cut off, [redacted] [redacted], 20[redacted]])

A crossover study was conducted to investigate the effect of food on PK of lenvatinib in 12 patients with solid cancer or malignant lymphoma (11 subjects included in PK analysis) using the film-coated tablets. In each of the 4-week treatment cycles, lenvatinib at 25 mg was administered orally QD for 4 weeks and on Day 15 or 22 in Cycle 1, lenvatinib was administered under fasted conditions or after high fat meals (of a total of 900-1000 kcal in the meal, approximately 15%, 25%, and 60% were from protein, carbohydrate, and fat, respectively).

PK parameters of lenvatinib following administration under fasted conditions or after high fat meals were as shown in the table below. The ratios of geometric mean C_{max} and AUC_{0-24h} of lenvatinib after high fat meals to those under fasted conditions (fed administration/fasted administration) [90% CI] were 0.98 [0.73, 1.31] and 1.00 [0.83, 1.20], respectively. t_{max} following fed administration was longer than that following fasted administration.

PK parameters of lenvatinib following administration under fasted conditions or after meals

	Fasted conditions	Fed conditions
C_{max} (ng/mL)	544 ± 249	509 ± 166
t_{max} (h)*	2.03 (1.00, 3.07)	4.98 (2.00, 5.07)
AUC_{0-24h} (ng·h/mL)	4040 ± 1570	3850 ± 993

Mean ± SD; n = 11; *, Median (range)

4.(i).A.(3).2) Foreign phase I study (5.3.1.1.1; Study E7080-A001-003 [[redacted] to [redacted] 20[redacted]])

A crossover study was conducted to investigate the effect of food on PK of lenvatinib in 16 healthy adult subjects using the capsules, following a single oral dose of lenvatinib at 10 mg under fasted conditions or after high fat meals (of a total of 800-1000 kcal, approximately 50% was from fat).

PK parameters of lenvatinib following administration under fasted conditions or after meals were as shown in the table below. The ratios of geometric mean C_{max}, AUC_{0-inf}, and AUC_{0-t} of lenvatinib after meals to those under fasted conditions [90% CI] were 0.955 [0.721, 1.26], 1.06 [0.957, 1.18], and 1.04 [0.923, 1.17], respectively. t_{max} of lenvatinib following fed administration was longer than that following fasted administration. $t_{1/2}$ of lenvatinib following fasted administration was comparable to that following fed administration.

PK parameters of lenvatinib following administration under fasted conditions or after meals

	Fasted conditions (n = 15)	Fed conditions (n = 16)
C_{max} (ng/mL)	104 ± 45.2	89.7 ± 18.5
t_{max} (h)*1	2.02 (2.00, 4.02)	4.02 (4.00, 8.02)
AUC_{0-inf} (ng·h/mL)	1060 ± 353*2	1060 ± 265
AUC_{0-t} (ng·h/mL)	1050 ± 341	1050 ± 265
$t_{1/2}$ (h)	24.7 ± 9.21*2	20.6 ± 8.82

Mean ± SD; *1, Median (range); *2, n = 14

The applicant explained the effect of food on PK of lenvatinib based on the results from Study 101 and Study E7080-A001-003 as follows:
The prolonged t_{max} after fed administration was considered to have occurred in the following manner: food intake delayed gastric emptying, then decreased absorption rate of lenvatinib, which led to the

prolonged t_{max}. With either the film-coated tablets or capsules, the 90% CI of the ratio of the geometric mean C_{max} (fed administration/fasted administration) fell slightly outside of the range from 0.80 to 1.25, but that for AUC fell within the range from 0.80 to 1.25. The effect of food on the PK of lenvatinib was considered to be clinically insignificant.

4.(i).A.(4) The applicant's assessment of the effect of gastric pH on the PK of lenvatinib

The solubility of lenvatinib is low in a solution near neutral pH: 970 μg/mL at pH 1; 5.3 μg/mL at pH 5; and 1.2 μg/mL at pH 7. The effect of concomitant use with drugs increasing gastric pH (H_2 receptor inhibitors, proton pump inhibitors, or antacids) on the PK of lenvatinib was investigated by population PK analysis (PPK analysis). As a result, the concomitant use with drugs increasing gastric pH was not identified as a significant covariate for the PK parameters of lenvatinib [see "4.(ii).A.(6) PPK analysis"]. Drugs increasing gastric pH were concomitantly administered with lenvatinib in 28.6% (223 of 779 subjects) of the subjects included in this analysis.

Based on the above, variations in gastric pH are considered unlikely to affect the PK of lenvatinib.

4.(ii) Summary of clinical pharmacology studies

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

The PK of lenvatinib in cancer patients was investigated in the following co-administration: lenvatinib alone; lenvatinib with temozolomide (TMZ); lenvatinib with carboplatin (CBDCA) and paclitaxel (PTX); and lenvatinib with ketoconazole or rifampicin.

4.(ii).A.(1) Cancer patients

4.(ii).A.(1).1) Foreign phase I study (5.3.3.2.5; Study E7080-E044-104 [[redacted] to [redacted]])

An open-label study was conducted in 6 patients with solid cancer to investigate the metabolites and mass balance of lenvatinib following a single oral dose of ^{14}C-lenvatinib at 24 mg.

The PK parameters of lenvatinib and radioactivity were as shown in the table below. The ratios of AUC of plasma concentrations of the radioactivity and lenvatinib to AUC of their blood concentrations were approximately 0.71 and 0.65, respectively. Unchanged lenvatinib accounted for approximately 60% and 64% of the radioactivity detected in the plasma and blood, respectively. The plasma concentrations of the metabolites (me88, me114, me107, me37) analyzed in this study were all roughly below the lower limit of quantification (0.25 ng/mL). The excretion of the radioactivity in feces and urine up to 10 days after dosing (% of the administered radioactivity) were 64% and 25%, respectively, and the total amount of unchanged lenvatinib and its metabolites (me88, me114, me107, me37) excreted in the urine and feces accounted for <8% of the administered radioactivity.

PK parameters of lenvatinib and radioactivity

Analyte	Specimen measured	C_{max}*1 (ng/mL)	t_{max}*2 (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$*3 (ng·h/mL)	$AUC_{0\text{-}inf}$*3 (ng·h/mL)	CL/F (L/h)	V_z/F (L)
Lenvatinib	Blood	267 ± 106	2.04 (0.95, 4.02)	11.8*4	2020 ± 742	1640*4	16.4*4	282*4
	Plasma	460 ± 180	2.01 (0.95, 2.12)	35.4 ± 8.20	3190 ± 1440	3800 ± 1790	7.38 ± 3.51	354 ± 132
Radioactivity	Blood	330 ± 100	1.51 (0.95, 2.12)	11.2*5	3140 ± 1060	4160 ± 2150*5	-	-
	Plasma	508 ± 149	1.51 (0.95, 2.12)	18.9 ± 7.77	4480 ± 1700	6270 ± 2630	-	-

Mean ± SD; n = 6; *1, C_{max} of the radioactivity expressed in ng eq/mL; *2, Median (range); *3, AUC of the radioactivity expressed in ng eq.·h/mL; *4, n = 2; *5, n = 4; -, Not calculated

In addition, the studies below were conducted to analyze metabolites of lenvatinib in the plasma, urine, and feces, using the plasma samples collected up to 24 hours after administration as well as urinary and fecal samples collected up to 168 hours after the administration.

- The plasma samples were extracted with methanol. Lenvatinib was the main compound detected in the plasma extract, and $AUC_{0\text{-}24h}$ of lenvatinib corresponded to 55% of $AUC_{0\text{-}24h}$ of the total radioactivity in the plasma. The major plasma metabolite was me86 (glucuronide conjugate of me114), and $AUC_{0\text{-}24h}$ of me86 corresponded to 3.21% and 1.78% of $AUC_{0\text{-}24h}$ of lenvatinib and total radioactivity, respectively, in the plasma.

- The excretion of the radioactivity into urine up to 168 hours after administration was 23%, while that of lenvatinib into urine was 0.38%. The applicant therefore explained that renal excretion is considered to marginally contribute to elimination of lenvatinib. In these samples, lenvatinib and at least 10 of its metabolites were detected. The urinary excretion of me10 (cysteine adduct at the 4-position of the quinoline ring), me29 (unidentified), me30 (unidentified), me46 (unidentified), me70 (unidentified), me78 (glucuronide conjugate of me104 without partial structure of *N*-cyclopropylformamide [decyclopropylcarbamoyl form of lenvatinib]), me93 (glucuronide conjugate of oxidized lenvatinib), me86, me115 (quinolone form), and me114 were 6.8%, 0.78%, 0.99%, 3.7%, 0.68%, 0.98%, 0.44%, 1.8%, 0.49%, and 0.13%, respectively.

- The excretion of the radioactivity in feces up to 168 hours after administration was 65%, while that of lenvatinib into feces was 2.5%. In these samples, lenvatinib and at least 5 of its metabolites were detected. The fecal excretion of me31 (unidentified), me111 (oxygen adduct), me115, me118 (quinolone form of me114), and me114 were 3.4%, 2.8%, 16%, 11%, and 4.3%, respectively. The metabolite found at the largest amount in the feces was me115, followed by me118.

4.(ii).A.(1).2) Foreign phase I study (5.3.3.2.4; Study E7080-E044-101 [ongoing since [redacted] 20[redacted]; date of data cut-off, [redacted] [redacted], 20[redacted]])

An open-label study was conducted in 81 patients with solid cancer to investigate the PK of lenvatinib etc., following multiple oral doses of lenvatinib at 0.2 to 32 mg QD.

The PK parameters of lenvatinib on Day 1 and Day 29 were as shown in the table below. In the investigated dose range, C_{max} and $AUC_{0\text{-}24h}$ of lenvatinib on Day 1 and Day 29 were proportional to the dose, while CL/F was almost constant irrespective of the dose. In the investigated dose range, t_{max} of lenvatinib was constant irrespective of the dose. $t_{1/2}$ of lenvatinib tended to decrease with the increasing dose in the low dose range following both single and multiple administration, but remained almost constant in the high dose range. The applicant explained why $t_{1/2}$ of lenvatinib decreased with the increasing dose as follows: lenvatinib is a substrate of P-gp [see "3.(ii).A.(5) Pharmacokinetic interactions"] and, with the increasing dose of lenvatinib, P-gp-mediated gastrointestinal excretion of lenvatinib may be saturated, resulting in a reduced effect of P-gp on the absorption rate of lenvatinib. The accumulation index was higher in the low dose groups (0.2-1.6 mg) than in the high dose groups (3.2-32 mg), and it remained almost constant in the dose range of 3.2 to 32 mg. The ratio of the maximum plasma lenvatinib concentration to the trough value (PTF ratio) tended to increase with dose.

PK parameters of lenvatinib

Dose (mg)	Timepoint (Day)	n	C_{max} (ng/mL)	t_{max}[*1] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)	Cumulative coefficient	PTF ratio
0.2	1	4	0.753 ± 0.218	5.00 (2.12, 5.00)	14.3 ± 4.50	–	–	–	–	–	–
	29	2	2.39	2.23 (1.95, 2.50)	43.3	–	29.5	4.71	206	3.11	57.1
0.4	1	4	1.74 ± 0.69	6.41 (2.50, 7.83)	30.2[*2] ± 14.5	–	–	–	–	–	–
	29	3	5.48 ± 1.60	3.00 (2.00, 3.04)	85.5 ± 37.1	–	26.4 ± 8.04	5.20 ± 1.80	209 ± 115	2.82[*3]	91.9 ± 22.5
0.8	1	4	4.26 ± 1.75	2.77 (2.50, 5.02)	61.9 ± 17.2	124[*3]	18.2[*3]	6.56[*3]	163[*3]	–	–
	29	2	9.61	13.48 (3.00, 23.95)	199[*4]	–	20.8[*4]	4.02[*4]	121[*4]	3.21[*4]	75.2[*4]
1.6	1	3	21.0 ± 11.7	3.07 (1.02, 7.83)	221 ± 130	377[*3]	10.7[*3]	6.47[*3]	65.8[*3]	–	–
	29	3	36.5 ± 10.9	3.00 (1.00, 3.08)	423 ± 271	–	10.8 ± 5.55	5.35 ± 3.94	65.4 ± 24.9	1.95 ± 0.91	233 ± 217
3.2	1	3	49.9 ± 16.0	2.50 (2.00, 24.17)	660 ± 209	780[*3]	12.8[*3]	4.23[*3]	80.4[*3]	–	–
	29	3	92.1 ± 29.0	2.50 (1.50, 2.52)	931 ± 180	–	9.97 ± 1.29	3.53 ± 0.747	51.5 ± 16.8	1.47 ± 0.27	191 ± 36
6.4	1	3	127 ± 91	2.00 (1.00, 3.07)	1170 ± 799	1340 ± 895	8.08 ± 0.749	8.19 ± 7.92	97.2 ± 95.4	–	–
	29	3	197 ± 137	2.00 (1.76, 2.55)	1690 ± 1170	–	8.33 ± 0.517	5.56 ± 4.20	67.7 ± 51.9	1.56 ± 0.39	249 ± 6
12	1	11	260 ± 108	2.53 (0.98, 5.05)	1660 ± 555	1900[*5] ± 467	5.98[*5] ± 0.484	6.61[*5] ± 1.34	57.0[*5] ± 11.9	–	–

Dose (mg)	Timepoint (Day)	n	C_{max} (ng/mL)	t_{max} [*1] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)	Cumulative coefficient	PTF ratio
	29	8	291 ± 146	1.54 (0.97, 4.98)	2050 ± 790	–	6.94 ±1.17	6.90 ± 3.36	70.9 ± 40.4	1.25 ± 0.26	266 ± 100
12.5	1	9	209 ± 112	2.03 (1.00, 3.00)	1540 ± 877	1690 ± 1010	6.57 ± 0.955	9.53 ± 4.31	88.1 ± 38.2	–	–
	29	7	187 ± 86	2.00 (1.03, 2.53)	1420 ± 698	–	6.83 ± 1.02	10.1 ± 3.32	100 ± 37.8	1.21 ± 0.18	288 ± 65
16	1	6	375 ± 158	2.12 (2.00, 2.97)	3250 ± 1830	3680 ± 2210	7.12 ± 1.09	6.16 ± 4.24	58.4 ± 32.3	–	–
	29	6	369 ± 149	2.54 (0.98, 3.05)	2950 ± 1290	–	6.94 ± 0.931	6.44 ± 3.67	60.7 ± 26.8	1.02 ± 0.37	287 ± 36
20	1	3	409 ± 106	3.00 (1.58, 3.02)	3710 ± 2060	4240 ± 2600	6.96 ± 1.23	5.98 ± 3.24	56.4 ± 22.9	–	–
	29	1	239	3.00	1930	-	8.09	10.3	121	0.960	291
25	1	24	631 ± 234	1.53 (0.98, 3.00)	4070 ± 1670	4410[*6] ± 1950	5.85[*6] ± 1.02	6.86[*6] ± 3.35	55.3[*6] ± 22.4	–	–
	29	4	545 ± 183	2.84 (1.33, 4.92)	4220 ± 1120	–	6.03 ± 0.704	6.38 ± 2.30	57.1 ± 28.6	1.28 ± 0.12	287 ± 53
32	1	7	650 ± 238	2.12 (1.00, 7.13)	4600 ± 1890	4380[*7] ± 1700	5.55[*7] ± 0.599	8.83[*7] ± 5.06	68.1[*7] ± 32.5	–	–
	29	4	562 ± 121	1.50 (1.00, 2.00)	4020 ± 899	–	6.68 ± 0.522	7.98 ± 2.76	76.6 ± 26.0	1.12 ± 0.40	311 ± 36

Mean ± SD; -, Not applicable; *1, Median (range); *2, n = 3; *3, n = 2; *4, n = 1; *5, n = 10; *6, n = 23; *7, n = 6

4.(ii).A.(1).3) Japanese phase I study (5.3.3.2.1; Study E7080-J081-103 [[redacted] to [redacted]])

An open-label study was conducted to investigate the PK of lenvatinib in 27 patients with solid cancer. Lenvatinib at 0.5 to 20 mg was administered orally in a single dose followed by a 7- to 9-day washout period, and then the same dose of lenvatinib was administered orally twice daily (BID) for 14 days to investigate the plasma and urine lenvatinib concentrations.

The PK parameters of lenvatinib following a single dose and multiple doses were as shown in the table below. In the investigated dose range, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}\tau}$, and C_{max} following the multiple doses of lenvatinib showed dose proportionality. C_{max} following the single dose increased dose-proportionally in the high dose range, while it tended to be increased less than dose-proportionally in the low dose range. The applicant explained the reason as follows: with the increasing dose of lenvatinib, which is a substrate of P-gp [see "3.(ii).A.(5) Pharmacokinetic interactions"], P-gp-mediated gastrointestinal excretion of lenvatinib may be saturated. The accumulation index calculated from $t_{1/2}$ following the single dose was 2.8 to 6.1, which was comparable to that from C_{max} or $AUC_{0\text{-}12}$ (1.5-6.9 and 1.6-5.6, respectively). The excretion of lenvatinib in urine ($F_{e\ 0\text{-}\tau}$) and renal clearance (CL_R) from the morning dose to 12 hours post-dose on Day 14 of the multiple-dose period did not show any constant trend in their relationships with the dose of lenvatinib.

PK parameters of lenvatinib

Dose (mg)		n	C_{max} (ng/mL)	t_{max} [*1] (h)	AUC [*2] (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)	$F_{e\ 0\text{-}\tau}$ (%)	CL_R (mL/h)
0.5	Single	3	2.5 ± 0.2	5 (3, 5)	115 ± 27	46.5 ± 5.9	4.5 ± 1.3	312 ± 128	-	-
	Multiple	3	16.7 ± 5.2	1 (1, 3)	128 ± 36	37.1 ± 1.0	4.1 ± 1.3	221 ± 66	1.4 ± 1.1	48.6 ± 30.4
1	Single	3	5.3 ± 2.5	3 (3, 5)	164 ± 76	30.3 ± 8.9	7.2 ± 3.7	299 ± 136	-	-
	Multiple	3	23.7 ± 9.4	3 (3, 3)	198 ± 86	32.7 ± 3.4	5.6 ± 2.0	261 ± 86	1.6 ± 1.0	80.4 ± 15.1
2	Single	3	18.4 ± 3.5	3 (1, 3)	429 ± 89	36.4 ± 4.0	4.8 ± 1.1	253 ± 63	-	-
	Multiple	3	68.6 ± 23.3	1 (1, 3)	483 ± 117	36.3 ± 6.4	4.3 ± 1.0	220 ± 30	1.2 ± 0.7	50.7 ± 30.7
4	Single	3	61.3 ± 25.6	1 (1, 3)	759 ± 89	32.0 ± 5.9	5.3 ± 0.6	247 ± 67	-	-
	Multiple	3	154 ± 33.8	3 (1, 3)	1020 ± 246	36.3 ± 1.7	4.1 ± 0.9	213 ± 52	2.0 ± 1.9	84.6 ± 87.5
6	Single	4	99.3 ± 20.6	3 (1, 3)	1200 ± 265	31.6 ± 5.0	5.2 ± 1.1	232 ± 33	-	-
	Multiple	3	178 ± 38.0	3 (1, 6)	1190 ± 141	32.6 ± 2.5	5.1 ± 0.6	242 ± 44	0.7 ± 0.2	35.1 ± 12.5
9	Single	3	201 ± 49.4	1 (1, 3)	1660 ± 460	28.6 ± 4.0	5.8 ± 1.9	236 ± 68	-	-
	Multiple	3	384 ± 169	1 (1, 1)	2170 ± 803	32.8 ± 2.7	4.7 ± 2.2	219 ± 94	0.5 ± 0.3	17.4 ± 7.5
13	Single	3	303 ± 72.5	1 (1, 3)	2740 ± 418	25.0 ± 8.2	4.8 ± 0.7	171 ± 54	-	-
	Multiple	3	557 ± 109	3 (1, 3)	3820 ± 622	32.6 ± 6.8	3.5 ± 0.6	165 ± 51	1.2 ± 0.5	39.7 ± 12.0
16	Single	3	472 ± 152	1 (1, 1)	3420 ± 515	19.1 ± 13.0	4.8 ± 0.7	136 ± 106	-	-
	Multiple	3	713 ± 277	3 (1, 3)	4230 ± 1490	25.6 ± 7.1	4.1 ± 1.2	155 ± 78	1.1 ± 0.5	45.2 ± 29.0
20[*3]	Single	2	329, 674	3, 3	2850, 5410	38.1, 31.6	7.0, 3.7	386, 169	-	-
	Multiple	1	394	3	2520	38.5	7.9	441	0.5	39.9

Mean ± SD; -, Not applicable; *1, Median (range); *2, $AUC_{0\text{-}inf}$ for a single dose, $AUC_{0\text{-}\tau}$ for multiple doses; *3, Individual value

4.(ii).A.(1).4) Japanese phase I study (5.3.3.2.3; Study E7080-J081-105 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 9 patients with solid cancer to investigate the PK of lenvatinib etc., following multiple oral doses of lenvatinib 20 and 24 mg QD. The PK parameters of lenvatinib on Day 1 and Day 15 were as shown in the table below. The increases with dose were seen in C_{max}, C_{min}, and AUC on both Day 1 and Day 15. The plasma trough concentrations on Days 8, 15, and 43 were 50.5 to 66.9 ng/mL in the 20 mg group and 38.7 to 87.0 ng/mL in the 24 mg groups, which remained constant irrespective of the number of doses in either group.

PK parameters of lenvatinib

Dose (mg)	n	Timepoint (Day)	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC[*2] (ng·h/mL)	C_{min} (ng/mL)	Accumulatioin index (C_{max})	Accumulation index (AUC)
20	3	1	309 ± 60.1	2.00 (2.00, 2.00)	2500 ± 647	-	-	-
	3	15	415 ± 267	2.00 (1.98, 2.10)	3690 ± 1790	41.2 ± 16.4	1.27 ± 0.562	1.44 ± 0.356
24	6	1	418 ± 167	2.01 (2.00, 4.02)	3150 ± 352[*3]	-	-	-
	6	15	518 ± 209	2.00 (2.00, 4.00)	4140 ± 1350[*4]	65.3 ± 29.8	1.42 ± 0.708	1.32 ± 0.417[*3]

Mean ± SD; -, Not applicable; *1, Median (range); *2, $AUC_{0\text{-}24h}$ on Day 1; $AUC_{0\text{-}\tau}$ on Day 15; *3, n = 4; *4, n = 5

4.(ii).A.(1).5) Foreign phase I/Ib study (5.3.3.2.6, 5.3.3.2.7; Study E7080-A001-102 [ongoing since [redacted] 20[redacted]; data cut-off, [redacted] [redacted], 20[redacted]])

An open-label study was conducted to investigate the PK of lenvatinib in 109 patients with solid cancer or malignant melanoma (77 subjects included in PK analysis in the phase I part, 32 subjects included in PK analysis in the phase Ib part).

In the phase I part, the following regimens were used for patients with solid cancer or malignant melanoma: Regimen (a), 1-week on/1-week off multiple oral doses of lenvatinib at 0.1 to 3.2 mg BID; Regimen (b), multiple oral doses of lenvatinib at 3.2 to 12 mg BID; and Regimen (c), for patients with malignant melanoma, multiple oral doses of lenvatinib at 10 mg BID. The plasma lenvatinib concentrations following the single administration in Regimen (a), following the single administration (Day 1) in Regimen (b), and following the single and multiple administration (on Day 1 and Day 29) in Regimen (c) were investigated (the table below). In the investigated dose range (0.1-24 mg), C_{max} and $AUC_{0\text{-}24h}$ of lenvatinib following the single administration showed dose proportionality. The excretion of lenvatinib in urine up to 24 hours after administration (percentage of dose) remained constant irrespective of the dose of lenvatinib. The mean accumulation index of $AUC_{0\text{-}24h}$ following Regimen (c) (Day 15/Day 1) was 2.24.

PK parameters of lenvatinib (phase I part)

Regimen	Dose (mg)	Timepoint (Day)	n	C_{max} (ng/mL)	t_{max}[*1] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Excretion in urine (%)
Regimen (a)	0.1	1	3	0.30 ± 0.18	24.00 (4.00, 24.17)	2.77, 5.37[*2]	0, 0.16[*2]
	0.2		3	0.72 ± 0.30	6.00 (4.00, 24.17)	12.4 ± 5.01	0.27 ± 0.25
	0.4		3	3.27 ± 3.12	3.00 (1.00, 6.00)	39.9 ± 25.9	0.27 ± 0.12
	0.8		3	5.73 ± 0.17	2.50 (1.50, 3.00)	86.2 ± 6.36	0.04, 0.87[*2]
	1.6		3	11.7 ± 2.30	2.0 (1.50, 4.00)	160 ± 43.4	0.48 ± 0.21
	3.2		3	41.8 ± 32.8	1.50 (1.00, 6.00)	376 ± 171	0.39 ± 0.24
Regimen (b)	3.2	1	3	51.4 ± 30.6	2.00 (2.00, 2.50)	407 ± 121	0.37 ± 0.10
	5		7	62.6 ± 25.5	2.50 (2.00, 24.50)	650 ± 256	1.47 ± 0.69
	8		10	177 ± 60.6	1.50 (1.00, 4.00)	1300 ± 442	0.83 ± 0.35[*3]
	12		4	232 ± 60.0	1.50 (1.00, 1.50)	1810 ± 649	0.68 ± 0.283
	16		6	273 ± 64.0	2.75 (2.00, 3.03)	2610 ± 1150	0.94 ± 0.73[*4]
	24		3	655 ± 97.0	1.50 (1.50, 2.00)	4900 ± 2140	1.02 ± 1.18
Regimen (c)	10	1	25	170 ± 68.8	2.00 (1.00, 4.00)	1370 ± 647	0.45 ± 0.28[*5]
	10	29	16	209 ± 107	3.00 (0, 6.00)	1980 ± 971[*6]	0.95 ± 0.99[*7]

Mean ± SD; *1, Median (range); *2, n = 2 (individual value); *3, n = 8; *4, n = 5; *5, n = 21; *6, n = 13; *7, n = 12

In the phase Ib part, multiple oral doses of lenvatinib at 20 or 24 mg were administered QD in 4-week treatment cycles concomitantly with TMZ (at 100 or 150 mg/m^2/day, from Day 1 to Day 5 of each cycle) to patients with malignant melanoma to investigate the plasma lenvatinib concentrations.

Distributions of C_{max} and AUC_{0-24h} values of lenvatinib in patients on Day 1 of the concomitant use of lenvatinib at 24 mg with TMZ at 100 or 150 mg/m^2 almost overlapped distributions of those following the single administration of lenvatinib at 24 mg in the phase I part. Based on the above, the applicant explained that concomitant use with TMZ is considered to have no clear effect on the PK of lenvatinib although the study was conducted in a limited number of subjects.

4.(ii).A.(1).6) Japanese phase I study (5.3.3.2.2; Study E7080-J081-110 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 11 patients with non-small cell lung cancer to investigate the PK of lenvatinib, CBDCA, and PTX following concomitant use of lenvatinib with CBDCA and PTX. Lenvatinib was to be administered orally at 4 or 6 mg BID for 7 days, and from Day 8, lenvatinib was to be administered orally at 4 or 6 mg BID concomitantly with CBDCA (equivalent to AUC of 6 mg·min/mL) and PTX (200 mg/m^2) in 3-week treatment cycles,.

The plasma lenvatinib trough concentration during the concomitant use of lenvatinib with CBDCA and PTX (Day 9, Day 15, Day 29) was 45.3 to 60.5 and 50.9 to 83.4 ng/mL in the 4 and 6 mg groups, respectively, which were comparable to the plasma lenvatinib trough concentration during the administration of lenvatinib alone (Day 8) (42.9 and 52.1 ng/mL in the 4 and 6 mg BID groups, respectively). The applicant therefore explained that the concomitant use with CBDCA and PTX does not have a clear effect on the PK of lenvatinib.

The PK parameters of CBDCA and PTX during the concomitant use with lenvatinib remained constant irrespective of the dose of lenvatinib as shown in the table below.

PK parameters of CBDCA and PTX

	Dose of lenvatinib (mg)	n	C_{end}*1 (μg/mL)	AUC*2 (μg·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
CBDCA	4	6	27.1 ± 4.14	79.9 ± 12.7	-	-	-
	6	5	26.4 ± 2.23	70.8 ± 5.19	-	-	-
PTX	4	6	7.27 ± 2.10	25.0 ± 8.18	6.65 ± 0.39	14.4 ± 6.42	69.1 ± 27.7
	6	5	6.56 ± 1.57	22.1 ± 5.26	6.77 ± 0.42	16.2 ± 2.91	80.9 ± 16.6

Mean ± SD; -, Not applicable; *1, Plasma concentration immediately after the end of administrationd; *2, AUC_{0-t} for CBDCA, AUC_{0-inf} for PTX

4.(ii).A.(2) Drug-drug interactions

4.(ii).A.(2).1) Drug interaction study with ketoconazole (5.3.3.4.1; Study E7080-A001-004 [[redacted] to [redacted] 20[redacted]])

A crossover study was conducted in 18 healthy adult foreign subjects (16 subjects included in PK analysis) to investigate the effect of ketoconazole (inhibitor against P-gp and CYP3A) on PK of lenvatinib. Ketoconazole at 400 mg or placebo was to be administered orally QD for 18 days, and on Day 5 of ketoconazole or placebo administration, lenvatinib was to be administered orally at 5 mg. The ratios [90% CI] of the geometric mean C_{max}, AUC_{0-t}, and AUC_{0-inf} of lenvatinib in concomitant use with ketoconazole to those of lenvatinib in concomitant use with placebo were 1.19 [1.05, 1.34], 1.15 [1.08, 1.21], and 1.15 [1.08, 1.21], respectively, indicating that concomitant use with ketoconazole slightly increased C_{max} and AUC of lenvatinib. On the other hand, concomitant use with ketoconazole did not affect t_{max} or $t_{1/2}$ of lenvatinib.

Based on the above results, the applicant explained as follows:
Lenvatinib has been shown to be a substrate of CYP3A and P-gp [see "3.(ii).A.(5) Pharmacokinetic interactions"]. In this study, concomitant use with ketoconazole increased C_{max} and AUC of lenvatinib, but $t_{1/2}$ of lenvatinib was not clearly affected. Consequently CYP3A is considered to marginally contribute to elimination of lenvatinib. The increased C_{max} and AUC of lenvatinib following concomitant use with ketoconazole is accordingly considered attributable to the increased gastrointestinal absorption of lenvatinib due to inhibited gastrointestinal P-gp by ketoconazole.

4.(ii).A.(2).2) Drug interaction study with rifampicin (5.3.3.4.2; Study E7080-A001-007 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 15 foreign healthy adult subjects to investigate the effect of rifampicin on the PK of lenvatinib. It has been reported that a single dose of rifampicin inhibits P-gp,

but multiple doses induce CYP3A and P-gp (*Clin Pharmacol Ther.* 2011;89:234-42). Lenvatinib was to be administered orally at 24 mg at Day 1, Day 15, and Day 43, while rifampicin was to be administered orally in a single dose at 600 mg on Day 15, and then was to be administered orally QD from Day 29 to Day 49.

The ratios of the geometric mean C_{max}, AUC_{0-t}, and AUC_{0-inf} of lenvatinib in concomitant use with a single dose of rifampicin (Day 15) and in concomitant use with multiple doses of rifampicin (Day 43) to those of lenvatinib in single-agent use (Day 1) were as shown in the table below. Both C_{max} and AUC of lenvatinib in concomitant use with a single dose of rifampicin were higher than those of in single-agent use. C_{max} of lenvatinib in concomitant use with multiple doses of rifampicin was comparable to that of lenvatinib in single-agent use, but AUC of that was lower than that of lenvatinib administered alone. Both C_{max} and AUC of lenvatinib in concomitant use with multiple doses of rifampicin were lower than those of lenvatinib in concomitant use with a single dose of rifampicin. $t_{1/2}$ of lenvatinib in concomitant use with a single dose of rifampicin (22.8 hours) was comparable to that of lenvatinib in single-agent use (23.2 hours), but that of lenvatinib in concomitant use with multiple doses of rifampicin (19.7 hours) was shorter than that of lenvatinib in single-agent use. t_{max} of lenvatinib was not affected by concomitant use with rifampicin.

The applicant explained that the above findings indicate that the concomitant use of lenvatinib with P-gp inhibitor increases the exposure of lenvatinib, while the concomitant use of lenvatinib with CYP3A and P-gp inducer decreases the exposure of lenvatinib.

Comparison of PK parameters of lenvatinib between single-agent use and concomitant use with rifampicin

Comparison	Ratio of geometric mean [90% CI]		
	C_{max}	AUC_{0-t}	AUC_{0-inf}
Concomitant use with a single dose of rifampicin/lenvatinib alone	1.33 [1.13, 1.58]	1.31 [1.23, 1.39]	1.31 [1.23, 1.39]
Concomitant use with multiple doses of rifampicin*/lenvatinib alone	1.00 [0.83, 1.21]	0.82 [0.73, 0.91]	0.82 [0.73, 0.91]
Concomitant use with multiple doses of rifampicin*/concomitant use with a single dose	0.76 [0.63, 0.90]	0.63 [0.56, 0.70]	0.63 [0.56, 0.70]

n = 15; *, n = 14

4.(ii).A.(3) Foreign phase I study in patients with hepatic impairment (5.3.3.3.1; Study E7080-A001-006 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, parallel-group study was conducted to investigate the effect of hepatic impairment on the PK of lenvatinib in 3 groups of 6 patients each with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment, and in 1 group of 8 healthy adult subjects. Lenvatinib was administered orally in a single dose at 10 mg to healthy adult subjects and patients with mild or moderate hepatic impairment and was administered orally in a single dose at 5 mg to patients with severe hepatic impairment to investigate the plasma lenvatinib concentrations (the table below). The applicant explained that dose-normalized C_{max} and AUC were used to compare the PK parameters of lenvatinib between the patients with severe hepatic impairment and healthy adult subjects.

CL/F and $t_{1/2}$ of lenvatinib were comparable between the patients with mild or moderate hepatic impairment and healthy adult subjects, but in the patients with severe hepatic impairment, CL/F was smaller and $t_{1/2}$ was longer than those in healthy adult subjects. C_{max} of lenvatinib in the patients with hepatic impairment was comparable to that in healthy adult subjects, but AUC of lenvatinib in the patients with severe hepatic impairment was higher than that in healthy adult subjects. The excretion rate of lenvatinib into urine tended to increase with the increasing severity of hepatic impairment. The applicant explained this trend was a surrogate mechanism which compensated for the decreased hepatic metabolism of lenvatinib with increased excretion of lenvatinib in urine.

Comparison of PK parameters of lenvatinib among patients with hepatic impairment by severity

	Healthy adult subjects	Severity of hepatic impairment		
		Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
Dose (mg)	10	10	10	5
PK parameters				
n	8	6	6	6
C_{max} (ng/mL)	114 ± 51.9	109 ± 56.7	107 ± 81.3	62.0 ± 34.6
AUC_{0-t} (ng·h/mL)	1140 ± 517	1360 ± 522	1350 ± 854	965 ± 177
AUC_{0-inf} (ng·h/mL)	1160 ± 518	1380 ± 526	1360 ± 856	982 ± 174
t_{max}*1 (h)	2.0 (1.0, 3.0)	2.5 (2.0, 4.0)	3.0 (1.0, 4.0)	2.5 (0.5, 4.0)
CL/F (L/h)	9.86 ± 3.35	8.74 ± 4.94	10.3 ± 6.67	5.21 ± 0.804
V_z/F (L)	408 ± 216	303 ± 123	376 ± 168	248 ± 91.3
$t_{1/2}$ (h)	28.8 ± 8.39	25.5 ± 5.53	28.6 ± 8.16	32.6 ± 9.72
Urinary excretion rate (%)	0.607 ± 0.497	1.11 ± 0.580	1.19 ± 0.792	2.16 ± 1.29
CL_R (mL/min)	0.910 ± 0.783	1.63 ± 1.17	1.88 ± 1.38	1.85 ± 1.08
Ratio of geometric mean*2 [90% CI]				
C_{max}	-	0.97 [0.55, 1.73]	0.79 [0.44, 1.41]	1.12 [0.63, 2.00]*3
AUC_{0-t}	-	1.19 [0.78, 1.81]	1.07 [0.71, 1.63]	1.80 [1.18, 2.74]*3
AUC_{0-inf}	-	1.18 [0.78, 1.79]	1.07 [0.71, 1.62]	1.80 [1.19, 2.73]*3

Mean ± SD; -, Not applicable; *1, Median (range); *2, Patients with hepatic impairment/healthy adult subjects; *3, Calculated from the dose-normalized PK parameters

4.(ii).A.(4) Foreign phase I study in patients with renal impairment (5.3.3.3.2; Study E7080-A001-005 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, parallel-group study was conducted to investigate the effect of renal impairment on the PK of lenvatinib following a single oral dose at 24 mg in 3 groups of 6 patients each with mild (creatinine clearance [CLcr], 60-89 mL/min), moderate (CLcr, 30-59 mL/min), or severe (CLcr, 15-29 mL/min) renal impairment, and in 1 group of 8 healthy adult subjects.

The PK parameters of lenvatinib in the patients with renal impairment and healthy adult subjects were as shown in the table below. No clear differences were found in any PK parameters between the patients with renal impairment and healthy adult subjects.

Comparison of PK parameters of lenvatinib among patients with renal impairment by severity

	Healthy adult subjects	Severity of renal impairment		
		Mild	Moderate	Severe
Dose (mg)	24	24	24	24
PK parameters				
n	8	6	6	6
C_{max} (ng/mL)	325 ± 105	323 ± 108	237 ± 124	310 ± 167
AUC_{0-t} (ng·h/mL)	2990 ± 974	2920 ± 750	2790 ± 1200	3620 ± 1270
AUC_{0-inf} (ng·h/mL)	3010 ± 974	2940 ± 763	2810 ± 1210	3640 ± 1250
t_{max}*1 (h)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	3.00 (2.00, 4.00)	3.50 (1.00, 4.00)
CL/F (L/h)	9.17 ± 4.64	8.58 ± 1.85	10.4 ± 5.66	7.34 ± 2.66
V_z/F (L)	428 ± 153	386 ± 87.1	464 ± 308	386 ± 253
$t_{1/2}$ (h)	34.3 ± 9.69	31.8 ± 6.26	30.6 ± 6.14	33.5 ± 12.1
Urinary excretion rate (%)	1.11 ± 0.583	0.878 ± 0.558	0.788 ± 0.253	0.819 ± 0.350
CL_R (mL/min)	0.0903 ± 0.0373	0.0771 ± 0.0575	0.0773 ± 0.0341	0.0569 ± 0.0221
Ratio of geometric mean*2 [90% CI]				
C_{max}	-	1.00 [0.59, 1.71]	0.61 [0.36, 1.04]	0.87 [0.51, 1.49]
AUC_{0-t}	-	1.01 [0.71, 1.45]	0.90 [0.63, 1.29]	1.22 [0.85, 1.74]
AUC_{0-inf}	-	1.01 [0.71, 1.44]	0.90 [0.63, 1.29]	1.22 [0.85, 1.74]

Mean ± SD; -, Not applicable; *1, Median (range); *2, Patients with renal impairment/healthy adult subjects

4.(ii).A.(5) Foreign phase I study (5.3.4.1.1; Study E7080-A001-002 [[redacted] to [redacted] 20[redacted]])

A crossover study was conducted to investigate the effect of lenvatinib on the cardiac conduction system (QT/QTc interval) in 52 healthy adult subjects (51 subjects included in the analysis). In this

study, lenvatinib at 32 mg was administered orally in a single dose with placebo or moxifloxacin at 400 mg administered in the controls.

Concerning the change in Fridericia-corrected QT (QTcF) from the baseline (ΔQTcF), the least squares mean of the difference from the placebo (ΔΔQTcF) was calculated. As a result, the upper limit of the two-sided 90% CI of the least squares mean was <10 msec at any timepoint. The least squares mean of ΔQTcF at 4 hours after oral administration of moxifloxacin, the positive control, was 10.7 msec.

In addition, the relationship between ΔΔQTcF and plasma lenvatinib concentration was analyzed using a linear mixed-effects model. As a result, the y-intercept and slope of the regression line in the population were -2.96 msec and -0.0045 msec/ng/mL, respectively.

Based on the above findings, the applicant explained that lenvatinib is considered unlikely to prolong the QT/QTc interval with clinical significance.

4.(ii).A.(6) PPK analysis

PPK analysis was performed using a nonlinear mixed-effects model (NONMEM v.7.2) based on the PK data (779 subjects; 10,265 timepoints) obtained from the following studies: Japanese and foreign clinical pharmacology studies in healthy adult subjects (Study E7080-A001-001, Study E7080-A001-002, Study E7080-A001-003, Study E7080-A001-004, Study E7080-A001-005 [Study 005], Study E7080-A001-006 [Study 006], Study E7080-A001-007, Study E7080-A001-008); studies in cancer patients including foreign phase I studies (Study 101, Study E7080-A001-102 [Study 102]), Japanese phase I studies (Study 103, Study 105), foreign phase II study (Study 201), Japanese phase II study (Study 208), and global phase III study (Study 303). The PK of lenvatinib was described in a 3-compartment model including the primary absorption process and primary elimination process.

In this analysis, factors investigated as potential covariates for CL/F of lenvatinib included demographic factors (age, body weight, gender, race, Eastern Cooperative Oncology Group Performance Status [ECOG PS]), clinical laboratory values (albumin, alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, CLcr), diseases (healthy adult subjects, DTC patients, patients with thyroidmedullary cancer [MTC], patients with malignant melanoma or the other cancers), formulation, and presence or absence of concomitant drugs (CYP3A inducer or inhibitor, H_2 receptor antagonist, proton pump inhibitor, antacid or gastric-pH-increasing drug). As a result, body weight, presence or absence of concomitant CYP3A inducer or inhibitor, albumin, ALP, and diseases were selected as significant covariates for CL/F.

The applicant explained the results of this analysis as follows:

- In the dose range of lenvatinib in the clinical studies included in the PPK analysis (3.2-32 mg), the PK of lenvatinib was estimated to show linearity.

- CL/F of lenvatinib was suggested to increase with the increasing body weight. Therefore, using the above PPK model, the Bayes estimator of AUC at steady state following multiple doses of lenvatinib (capsules) at 24 mg was calculated to investigate the relationship between AUC and the body weight. As a result, AUC tended to decrease with the increasing body weight, but it was considered mostly unnecessary to adjust the dose of lenvatinib based on the body weight in light of the large inter-individual variability of AUC.

- CL/F of lenvatinib in healthy adult subjects was estimated to be 15% higher than that in cancer patients, but there were no clear differences in CL/F of lenvatinib among the DTC patients, MTC patients, and patients with the other cancers. The reason for the difference in CL/F of lenvatinib between the cancer patients and healthy adult subjects was unclear, but the difference was considered attributable to lower CYP3A expression or enzyme activity levels in cancer patients than those in healthy adult subjects, because the CYP3A-mediated metabolism is recognized as one of the major elimination pathways (*Clin Pharmacol Ther.* 2014;96:449-57).

4.(ii).A.(7) Relationship between exposure and efficacy/safety

4.(ii).A.(7).1) Relationship between exposure and efficacy

Based on the results from the global phase III study (Study 303) in patients with radioactive iodine (RAI)-refractory locally advanced or metastatic DTC, the relationship between exposure to lenvatinib (dose-normalized AUC) and efficacy (reduction in sum of the target lesion sizes [total target lesion size] and progression-free survival [PFS]) was investigated. The results were as shown below.

- Using the tumor-growth inhibition model, the relationship between exposure to lenvatinib (dose-normalized AUC) and reduction in total target lesion size was investigated. In addition, the effects of the following factors on the reduction in total target lesion size were investigated: body weight, race, age, sex, ECOG PS, total target lesion size at baseline, presence or absence of treatment history targeting vascular endothelial growth factor (VEGF) or VEGF receptor (VEGFR) (VEGF/VEGFR-targeted treatment history), cell type of thyroid cancer, presence or absence of distant metastasis, and development or no development of Grade ≥2 hypertension during the treatment period. The results indicated that the total target lesion size tended to decrease with the increasing dose-normalized AUC. In addition, ECOG PS, sex, and total target lesion size at baseline were selected as covariates for the effect of lenvatinib on the reduction in the total target lesion size. The effect was estimated to be as follows: (a) 15.7% lower in the patients with ECOG PS ≥1 than in those with ECOG PS of 0; (b) 22.1% lower in female patients than in male patients; and (c) decreased with the increasing total target lesion size at baseline (power function, -0.45).

- The patients in the lenvatinib group were divided into 4 subgroups by quartile of dose-normalized AUC, and the PFS was estimated in each exposure subgroup by the Kaplan-Meier method. As a result, the exposure subgroup with the highest dose-normalized AUC (AUC range, 2730-8080 ng·h/mL) was found to have shorter PFS than that in the other 3 exposure subgroups (AUC range, 518-2730 ng·h/mL). The concerned difference was remarkable at the early stage of the treatment. The applicant explained the concerned trend as follows: in patients who were judged to have a progressive disease (PD) before dose reduction or treatment interruption or those who dropped out at the early stage of the treatment, the dose strength was estimated to be high; in Study 303, most of the patients in the lenvatinib group experienced the dose reduction (78.5%) or interruption (56.3%); in light of the above aspects, patients with long PFS were considered to experience multiple dose reduction or withdrawal, which resulted in the low dose strength.

4.(ii).A.(7).2) Relationship between exposure and safety

The relationships between exposure to lenvatinib and adverse events (hypertension, proteinuria, fatigue, body weight decreased, thromboembolism) and time to the first dose reduction were investigated based on the results from the foreign phase II study (Study 201), Japanese phase II study (Study 208), and global phase III study (Study 303) in patients with thyroid cancer. The results were as shown below.

- The relationships between exposure to lenvatinib and the incidences of hypertension, proteinuria, fatigue, and body weight decreased were investigated. Of the parameters indicating the exposure to lenvatinib, the best predictive factors for these adverse events were C_{min} for hypertension, logarithmic cumulative AUC for proteinuria, dose-normalized AUC for fatigue, and dose-normalized AUC for body weight decreased. The incidence of thromboembolism in the clinical studies was low, making it difficult to construct a model for the relationship between exposure to lenvatinib and onset of thromboembolism. The relationship between AUC at 24 mg or dose-normalized AUC and onset of thromboembolism was, therefore, visually investigated, and as a result, no clear relationship was observed for either parameter.

- The patients in the lenvatinib group were divided into 4 subgroups by quartiles of AUC (Bayes estimator) of lenvatinib at the dose of 24 mg, and time to the first dose reduction was estimated in each exposure subgroup by the Kaplan-Meier method. As a result, the median time to the first dose reduction [90% CI] (weeks) was 24.3 [18.3, 36.3], 16.1 [12.1, 20.1], 11.4 [7.29, 12.7], and 4.86 [4.14, 9] in the subgroups in increasing order of the exposure, indicating that, following the administration of lenvatinib at 24 mg, exposure subgroups with the higher AUC had shorter time to the first dose reduction.

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

4.(ii).B.(1) Difference in PK of lenvatinib between Japanese and non-Japanese patients

The applicant explained the difference in PK of lenvatinib between Japanese and non-Japanese patients as follows:

Differences in the PK of lenvatinib between Japanese and non-Japanese patients were investigated based on C_{max} and $AUC_{0\text{-}24h}$ (both dose-normalized) of lenvatinib obtained following a single oral dose of 4 to 25 mg in tablets in a Japanese phase I study (Study 103) and the foreign phase I studies (Study 101, Study 102) in patients with solid cancer (the table below). As a result, the mean dose-normalized C_{max} and $AUC_{0\text{-}24h}$ were similar between these studies, although the inter-individual variabilities were large.

Comparison of the PK of lenvatinib between Japanese and non-Japanese patients

	Study	Dose (mg)	n	Dose-normalized C_{max}* (ng/mL/mg)	Dose-normalized $AUC_{0\text{-}24h}$* (ng·h/mL/mg)
Japanese patients	Study E7080-J081-103	4	3	15.3 ± 6.41	128 ± 27.7
		6	4	16.6 ± 3.43	146 ± 27.5
		9	3	22.4 ± 5.49	148 ± 42.0
		13	3	23.3 ± 5.58	178 ± 26.0
		16	3	29.5 ± 9.48	190 ± 37.3
		20	2	25.1	176
Non-Japanese patients	Study E7080-E044-101	6.4	3	19.9 ± 14.3	183 ± 125
		12	11	21.7 ± 9.01	138 ± 46.3
		12.5	9	16.7 ± 8.96	123 ± 70.1
		16	6	23.4 ± 9.89	203 ± 114
		20	3	20.4 ± 5.28	185 ± 103
		25	24	25.2 ± 9.37	163 ± 66.7
	Study E7080-A001-102	5	7	12.5 ± 5.09	130 ± 51.2
		8	10	22.2 ± 7.57	163 ± 55.2
		10	25	17.0 ± 6.88	137 ± 64.7
		12	4	19.3 ± 5.00	151 ± 54.1
		16	6	17.0 ± 4.00	163 ± 71.8
		24	3	27.3 ± 4.04	204 ± 89.4

Mean ± SD; *, Calculated from the dose-normalized PK parameters

Based on the PPK model constructed in the above PPK analysis [see "4.(ii).A.(6) PPK analysis"], the PK parameters of lenvatinib (CL/F and AUC at steady state following multiple oral doses of lenvatinib 24 mg QD) following administration in capsules, to-be-marketed formulation, were estimated and were compared between Japanese and non-Japanese patients. As a result, with the increasing body weight, CL/F of lenvatinib tended to increase while AUC tended to decrease. These trends were observed in both Japanese and non-Japanese populations. Between Japanese and non-Japanese patients, there were no clear differences in distribution of the CL/F or AUC values of lenvatinib in patients.

Based on the above, the applicant considered that the PK of lenvatinib does not clearly differ between Japanese and non-Japanese patients.

PMDA considers as follows:

The applicant's explanation that the submitted data did not show a clear difference in the PK of lenvatinib between Japanese and non-Japanese patients is acceptable, although the strict evaluation of differences in the PK of lenvatinib between Japanese and non-Japanese patients is limited for the following reasons:

- The PK data of lenvatinib obtained from Japanese and non-Japanese patients with the same dosage and administration were limited.

- Comparison of the PK of lenvatinib with the proposed dosage and administration (multiple oral doses of lenvatinib 24 mg QD) using the to-be-marketed formulation was only based on the estimated values.

4.(ii).B.(2) Use of lenvatinib in patients with severe hepatic impairment

The proposed Precautions for dosage and administration included a caution statement that reduction of the starting dose of lenvatinib to 14 mg should be considered for patients with severe hepatic impairment. PMDA asked the applicant to explain the rationale for this precaution.

The applicant responded as follows:

In Study 006 in patients with hepatic impairment, C_{max} of lenvatinib in patients with severe hepatic impairment was comparable to that in healthy adult subjects, but $AUC_{0\text{-}inf}$ was 1.8 times higher than that in healthy adult subjects [see "4.(ii).A.(3) Foreign phase I study in patients with hepatic impairment"]. Accordingly, the above precaution was included in the package insert so that, in clinical practice, AUC of lenvatinib in patients with severe hepatic impairment is comparable to that achieved in healthy adult subjects receiving lenvatinib under the proposed dosage and administration, in consideration of the following points.

- As a result of the PPK analysis, the PK of lenvatinib was estimated to be linear in the dose range from 3.2 to 32 mg [see "4.(ii).A.(6) PPK analysis"].

- Although no clear relationship was identified between the exposure to lenvatinib and prolongation of the PFS, the relationships between the exposure and the incidences of the major adverse events of lenvatinib including hypertension, proteinuria, fatigue, and body weight decreased, and between the exposure and the decrease of the total target lesion size were suggested [see "4.(ii).A.(7) Relationship of exposure with efficacy and safety"].

PMDA considers as follows:

In consideration of the results from Study 006, the dose reduction is possibly necessary in administration of lenvatinib to patients with severe hepatic impairment, because AUC potentially increases in such patients. However, clinical data on the efficacy and safety of lenvatinib at the starting dose of 14 mg in such patients are not available, and the appropriateness of this starting dose is unclear at present. Thus, the results from Study 006 should be provided to healthcare providers in clinical settings via the package insert etc., appropriately. Also, when administered to patients with severe hepatic impairment, the dose reduction of lenvatinib should be considered based on the results from Study 006, and during the treatment with lenvatinib, the patient should be carefully monitored with close attention to adverse events [see "4.(iii).B.(5) Dosage and administration"].

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from a total of 15 studies including 2 Japanese phase I studies, 1 Japanese phase II study, 1 global phase III study, 10 foreign phase I studies, and 1 foreign phase II study were submitted. As the reference data, the results from a total of 7 studies including 1 Japanese phase Ib study, 1 foreign phase I/Ib study, 2 foreign phase Ib/II studies, and 3 foreign phase II studies were submitted.

List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of enrollment	Outline of Dosage regimen*	Primary endpoint
Evaluation	Japan	Study E7080-J081-103	I	Patients with solid cancer	28	A single dose of lenvatinib 0.5 to 20 mg on Day 1 followed by a 7 to 9-day rest, then in 21-day treatment cycles, multiple doses of lenvatinib 0.5 to 20 mg BID for 2 weeks followed by a 1-week rest	Tolerability Safety PK
		Study E7080-J081-105	I	Patients with solid cancer	9	Lenvatinib 20 or 24 mg QD	Tolerability Safety
		Study E7080-J081-208	II	Patients with RAI-refractory DTC, MTC, and ATC	36	Lenvatinib 24 mg QD	Safety
	Global	Study E7080-G000-303	III	Patients with RAI-refractory DTC	392 (a) 261 (b) 131	(a) Lenvatinib 24 mg QD (b) Placebo QD	Efficacy Safety
	Foreign	Study E7080-E044-101	I	Patients with solid cancer or malignant lymphoma	82	Lenvatinib 0.2 to 32 mg QD	Tolerability Safety PK
		Study E7080-G000-201	II	Patients with RAI-refractory DTC and MTC	117	Lenvatinib 24 mg QD	Efficacy Safety PK
		Study E7080-E044-104	I	Patients with solid cancer and malignant lymphoma	6	A single dose of lenvatinib 24 mg as a solution containing ^{14}C-lenvatinib on Day 1, and lenvatinib 24 mg QD from Day 8 onward	PK Safety
		Study E7080-A001-001	I	Healthy adult subjects	20	A single dose of lenvatinib 10 mg in tablet or in capsule, followed by a 7-day washout, and another single dose of lenvatinib 10mg in a crossover manner	PK Safety
		Study E7080-A001-002	I	Healthy adult subjects	52	A single dose of placebo on Day 1; a single dose of lenvatinib 32 mg, moxifloxacin 400 mg, or placebo on Day 2; and in a crossover manner, single doses of them on Day 15 and Day 29	Safety
		Study E7080-A001-003	I	Healthy adult subjects	16	Single doses of lenvatinib 10 mg under fasted conditions or after a high fat meal on Day 1 and Day 15 in a crossover manner	PK
		Study E7080-A001-004	I	Healthy adult subjects	18	Single doses of ketoconazole 400 mg or placebo QD on Day 1 to Day 19; then in a crossover manner on Day 34 to Day 52; while single doses of lenvatinib 5 mg QD concomitantly only on Day 5 and Day 38	PK
		Study E7080-A001-005	I	Healthy adult subjects and subjects with renal impairment	26	A single dose of lenvatinib 24 mg	PK
		Study E7080-A001-006	I	Healthy adult subjects and subjects with hepatic impairment	26	A single dose of lenvatinib 10 mg to healthy adult subjects and patients with mild to moderate hepatic impairment, and a single dose of lenvatinib 5 mg to patients with severe hepatic impairment	PK
		Study E7080-A001-007	I	Healthy adult subjects	15	A single dose of lenvatinib 24 mg on Day 1; a single concomitant dose of rifampicin 600 mg and lenvatinib 24 mg on Day 15; multiple doses of rifampicin 600 mg QD on Day 29 to Day 49; while a single dose of lenvatinib 24 mg concomitantly on Day 43	PK
		Study E7080-A001-008	I	Healthy adult subjects	60	Single doses of lenvatinib 10 mg in low, standard, and high crystal content formulations in a crossover manner with 7-day washout periods between doses	BE

Data category	Region	Study	Phase	Study population	No. of enrollment	Outline of Dosage regimen*	Primary endpoint
Reference	Japan	Study E7080-J081-110	Ib	Patients with progressive or metastatic non-small cell lung cancer	28	In 21-day treatment cycles, concomitant use of lenvatinib 4 to 6 mg BID with CBDCA at a dose providing AUC of 6 mg·min/mL and PTX 200 mg/m^2	Tolerability Safety PK
	Foreign	Study E7080-A001-102	I/Ib	Patients with solid cancer, progressive or metastatic malignant melanoma	Phase I, 77 (a) 18 (b) 33 (c) 26 Phase Ib, 32 (a) 10 (b) 22	Phase I, (a) Lenvatinib 0.1 to 3.2 mg BID for 1 week followed by a 1-week rest (b) Lenvatinib 3.2 to 12 mg BID (c) Lenvatinib 10 mg BID Phase Ib, (a) Lenvatinib 20 to 24 mg and TMZ 100 mg/m^2 QD concomitantly (b) Lenvatinib 24 mg and TMZ 150 mg/m^2 QD concomitantly	Tolerability Safety PK
		Study E7080-701	Ib/II	Patients with recurrent ovary cancer sensitive to platinum antineoplastic drugs	7	In 21-day treatment cycles, lenvatinib 8 to 16 mg QD with GEM 1000 mg/m^2 and CBDCA at a dose providing AUC of 4 mg·min/mL concomitantly	Tolerability Safety
		Study E7080-702	Ib/II	Patients with chemotherapy-naïve malignant melanoma with metastasis	Phase Ib, 16 Phase II, (a) 42 (b) 40	Phase Ib, In 21-day treatment cycles, concomitant use of lenvatinib 16 to 22 mg QD with DTIC 1000 mg/m^2 Phase II, In 21-day treatment cycles, (a) concomitant use of lenvatinib 20 mg QD with DTIC 1000 mg/m^2 (b) DTIC 1000 mg/m^2	Tolerability Efficacy Safety
		Study E7080-G000-203	II	Patients with recurrent malignant glioma	Cohort 1, (a) 42 (b) 39 Cohort 2, 39 Cohort 3, 32	Cohort 1, In 28-day treatment cycles, (a) lenvatinib 24 mg QD (b) bevacizumab (genetical recombination) 10 mg/kg on Day 1 and Day 15 Cohort 2, 3, Lenvatinib 24 mg QD	Efficacy Safety
		Study E7080-G000-204	II	Patients with unresectable or metastatic endometrial cancer progressed after chemotherapy with platinum antineoplastic drugs	133	Lenvatinib 24 mg QD	Efficacy Safety
		Study E7080-G000-206	II	Patients with unresectable malignant melanoma	Cohort 1, 93 Cohort 2, 89	Lenvatinib 24 mg QD	Efficacy Safety

BID, Twice daily; QD, Once daily; RAI, Radioactive iodine; DTC, Differentiated thyroid cancer; MTC, Medullary thyroid carcinoma; ATC, Anaplastic thyroid carcinoma; PK, Pharmacokinetics; BE, Bioequivalence; CBDCA, Carboplatin; TMZ, Temozolomide; GEM, Gemcitabine hydrochloride; DTIC, Dacarbazine; *, Lenvatinib administered orally

The outline of each clinical study is as described below.

Major adverse events reported other than death in each clinical study are described in “4.(iv) Adverse events etc., observed in clinical studies,” and PK data etc., in “4.(i) Summary of biopharmaceutic studies and associated analytical methods” and in “4.(ii) Summary of clinical pharmacology studies.”

Evaluation data

(1) Clinical pharmacology studies

Clinical pharmacology data from 9 studies in healthy adult subjects, patients with renal impairment, and patients with hepatic impairment as well as patients with solid cancer and patients with malignant lymphoma, listed below, were submitted [see “4.(i) Summary of biopharmaceutic studies and associated analytical methods” and “4.(ii) Summary of clinical pharmacology studies”]. During the treatment period or within 30 days after the end of the treatment, 2 subjects in Study 104 died. In both

subjects, the death was considered attributable to the disease progression and a causal relationship to lenvatinib was ruled out.

1) Foreign phase I study (5.3.3.2.5; Study E7080-E044-104 [20 to 20])
2) Foreign phase I study (5.3.1.2.1; Study E7080-A001-001 [20 to 20])
3) Foreign phase I study (5.3.4.1.1; Study E7080-A001-002 [20 to 20])
4) Foreign phase I study (5.3.1.1.1; Study E7080-A001-003 [20 to 20])
5) Foreign phase I study (5.3.3.4.1; Study E7080-A001-004 [20 to 20])
6) Foreign phase I study (5.3.3.3.2; Study E7080-A001-005 [20 to 20])
7) Foreign phase I study (5.3.3.3.1; Study E7080-A001-006 [20 to 20])
8) Foreign phase I study (5.3.3.4.2; Study E7080-A001-007 [20 to 20])
9) Foreign phase I study (5.3.1.2.2; Study E7080-A001-008 [20 to 20])

(2) Japanese clinical studies

1) Japanese phase I study (5.3.3.2.1; Study E7080-J081-103 [20 to 20])

An open-label, uncontrolled study was conducted in patients with solid cancer (target sample size: 40 subjects) to investigate the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of lenvatinib at a single medical institution in Japan.

Lenvatinib was to be administered orally in a single dose at 0.5, 1, 2, 4, 6, 9, 13, 16, or 20 mg followed by a 7- to 9-day rest (Cycle 0), and then, lenvatinib was to be administered orally at 0.5, 1, 2, 4, 6, 9, 13, 16, or 20 mg BID for 2 weeks followed by a 1-week rest in Cycle 1 and the subsequent cycles (each cycle consisting of 3 weeks) until the discontinuation criteria were met.

Of the 28 patients enrolled in the study, 27 patients received lenvatinib and were included in the safety analysis.

DLT was evaluated until Cycle 1 and the tolerability was assessed. DLT was not observed at doses up to 13 mg BID, but 1 of 3 patients in the 16 mg BID group experienced AST increased and ALT increased, and 2 of 2 patients in the 20 mg BID group experienced platelet count decreased. Of the patients without DLT in the 16 mg BID group, 1 patient experienced Grade 2 platelet count decreased and fatigue, and 1 patient experienced Grade 3 fatigue and protein urine present and Grade 2 oedema. The MTD was therefore determined to be 13 mg BID.

For the safety, death during the treatment period of lenvatinib or within 30 days after the end of treatment occurred in 1 patient in the 9 mg group. The cause of death was disease progression, for which a causal relationship to lenvatinib was ruled out.

2) Japanese phase I study (5.3.3.2.3, Study E7080-J081-105 [20 to 20])

An open-label, uncontrolled study was conducted in patients with solid cancer (target sample size: 9-18 subjects) to investigate the tolerability and safety of lenvatinib at a single medical institution in Japan.

Lenvatinib was to be administered orally at 20 or 24 mg QD in 4-week treatment cycles until the discontinuation criteria were met.

All of the 9 patients enrolled in the study received lenvatinib and were included in the safety analysis.

DLT was to be evaluated until Cycle 1 and the tolerability was assessed. DLT was not observed in either 20 mg QD group or 24 mg QD group, and the tolerability of the doses of 24 mg QD was confirmed.

For the safety, death during the treatment period of lenvatinib or within 30 days after the end of treatment did not occur.

3) Japanese phase II study (5.3.5.2.2; Study E7080-J081-208 [ongoing since ■ 20■; data cut-off, ■ ■, 20■])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of lenvatinib in patients with locally advanced or metastatic RAI-refractory DTC,* MTC, and ATC (target sample size: ≥16 subjects) at 3 medical institutions in Japan.

Lenvatinib was administered orally at 24 mg QD until the discontinuation criteria were met.

*: Patients meeting any of the following criteria were included in the study as those with RAI-refractory DTC.
(a) Patients with at least 1 measurable lesion that does not demonstrate iodine uptake on radioiodine scan (RAI scan)
(b) Patients with at least 1 measurable lesion that has progressed according to RECIST Ver.1.1 within 12 months after RAI therapy, despite demonstration of iodine uptake on RAI scan before and after RAI therapy
(c) Patients who received RAI therapy at the cumulative dose of >600 mCi or 22 GBq, of which the last dose was at least 6 months before the registration, irrespective of the presence or absence of the measurable lesion

In this study, of the 51 patients screened, 43 patients were enrolled and given lenvatinib (23 DTC patients, 9 MTC patients, 11 ATC patients). All of the patients enrolled were included in the safety analysis as the Full Analysis Set (FAS).

For the efficacy, the response rate based on the investigator's assessment was as shown in the table below.

Best overall response and response rate (RECIST Ver.1.1, investigator's assessment; FAS, N = 43[*1])

Best overall response	Number of subjects (%)		
	DTC N = 23	MTC N = 8	ATC N = 11
Complete response (CR)	0	0	0
Partial response (PR)	16 (69.6)	1 (12.5)	3 (27.3)
Stable disease (SD)[*2]	7 (30.4)	7 (87.5)	7 (63.6)
Progressive disease (PD)	0	0	1 (9.1)
Not evaluable (NE)	0	0	0
Response (CR + PR) rate (%)	69.6	12.5	27.3
[95% CI]	[47.1, 86.8]	[0.3, 52.7]	[6.0, 61.0]

*1, One patient with MTC was excluded from the analysis, because the best overall response was not assessed until the date of data cut-off.
*2, Continued stable condition for ≥7 weeks in patients with DTC and MTC, and for ≥3 weeks in patients with ATC

For the safety, death occurred in 2 subjects during the treatment period of lenvatinib or within 30 days after the end of treatment and in 8 subjects during the follow-up period (the period from 31 days after the end of study treatment to the data cut-off date). In all these subjects, the death was considered attributable to the disease progression, and a causal relationship to lenvatinib was ruled out.

(3) Global study

Global phase III study (5.3.5.1.1, 5.3.5.1.2; Study E7080-G000-303 [ongoing since ■ 20■; efficacy data cut-off, ■ ■ 20■; safety data cut-off, ■ ■ 20■])

A double-blind, randomized, controlled study was conducted to compare the efficacy and safety between lenvatinib and placebo in patients with locally advanced or metastatic RAI-refractory DTC* (target sample size: 360 subjects) at 117 medical institutions in 21 countries including Japan.

*: Patients who met any of the following criteria and with whom DTC was assessed as disease progression by central radiographic review according to RECIST version 1.1 within 12 months before obtainment of the informed consent were included as those with RAI-refractory DTC.
(a) Patients with at least 1 measurable lesion that does not demonstrate iodine uptake on RAI scan
(b) Patients with DTC for which radical resection was not indicated and with at least 1 measurable lesion that has progressed according to RECIST Ver.1.1 within 12 months after RAI therapy, despite the observed iodine uptake on RAI scan before and after RAI therapy

(c) Patients who received RAI therapy at the cumulative dose of >600 mCi or 22 GBq, of which the last dose was at least 6 months before the registration, irrespective of the presence or absence of the measurable lesion

Oral administration of lenvatinib at 24 mg or placebo QD was continued until disease progression was assessed by imaging or the discontinuation criteria were met (in the randomized period). In addition, the patients who received placebo in the randomized period and had disease progression confirmed by imaging were allowed to receive lenvatinib in an open-label manner (in the open-label period). The patients who were included in the lenvatinib group and in whom disease progression was confirmed by imaging, on the other hand, were not allowed to continue lenvatinib.

All of the 392 subjects enrolled in the study (261 subjects in the lenvatinib group, 131 subjects in the placebo group) were included in the efficacy analysis as the FAS. The same population was subjected to safety analysis.

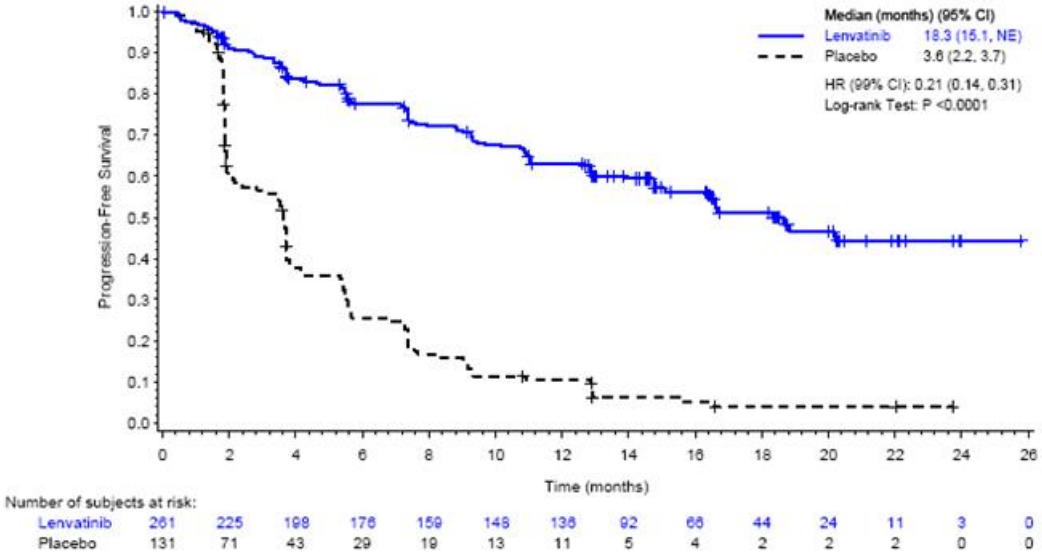
The primary endpoint of this study was the PFS assessed by the central imaging assessment institution (the centrally assessed PFS).

For the efficacy, the results on the centrally assessed PFS and Kaplan-Meier curves were as shown in the table and figure below, respectively. The *P* value was below the pre-determined significance level (two-sided, 0.01), demonstrating the superiority of the lenvatinib group to the placebo group.

Analysis results on PFS (FAS, central assessment; date of data cut-off, [redacted], 20[redacted])

	Lenvatinib group	Placebo group
Number of subjects	261	131
Number of death or progression (%)	107 (41.0)	113 (86.3)
Median [95% CI] (months)	18.3 [15.1, NE]	3.6 [2.2, 3.7]
Hazard ratio [99% CI][*1]	0.21 [0.14, 0.31]	
P value (two-sided)[*2,*3]	<0.0001	

NE, Not estimable; *1, Cox regression adjusted by stratification factors (age [≤65 years, >65 years], region [Europe, North America, others], presence or absence of VEGF/VEGFR-targeted treatment history); *2, Stratified log-rank test using age (≤65 years, >65 years), region (Europe, North America, others), presence or absence of VEGF/VEGFR-targeted treatment history as stratification factors; *3, Two-sided level of significance of 0.01



Kaplan-Meier curve of PFS (FAS, central assessment; date of data cut-off, [redacted], 20[redacted])

For the safety in the randomized period, death during the treatment period or within 30 days after the end of treatment occurred in 20 of 261 subjects (7.7%) in the lenvatinib group and 6 of 131 subjects (4.6%) in the placebo group. The causes of death included general physical health deterioration (3 subjects), pulmonary embolism, death, and cardio-respiratory arrest (2 subjects each), pneumonia/sepsis, acute kidney injury, lung infection, myocardial infarction, intracranial tumour

haemorrhage, sudden death, multi-organ failure, acute respiratory failure, haemorrhagic stroke, malignant neoplasm progression, and hepatic failure (1 subject each) in the lenvatinib group, and dyspnoea, sepsis, myocardial infarction, sudden death, disease progression, and dyspnoea/haemothorax (1 subject each) in the placebo group. Of these, a causal relationship to lenvatinib could not be ruled out for death (2 subjects), general physical health deterioration, pulmonary embolism, sudden death, or haemorrhagic stroke (1 subject each) in the lenvatinib group.

(4) Foreign clinical studies

1) Foreign phase I study (5.3.3.2.4; Study E7080-E044-101 [ongoing since ■ 20■; date of data cut-off, ■ ■, 20■])

An open-label, uncontrolled study was conducted to investigate the MTD, safety, and PK of lenvatinib in patients with solid cancer and malignant lymphoma (target sample size: 50-70 subjects; 3-24 subjects per cohort) at 2 medical institutions overseas.

Lenvatinib was administered orally at 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12, 12.5, 16, 20, 25, or 32 mg QD in a dose escalation manner in 4-week treatment cycles until disease progression was confirmed or the discontinuation criteria were met.

All of the 82 subjects enrolled in the study received the study drug and were included in the efficacy analysis as the intent-to-treat (ITT) population. The same population was subjected to safety analysis.

Grade 3 proteinuria was observed in 2 of 7 subjects in the lenvatinib 32 mg cohort, and thus the MTD of lenvatinib was determined to be 25 mg QD.

For the safety, death during the treatment period of lenvatinib or within 30 days after the end of treatment occurred in 15 subjects. Except for deaths due to disease progression (14 subjects), the cause of death was haemoptysis (1 subject), for which a causal relationship to lenvatinib was ruled out.

2) Foreign phase II study (5.3.5.2.1; Study E7080-G000-201 [ongoing since ■ 20■; date of data cut-off, ■ ■, 20■])

An open-label uncontrolled study was conducted to investigate the efficacy, safety, and PK of lenvatinib in patients with RAI-refractory DTC* and MTC (target sample size: 104 subjects) at 30 medical institutions overseas.

*: Patients with at least 1 measurable lesion which met the following (a) or (b) were allowed to be included: (a) no iodine uptake observed on radioiodine scan; (b) progression present based on modified RECIST within 12 months after RAI therapy, despite iodine uptake observed. Patients who received RAI therapy at the cumulative dose of >600 mCi or 22 GBq, of which the last dose was at least 6 months before the registration, irrespective of the presence or absence of the measurable lesion were also allowed to be included.

Lenvatinib was administered orally at 10 mg BID to the first 2 subjects, and at 24 mg QD to the third and subsequent subjects in 4-week treatment cycles until disease progression was confirmed or the discontinuation criteria were met.*

*: In response to the amendment of the protocol (dated ■ ■, 20■), the dosage and administration was changed to 24 mg QD in 2 DTC subjects who had received 10 mg BID.

All of the 117 subjects enrolled in the study (58 DTC subjects, 59 MTC subjects) received lenvatinib and were included in the efficacy analysis as the ITT population. The same population was subjected to safety analysis.

For the efficacy, the results on the response rate (central assessment) according to the modified RECIST v1.0 criteria,* the primary endpoint in this study, were as shown in the table below.

*: A measurable lesion was defined as a lesion of ≥15 mm in long diameter for a non-lymph node or a lesion of ≥20 mm in long diameter for a lymph node on CT or MRI imaging.

Response rate (ITT population, central assessment; data cut-off date, [redacted])

Best overall response	Number of subjects (%)	
	DTC N = 58	MTC N = 59
Complete response (CR)	0	0
Partial response (PR)	29 (50.0)	21 (35.6)
Stable disease (SD)	25 (43.1)	26 (44.1)
Progressive disease (PD)	3 (5.2)	7 (11.9)
Not evaluable (NE)	1 (1.7)	2 (3.4)
Unknown	0	3 (5.1)
Response (CR + PR)	29	21
Response rate [95% CI] (%)	50.0 [36.6, 63.4]	35.6 [23.6, 49.1]

For the safety, death during the treatment period of lenvatinib or within 30 days after the end of treatment occurred in 7 of 117 subjects (6.0%) (3 DTC subjects, 4 MTC subjects). Except for deaths due to disease progression (1 DTC subject, 1 MTC subject), the causes of death were cardiac arrest and arterial haemorrhage (1 DTC subject each), and respiratory arrest, respiratory failure, and paraneoplastic syndrome (1 MTC subject each). A causal relationship to lenvatinib could not be ruled out for respiratory failure (1 subject).

Reference data

(1) Japanese phase I study (5.3.3.2.2; Study E7080-J081-110 [20 to 20])

An open-label, uncontrolled study was conducted in patients with progressive or metastatic non-small cell lung cancer (target sample size: 27-33 subjects) to investigate the tolerability, safety, and PK of lenvatinib added to the combination therapy of CBDCA and PTX at 3 medical institutions in Japan.

All of the 28 subjects enrolled in the study received lenvatinib and were included in the safety analysis set.

For the safety, death during the treatment period or within 30 days after the end of treatment did not occur.

(2) Foreign clinical studies

1) Foreign phase I/Ib study (5.3.3.2.6, 5.3.3.2.7; Study E7080-A001-102 [ongoing since 20; date of data cut-off, 20])

An open-label, uncontrolled study was conducted to investigate the tolerability, safety, and PK of monotherapy and combination therapy with lenvatinib at 2 medical institutions overseas. In the phase I, lenvatinib was administered alone to patients with solid cancer, malignant lymphoma, and malignant melanoma (target sample size: ≥40 subjects), and in the phase Ib, lenvatinib was administered concomitantly with TMZ to patients with malignant melanoma.

All of the 77 subjects enrolled in the phase I and all of the 32 subjects enrolled in the phase Ib were included in the safety analysis set.

In the phase I, death during the treatment period or within 30 days after the end of treatment occurred in 13 of 77 subjects (16.9%). Except for death due to disease progression (11 subjects), the causes of death were cardiopulmonary failure and *Clostridium difficile* colitis (1 subject each), for both of which a causal relationship to lenvatinib was ruled out. In the phase Ib, death during the treatment period or within 30 days after the end of treatment occurred in 3 subjects, and the cause of all the deaths was disease progression, for which a causal relationship to the study drug was ruled out.

2) Foreign phase Ib/II study (5.3.5.2.6; Study E7080-701 [20 to 20])

An open-label, uncontrolled study was conducted to investigate the tolerability and safety of lenvatinib added to the combination therapy of CBDCA and gemcitabine hydrochloride (GEM) in patients with recurrent ovary cancer sensitive to platinum antineoplastics (target sample size: approximately 10-20 subjects) at 4 medical institutions overseas. [redacted].

All of the 7 subjects enrolled in the study received lenvatinib and were included in the safety analysis set.

For the safety, death during the treatment period or within 7 days after the end of treatment did not occur.

3) Foreign phase Ib/II study (5.3.5.2.7, Study E7080-702 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A study (phase Ib, open-label, uncontrolled study; phase II, open-label, randomized, controlled study) was conducted to investigate the tolerability and safety of concomitant use of lenvatinib with dacarbazine (DTIC) in patients with chemotherapy-naïve metastatic malignant melanoma (target sample size: 10-20 subjects in the phase Ib; 80 subjects in the phase II) at 19 medical institutions overseas.

All of the 16 subjects enrolled in the phase Ib received lenvatinib and were included in the safety analysis set. Of 82 subjects enrolled in the phase II, 81 subjects who were subjected to at least 1 safety evaluation after the first dose (42 subjects in the lenvatinib + DTIC group, 39 subjects in the DTIC alone group) were included in the safety analysis set.

For the safety in the phase Ib, death during the study period or within 7 days after the end of treatment did not occur. In the phase II, deaths during the treatment period or after the end of treatment occurred in 10 subjects (7 subjects in the lenvatinib + DTIC group, 3 subjects in the DTIC alone group). Except for deaths due to disease progression (6 subjects in the lenvatinib + DTIC group, 3 subjects in the DTIC alone group), the cause of remaining death was unknown (1 subject), for which a causal relationship to the study drug could not be ruled out.

4) Foreign phase II study (5.3.5.2.3; Study E7080-G000-203 [ongoing since [redacted] 20[redacted]; date of data cut-off, [redacted] [redacted], 20[redacted]])

A study (Cohort 1, open-label, randomized, controlled study; Cohorts 2 and 3, open-label, uncontrolled study) was conducted to compare the efficacy and safety between lenvatinib and bevacizumab (recombinant) in patients with recurrent malignant glioma (GBM) (target sample size: 98 subjects in Cohort 1, 40 subjects in Cohort 2, 32 subjects in Cohort 3) at 6 medical institutions overseas. Cohort 1 included patients with bevacizumab-naïve recurrent GBM at Grade IV under WHO classification, Cohort 2 included patients with bevacizumab-naïve recurrent GBM at Grade III under WHO classification, and Cohort 3 included patients with recurrent GBM progressed after bevacizumab treatment.

A total of 151 subjects (Cohort 1, 42 in the lenvatinib group, 38 subjects in the bevacizumab group; Cohort 2, 39 subjects; Cohort 3, 32 subjects) who were enrolled in the study and given at least 1 dose of the study drug were included in the safety analysis set.

For the safety in Cohort 1, death during the treatment period or within 30 days after the end of treatment occurred in 18 subjects (9 subjects in the lenvatinib group, 9 subjects in the bevacizumab group). Of them, except for death due to disease progression (8 subjects in the lenvatinib group, 9 subjects in the bevacizumab group), the cause of death was tumour haemorrhage (1 subject in the lenvatinib group), for which a causal relationship to the study drug could not be ruled out. In Cohort 2, death during the treatment period or within 30 days after the end of treatment occurred in 2 subjects. Except for death due to disease progression, the cause of death was myocardial infarction (1 subject), for which a causal relationship to lenvatinib was ruled out. In Cohort 3, death during the treatment period or within 30 days after the end of treatment occurred in 4 subjects. Except for death due to disease progression (3 subjects), the cause of death was pulmonary embolism (1 subject), for which a causal relationship to the study drug could not be ruled out.

5) Foreign phase II study (5.3.5.2.7; Study E7080-G000-204 [ongoing since [redacted] 20[redacted]; date of data cut-off, [redacted] [redacted], 20[redacted]])

An open-label uncontrolled study was conducted to investigate the efficacy and safety of lenvatinib in patients with unresectable or metastatic endometrial cancer progressed after chemotherapy with platinum antineoplastics (target sample size: 130 subjects) at 69 medical institutions overseas.

A total of 133 subjects enrolled in the study received lenvatinib, and death during the treatment period or within 30 days after the end of treatment occurred in 18 subjects. Except for deaths due to disease progression (10 subjects), the causes of death were general physical health deterioration, asthenia, renal failure, cerebrovascular accident, cardiopulmonary failure, tumour lysis syndrome, cardiac failure, and hepatic failure (1 subject each). Of these, a causal relationship to lenvatinib could not be ruled out for general physical health deterioration, asthenia, or renal failure (1 subject each).

6) Foreign phase II study (5.3.5.2.5; Study E7080-G000-206 [ongoing since [redacted] 20[redacted]; date of data cut-off, (Cohort 1) [redacted], 20[redacted], (Cohort 2) [redacted], 20[redacted]])

An open-label uncontrolled study was conducted to investigate the efficacy and safety of lenvatinib in patients with unresectable malignant melanoma (target sample size: 60-178 subjects) at 40 medical institutions overseas.

A total of 182 subjects enrolled in the study received lenvatinib, and death during the treatment period or within 30 days after the end of treatment occurred in 27 subjects. Except for deaths due to disease progression (24 subjects), the causes of death were hepatic failure, septic shock, and wound infection (1 subject each), and a causal relationship to lenvatinib could not be ruled out for hepatic failure (1 subject).

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

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

PMDA concluded that, among the submitted evaluation data, the most important clinical study for evaluating the efficacy and safety of lenvatinib was the global phase III study (Study 303), in which the efficacy and safety of lenvatinib had been investigated in patients with RAI-refractory DTC. Thus, PMDA decided to evaluate the submitted data, focusing on the Study 303.

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

Based on the following review, PMDA has concluded that the efficacy of lenvatinib in patients with RAI-refractory DTC was demonstrated.

4.(iii).B.(2).1) Use of control group

PMDA asked the applicant to explain the reason for having chosen placebo as the control drug in the randomized period of Study 303.

The applicant responded as follows:
At the time when Study 303 was planned, the standard therapy against RAI-refractory DTC, of which a response was investigated in this study, had not been established, and therefore the placebo was chosen as the control drug.

PMDA accepted the applicant's explanation.

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

PMDA asked the applicant to explain the appropriateness of the centrally assessed PFS selected as the primary endpoint in Study 303.

The applicant responded as follows:
Most of the patients with RAI-refractory DTC have metastases to the lungs or bones, and pathological conditions attributable to the metastases such as obstructive pneumonia, haemoptysis, pathological fracture, and spinal cord compression affect the life expectancy (*Minerva Endocrinol.* 2012;37:335-56). Prolonged PFS in these patients is expected to delay the onset of these conditions and is therefore considered to have clinical significance.

Thyroid cancer in some of the patients, on the other hand, has a slow progression, which is assessed as stable disease (SD) according to the RECIST criteria and thus not identified as an event in assessment of PFS. It has been, however, reported that the efficacy of a drug can be investigated based on the PFS by limiting the subjects to thyroid cancer patients with progression in the past 12 months, which is not

considered slow (*Head & Neck.* 2012;34:736-45.). Study 303, therefore, included only patients with RAI-refractory DTC with progression in the past 12 months.

Based on the above, the applicant considered it appropriate to set the PFS as the primary endpoint in Study 303.

PMDA considers as follows:
The treatment purpose in patients with RAI-refractory DTC is survival and it is appropriate to set the overall survival (OS) as the primary endpoint for evaluation of the efficacy of lenvatinib in these patients. It is, on the other hand, considered possible to evaluate the efficacy based on the PFS, because prolonged PFS, which indicates a delay in the onset of event attributable to the local progression and metastasis, has a certain clinical significance in these patients.

Based on the above, the efficacy in Study 303 should be evaluated by the results not only on the centrally assessed PFS, the primary endpoint, but also on OS.

4.(iii).B.(2).3) Efficacy evaluation results
The results on the centrally assessed PFS, the primary endpoint, in Study 303 showed superiority of lenvatinib to the placebo [see "4.(iii).A. *Evaluation data* (3) Global study"].

In addition, the results on the PFS by investigator's assessment, which was performed as a sensitivity analysis, were as shown in the table below.

Analysis results on PFS (investigator's assessment, FAS; date of data cut-off, [redacted], 20[redacted])

	Lenvatinib group	Placebo group
Number of subjects	261	131
Number of death or progression (%)	107 (41.0)	110 (84.0)
Median [95% CI] (months)	16.6 [14.8, NE]	3.7 [3.5, 5.4]
Hazard ratio [95% CI][*1]	0.24 [0.16, 0.35]	
P value (two-sided)[*2,*3]	<0.0001	

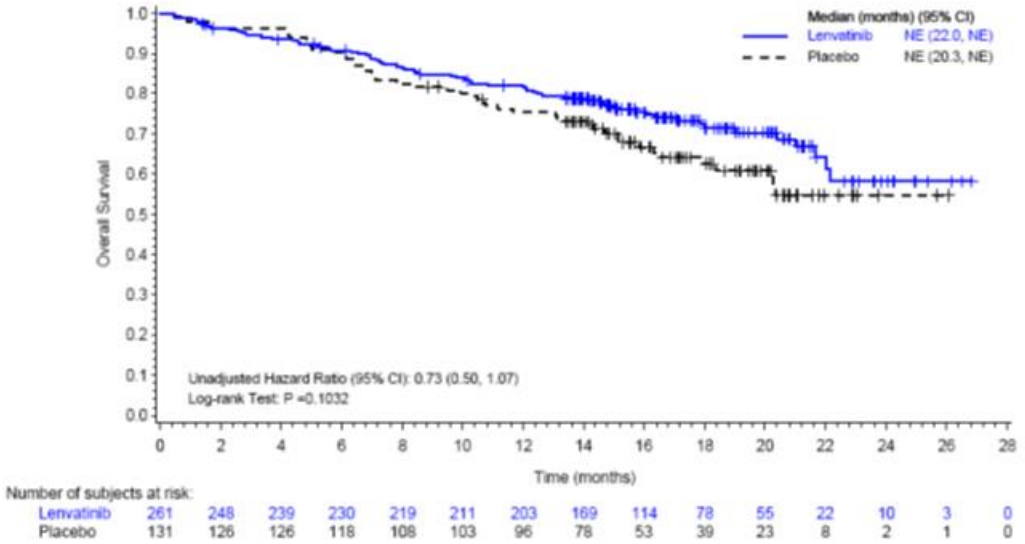
*1, Cox regression adjusted by stratification factors (age [≤65 years, >65 years], region [Europe, North America, others], presence or absence of VEGF/VEGFR-targeted treatment history); *2, Stratified log-rank test (stratified by age [≤65 years, >65 years], region [Europe, North America, others], presence or absence of VEGF/VEGFR-targeted treatment history)

The results on the OS, one of the secondary endpoints, and the Kaplan-Meier curves were shown in the table and figure below, respectively. By the time when the OS was analyzed, 109 of 131 subjects (83.2%) in the placebo group had entered the open-label period, receiving lenvatinib.

Analysis results on OS (FAS; date of data cut-off, [redacted], 20[redacted])

	Lenvatinib group	Placebo group
Number of subjects	261	131
Death (%)	71 (27.2)	47 (35.9)
Median [95% CI] (months)	NE [22.0, NE]	NE [20.3, NE]
Hazard ratio [95% CI][*1]	0.73 [0.50, 1.07]	
P value (two-sided)[*2]	0.1032	

NE, Not estimable; *1, Cox regression adjusted by stratification factors (age [≤65 years, >65 years], region [Europe, North America, others], presence or absence of VEGF/VEGFR-targeted treatment history); *2, Stratified log-rank test (stratified by age [≤65 years, >65 years], region [Europe, North America, others], presence or absence of VEGF/VEGFR-targeted treatment history)



Kaplan-Meier curves on the OS (FAS; date of data cut-off, [redacted], 20[redacted])

PMDA considers as follows:
In Study 303, not only the results on the centrally assessed PFS, the primary endpoint, but also those on the PFS by investigator's assessment showed the superiority of lenvatinib to placebo, and the magnitude of the observed effect had clinical significance. In addition, the OS in lenvatinib group did not show tendency of being inferior to that in placebo group.

Based on the above results, PMDA has considered that the efficacy of lenvatinib in the target patients in Study 303 was demonstrated.

4.(iii).B.(2).4) Efficacy by cell type
PMDA asked the applicant to explain the efficacy of lenvatinib on cancer by cell type in Study 303.

The applicant responded as follows:
The results on the PFS in patients with papillary and follicular cancer, the cancer types eligible for Study 303, were as shown in the table below. Subgroup analysis in the patients with papillary and follicular cancer showed that the PFS in the lenvatinib group was longer than that in the placebo group, indicating that lenvatinib is expected to have efficacy on the cell types included in Study 303.

Analysis results on PFS by cell type (FAS, central assessment; date of data cut-off, [redacted], 20[redacted])

Cell type	Lenvatinib group		Placebo group		Hazard ratio [95% CI]*
	Number of subjects	Median [95% CI] (months)	Number of subjects	Median [95% CI] (months)	
Papillary cancer	169	16.4 [12.8, 20.2]	90	3.5 [1.9, 3.7]	0.27 [0.19, 0.38]
Follicular cancer	92	NE [16.6, NE]	41	3.7 [2.4, 5.5]	0.10 [0.05, 0.19]

NE, Not estimable; *, Cox regression adjusted by stratification factors (age [≤65 years, >65 years], region [Europe, North America, others], presence or absence of VEGF/VEGFR-targeted treatment history)

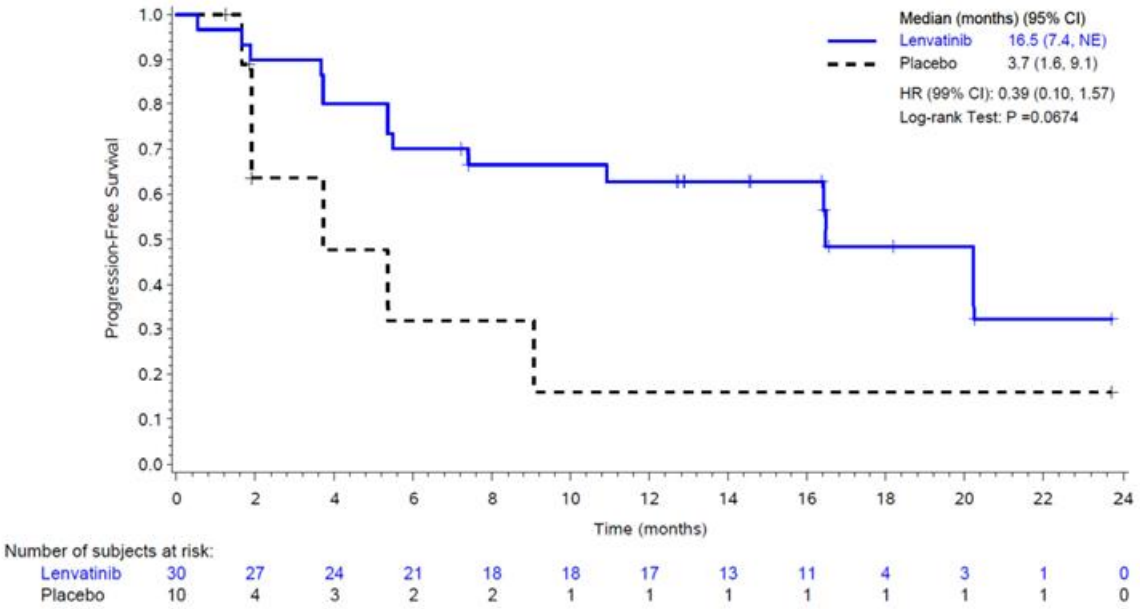
PMDA accepted the applicant's explanation.

4.(iii).B.(2).5) Efficacy in Japanese patients
The results on the PFS by central assessment in the Japanese population in Study 303 were as shown in the table and figure below.

Analysis results on PFS in Japanese patients (FAS, central assessment; date of data cut-off, [redacted], 20[redacted])

	Lenvatinib group	Placebo group
Number of subjects	30	10
Number of death or progression (%)	14 (46.7)	6 (60.0)
Median [95% CI] (months)	16.5 [7.4, NE]	3.7 [1.6, 9.1]
Hazard ratio [99% CI][*1]	0.39 [0.10, 1.57]	
P value (two-sided)[*2]	0.0674	

*1, Cox regression adjusted by stratification factors (age [≤65 years, >65 years], presence or absence of VEGF/VEGFR-targeted treatment history); *2, Stratified log-rank test (stratified by age [≤65 years, >65 years], presence or absence of VEGF/VEGFR-targeted treatment history)



Kaplan-Meier curves of PFS in Japanese patients (FAS, central assessment; date of data cut-off, [redacted], 20[redacted])

PMDA considers as follows:
Numbers of Japanese patients enrolled and events observed in Study 303 were limited, and therefore there is a limitation in evaluating the efficacy of lenvatinib in Japanese patients with thyroid cancer. Based on the results on the point estimate of the hazard ratio for the PFS, however, the efficacy in the Japanese population is expected to be comparable to that in the overall population.

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

As a result of the reviews described below, PMDA considers that caution is required in treatment with lenvatinib for the following adverse events: hypertension/hypertensive crisis, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood thyroid stimulating hormone (TSH) increased.

In addition, PMDA has concluded that although caution should be paid to these adverse events during treatment with lenvatinib, lenvatinib is tolerable as long as adverse events are monitored and controlled as well as appropriate measures such as dose reduction, treatment interruption, or discontinuation of lenvatinib are taken by physicians with sufficient knowledge and experience in cancer chemotherapy. However, the currently available safety information is limited, and thus such information needs to be continuously collected after the market launch.

4.(iii).B.(3).1) Safety profile and its differences between Japanese and non-Japanese patients

Based on the safety information obtained in Study 303, the applicant explained the safety profile of lenvatinib in patients with RAI-refractory DTC as follows:

The outline of safety profile in the lenvatinib group and placebo group in Study 303 was as shown in the table below.

Outline of safety (Study 303)

	Number of subjects (%)	
	Lenvatinib group N = 261	Placebo group N = 131
All adverse events	260 (99.6)	118 (90.1)
Adverse events of Grade ≥3	227 (87.0)	39 (29.8)
Serious adverse events	139 (53.3)	31 (23.7)
Adverse events resulting in death	20 (7.7)	6 (4.6)
Adverse events leading to treatment discontinuation	46 (17.6)	6 (4.6)
Adverse events leading to treatment interruption	217 (83.1)	24 (18.3)
Adverse events leading to dose reduction	178 (68.2)	6 (4.6)

Adverse events of all Grades of which the incidence was ≥20% higher in the lenvatinib group than in the placebo group included diarrhoea (67.4% in the lenvatinib group, 16.8% in the placebo group), nausea (46.7%, 25.2%), stomatitis (36.8%, 6.9%), vomiting (35.6%, 14.5%), hypertension (69.3%, 15.3%), dysphonia (31.4%, 5.3%), headache (38.3%, 11.5%), proteinuria (33.7%, 3.1%), decreased appetite (54.4%, 18.3%), palmar-plantar erythrodysaesthesia syndrome (32.2%, 0.8%), and body weight decreased (51.3%, 14.5%). Adverse events of Grade ≥3 of which the incidence was ≥10% higher in the lenvatinib group than in the placebo group included hypertension (42.9%, 3.8%), proteinuria (10.7%, 0%), and body weight decreased (13.4%, 0.8%).

Serious adverse events of which the incidence was ≥1% higher in the lenvatinib group than in the placebo group included pneumonia (3.8%, 2.3%), hypertension (3.4%, 0%), dehydration (2.7%, 0%), general physical health deterioration (2.7%, 0%), acute kidney injury (1.9%, 0.8%), lower respiratory tract infection (1.5%, 0%), hypocalcaemia (1.5%, 0%), headache (1.5%, 0%), vomiting (1.5%, 0%), hypotension (1.5%, 0%), urinary tract infection (1.1%, 0%), back pain (1.1%, 0%), osteoarthritis (1.1%, 0%), convulsion (1.1%, 0%), and cancer pain (1.1%, 0%). Adverse events leading to treatment discontinuation of which the incidence was ≥1% higher in the lenvatinib group than in the placebo group included hypertension (1.1%, 0%) and asthenia (1.1%, 0%).

The applicant explained the difference in the safety of lenvatinib between patients in and out of Japan based on the data from Study 303 as follows:

The outline of safety in the Japanese and non-Japanese patients and adverse events with an incidence of ≥20% in either Japanese or non-Japanese patients were as shown in the tables below.

Outline of safety (Study 303)

	Number of subjects (%)			
	Japanese patients		Non-Japanese patients	
	Lenvatinib group N = 30	Placebo group N = 10	Lenvatinib group N = 231	Placebo group N = 121
All adverse events	30 (100)	9 (90.0)	230 (99.6)	109 (90.1)
Adverse events of Grade ≥3	28 (93.3)	1 (10.0)	199 (86.1)	38 (31.4)
Serious adverse events	14 (46.7)	0	125 (54.1)	31 (25.6)
Adverse events resulting in death	1 (3.3)	0	19 (8.2)	6 (5.0)
Adverse events leading to treatment discontinuation	2 (6.7)	0	44 (19.0)	6 (5.0)
Adverse events leading to treatment interruption or dose reduction	28 (93.3)	3 (30.0)	206 (89.2)	22 (18.2)

Adverse events with an incidence of ≥20% in either Japanese or non-Japanese patients in the lenvatinib group (Study 303)

Preferred term (MedDRA Ver.16.1)	Number of subjects (%)			
	Japanese patients N = 30		Non-Japanese patients N = 231	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension	26 (86.7)	24 (80.0)	155 (67.1)	88 (38.1)
Palmar-plantar erythrodysaesthesia syndrome	21 (70.0)	1 (3.3)	63 (27.3)	8 (3.5)
Diarrhoea	21 (70.0)	0	155 (67.1)	24 (10.4)
Proteinuria	20 (66.7)	7 (23.3)	68 (29.4)	21 (9.1)
Fatigue	19 (63.3)	4 (13.3)	92 (39.8)	8 (3.5)
Decreased appetite	18 (60.0)	4 (13.3)	124 (53.7)	14 (6.1)
Stomatitis	16 (53.3)	0	80 (34.6)	11 (4.8)
Thrombocytopenia	14 (46.7)	2 (6.7)	9 (3.9)	2 (0.9)
Nausea	14 (46.7)	0	108 (46.8)	6 (2.6)
Oedema peripheral	13 (43.3)	0	41 (17.7)	1 (0.4)
Vomiting	12 (40.0)	0	81 (35.1)	5 (2.2)
Constipation	10 (33.3)	0	65 (28.1)	1 (0.4)
Weight decreased	10 (33.3)	3 (10.0)	124 (53.7)	32 (13.9)
Blood TSH increased	9 (30.0)	0	8 (3.5)	0
Nasopharyngitis	8 (26.7)	0	16 (6.9)	0
Hypoalbuminaemia	8 (26.7)	1 (3.3)	17 (7.4)	0
Arthralgia	8 (26.7)	0	60 (26.0)	1 (0.4)
Dysphonia	8 (26.7)	0	74 (32.0)	3 (1.3)
Pyrexia	7 (23.3)	0	31 (13.4)	1 (0.4)
Back pain	7 (23.3)	0	39 (16.9)	5 (2.2)
Headache	7 (23.3)	0	93 (40.3)	8 (3.5)
Hepatic function abnormal	6 (20.0)	1 (3.3)	0	0
Dysgeusia	6 (20.0)	0	41 (17.7)	0
Epistaxis	6 (20.0)	0	25 (10.8)	0
Rash	6 (20.0)	0	43 (18.6)	1 (0.4)
Cough	5 (16.7)	0	57 (24.7)	0
Asthenia	1 (3.3)	0	65 (28.1)	16 (6.9)

TSH, Thyroid stimulating hormone

Adverse events of which the incidence was ≥20% higher in the Japanese patients than in the non-Japanese patients in the lenvatinib group included palmar-plantar erythrodysaesthesia syndrome, proteinuria, fatigue, thrombocytopenia, oedema peripheral, blood TSH increased, and hepatic function abnormal. Adverse events of Grade ≥3 of which the incidence was ≥10% higher in the Japanese patients than in the non-Japanese patients in the lenvatinib group included hypertension and proteinuria.

The serious adverse event that occurred only in ≥2 Japanese patients was cancer pain (3 of 30 subjects [10.0%]), but a causal relationship to lenvatinib was ruled out for all of the event.

Among the adverse events leading to treatment discontinuation, there were no events that occurred only in ≥2 Japanese patients.

Adverse events leading to dose reduction or treatment interruption of which the incidence was ≥10% higher in the Japanese patients than in the non-Japanese patients in the lenvatinib group included the following events: palmar-plantar erythrodysaesthesia syndrome (12 of 30 Japanese subjects [40.0%], 20 of 231 non-Japanese subjects [8.7%]), proteinuria (12 of 30 subjects [40.0%], 38 of 231 subjects [16.5%]), hypertension (11 of 30 subjects [36.7%], 41 of 231 subjects [17.7%]), decreased appetite (10 of 30 subjects [33.3%], 41 of 231 subjects [17.7%]), fatigue (8 of 30 subjects [26.7%], 17 of 231 subjects [7.4%]), thrombocytopenia (5 of 30 subjects [16.7%]), 2 of 231 subjects [0.9%]), platelet count decreased (5 of 30 subjects [16.7%], 1 of 231 subjects [0.4%]), and oedema peripheral (4 of 30 subjects [13.3%], 2 of 231 subjects [0.9%]).

PMDA considers as follows:
In Study 303, the incidences of Grade ≥3 adverse events and serious adverse events were higher in the lenvatinib group than in the placebo group, but the incidence of adverse events resulting in death was not largely different between these groups. Lenvatinib is therefore considered to be tolerable with

appropriate measures such as dose reduction, treatment interruption, and discontinuation. However, during the treatment with lenvatinib, special attention needs to be paid to the following adverse events with a higher incidence in the lenvatinib group than in the placebo group: diarrhoea, nausea, stomatitis, vomiting, hypertension, dysphonia, headache, proteinuria, decreased appetite, palmar-plantar erythrodysaesthesia syndrome, and body weight decreased. The relevant information should be appropriately provided to healthcare providers in clinical settings accordingly.

Only limited number of Japanese patients with thyroid cancer have received lenvatinib, and thus the safety profile of lenvatinib can be compared between Japanese and non-Japanese patients with thyroid cancer to a limited extent. Attention still should be paid to Grade ≥3 adverse events with a higher incidence in Japanese patients than in non-Japanese patients in Study 303, such as palmar-plantar erythrodysaesthesia syndrome, proteinuria, and thrombocytopenia. The results of the investigation of the difference in safety profile of lenvatinib between Japanese and non-Japanese patients in clinical studies should be provided to healthcare providers in the clinical settings.

In the following sections, each of the adverse events with a higher incidence in the lenvatinib group than in the placebo group in the randomized period of Study 303 as well as adverse events and serious adverse events with a higher incidence in the Japanese patients than in the non-Japanese patients is reviewed.

4.(iii).B.(3).2) Hypertension/hypertensive crisis

The applicant explained hypertension during the treatment with lenvatinib as described in the subsequent paragraphs.

Adverse events of hypertension, blood pressure increased, blood pressure diastolic increased, and prehypertension were included in the tabulation as those indicating hypertension.

In Study 303, hypertension occurred in 191 of 261 subjects (73.2%) in the lenvatinib group and in 21 of 131 subjects (16.0%) in the placebo group. Grade ≥3 events occurred in 116 of 261 subjects (44.4%) in the lenvatinib group and in 5 of 131 subjects (3.8%) in the placebo group. Of the subjects experiencing Grade ≥3 hypertension, 92 subjects in the lenvatinib group and 7 subjects in the placebo group had hypertension at the start of this study. Serious hypertension occurred in 9 of 261 subjects (3.4%) in the lenvatinib group but did not occur in the placebo group. A causal relationship of the event in the 9 subjects in the lenvatinib group to lenvatinib could not be ruled out. In the lenvatinib group, treatment interruption, dose reduction, or discontinuation due to hypertension occurred in 34 of 261 subjects (13.0%), 35 of 261 subjects (13.4%), and 3 of 261 subjects (1.1%), respectively. In the placebo group, treatment interruption occurred in 1 of 131 subjects (0.8%), and neither dose reduction nor discontinuation occurred.

The time of onset of hypertension (median) was 2.3 weeks in the lenvatinib group and 6.1 weeks in the placebo group.

Hypertensive crisis occurred in 2 subjects who received lenvatinib in the open-label period of Study 303, but a causal relationship to lenvatinib was ruled out in both subjects.

PMDA considers as follows:

Attention should be paid to hypertension during the treatment with lenvatinib, because Grade ≥3 hypertension occurred in the Japanese patients at a high incidence [see “4.(iii).B.(3).1) Safety profile and its differences between Japanese and non-Japanese patients”] and patients who also had hypertension at the start of administration of lenvatinib frequently experienced Grade ≥3 hypertension. It is therefore necessary to provide the information on the incidence of hypertension in clinical studies to healthcare providers in clinical settings appropriately. In addition, patients should be monitored through blood pressure measurements before the start of administration of lenvatinib and periodically during the treatment, and the package insert etc., should include a caution statement so that appropriate measures such as administration of an antihypertensive drug, dose reduction or treatment interruption of lenvatinib should be taken if hypertension is observed.

4.(iii).B.(3).3) Infections

The applicant explained infections during the treatment with lenvatinib as described in the subsequent paragraph.

Events classified under MedDRA SOC "Infections and infestations" were included in the tabulation as those indicating infections.

In Study 303, infections occurred in 162 of 261 subjects (62.1%) in the lenvatinib group and in 44 of 131 subjects (33.6%) in the placebo group. Grade 3 or 4 infections occurred in 32 of 261 subjects (12.3%) in the lenvatinib group and in 5 of 131 subjects (3.8%) in the placebo group. Grade 5 infections occurred in 2 subjects (pneumonia/sepsis and lung infection in 1 subject each) in the lenvatinib group and in 1 subject (sepsis) in the placebo group, and a causal relationship to lenvatinib was ruled out for all the events. Infections classified as serious adverse events occurred in 34 of 261 subjects (13.0%) in the lenvatinib group and in 7 of 131 subjects (5.3%) in the placebo group.

PMDA considers as follows:

The incidence of infections was higher in the lenvatinib group than in the placebo group, and serious adverse events also occurred. Therefore attention should be paid to infections during the treatment with lenvatinib. Patients should be carefully monitored for the signs of infection during the treatment with lenvatinib and cautions should be provided to healthcare providers in the clinical settings using the package insert etc., to ensure appropriate measures in the event of abnormal findings.

4.(iii).B.(3).4) Renal disorder

The applicant explained renal disorder during the treatment with lenvatinib as follows:

The incidence of events related to renal disorder in Study 303 was as shown in the table below.

Incidence of events related to renal disorder (Study 303)

Preferred term (MedDRA Ver 16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal disorder	110 (42.1)	35 (13.4)	7 (5.3)	1 (0.8)
Proteinuria	88 (33.7)	28 (10.7)	4 (3.1)	0
Blood creatinine increased	19 (7.3)	0	2 (1.5)	0
Blood urea increased	8 (3.1)	0	0	0
Renal failure acute	7 (2.7)	4 (1.5)	1 (0.8)	1 (0.8)
Renal impairment	5 (1.9)	1 (0.4)	0	0
Renal failure	4 (1.5)	1 (0.4)	0	0
Acute prerenal failure	1 (0.4)	1 (0.4)	0	0
Renal tubular necrosis	1 (0.4)	1 (0.4)	0	0
Hypercreatininaemia	1 (0.4)	0	0	0
Renal failure chronic	1 (0.4)	0	0	0
Protein urine present	1 (0.4)	0	0	0
Nephrotic syndrome	1 (0.4)	0	0	0
Renal ischaemia	1 (0.4)	0	0	0

In Study 303, serious renal disorder occurred in 10 of 261 subjects (3.8%) in the lenvatinib group and in 1 of 131 subjects (0.8%) in the placebo group. Treatment interruption, dose reduction, or treatment discontinuation due to renal disorder occurred in 49 of 261 subjects (18.8%), 31 of 261 subjects (11.9%), and 4 of 261 subjects (1.5%), respectively, in the lenvatinib group, while none of them occurred in the placebo group. Grade 5 renal disorder occurred in 1 subject (acute kidney injury) in the lenvatinib group, and a causal relationship to lenvatinib was ruled out for the disorder.

The time of onset of renal disorder (median) was 6.1 weeks in the lenvatinib group.

PMDA considers as follows:

Attention should be paid to renal disorder during the treatment with lenvatinib, because renal disorder frequently occurred following administration of lenvatinib, and some events were serious or resulted in death. It is therefore necessary to provide the following caution statement using the package insert etc.,: renal function test and electrolyte test should be performed periodically during the treatment with

lenvatinib and if renal disorder is observed, appropriate measures such as treatment discontinuation should be taken. In addition, information on the incidence of renal disorder in clinical studies should be appropriately provided to healthcare providers in the clinical settings via package insert etc., to raise caution.

4.(iii).B.(3).5) Haemorrhage-related events

The applicant explained haemorrhage-related events associated with lenvatinib as described in the subsequent paragraphs.

The following events were included in the tabulation as haemorrhage-related events: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechiae, rectal haemorrhage, vaginal haemorrhage, blood urine present, pulmonary haemorrhage, post procedural haemorrhage, haematoma, conjunctival haemorrhage, haemorrhoidal haemorrhage, intracranial tumour haemorrhage, ecchymosis, eye haemorrhage, increased tendency to bruise, laryngeal haemorrhage, nail bed bleeding, purpura, skin haemorrhage, splinter haemorrhages, tumour haemorrhage, aneurysm ruptured, arterial haemorrhage, gastric haemorrhage, gastroduodenitis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhagic stroke, injection site haemorrhage, intra-abdominal haematoma, melaena, menorrhagia, metrorrhagia, mouth haemorrhage, pleural haemorrhage, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, subarachnoid haemorrhage, and tracheal haemorrhage.

In Study 303, haemorrhage-related events occurred in 91 of 261 subjects (34.9%) in the lenvatinib group and in 24 of 131 subjects (18.3%) in the placebo group. Grade 3 events occurred in 3 of 261 subjects (1.1%; intracranial tumour haemorrhage, pleural haemorrhage, and splenic haemorrhage in 1 subject each) in the lenvatinib group and in 3 of 131 subjects (2.3%; haemoptysis in 2 subjects, pulmonary haemorrhage in 1 subject) in the placebo group, and no Grade 4 events occurred. Intracranial tumour haemorrhage and haemorrhagic stroke (1 subject each) in the lenvatinib group as well as haemothorax (1 subject) in the placebo group resulted in deaths, and of these, a causal relationship to lenvatinib could not be ruled out for haemorrhagic stroke (1 subject) in the lenvatinib group.

In Study 303, intracranial tumour haemorrhage occurred in 3 subjects receiving lenvatinib who had brain metastasis. Thus, caution will be included in the package insert so that attention should be paid to the event in patients with brain metastasis.

PMDA considers as follows:

Attention should be paid to haemorrhage-related events during the treatment with lenvatinib, because haemorrhage-related events resulting in death occurred in Study 303, and in patients with brain metastasis, special attention needs to be paid to intracranial tumour haemorrhage. It is therefore necessary to provide information to healthcare providers in clinical settings that haemorrhage-related events resulting in death occurred in clinical studies, and in patients with brain metastasis, attention needs to be paid to intracranial tumour haemorrhage, and then the following caution statement should be included in the package insert etc.,: suitable patients should be carefully selected and appropriate measures should be taken in the event of haemorrhage-related events.

4.(iii).B.(3).6) Palmar-plantar erythrodysaesthesia syndrome

The applicant explained palmar-plantar erythrodysaesthesia syndrome associated with lenvatinib as described in the subsequent paragraphs.

Adverse events of palmar-plantar erythrodysaesthesia syndrome, palmar erythema, rash erythematous, and skin reaction were included in the tabulation as those indicating palmar-plantar erythrodysaesthesia syndrome.

In Study 303, palmar-plantar erythrodysaesthesia syndrome occurred in 88 of 261 subjects (33.7%) in the lenvatinib group and in 1 of 131 subjects (0.8%) in the placebo group. Grade ≥3 events occurred in 9 of 261 subjects (3.4%) in the lenvatinib group and did not occur in the placebo group.

Palmar-plantar erythrodysaesthesia syndrome leading to treatment interruption and dose reduction of the study drug occurred in 27 of 261 subjects (10.3%) and 20 of 261 subjects (7.7%), respectively, in

the lenvatinib group, but no palmar-plantar erythrodysaesthesia syndrome leading to discontinuation occurred. In the placebo group, none of treatment interruption, dose reduction, or discontinuation due to the event occurred.

The time of onset of palmar-plantar erythrodysaesthesia syndrome (median) was 5.9 weeks in the lenvatinib group.

PMDA considers as follows:
Palmar-plantar erythrodysaesthesia syndrome following administration of lenvatinib frequently occurred in Japanese patients [see "4.(iii).B.(3).1) Safety profile and its differences between Japanese and non-Japanese patients"]. However, none of the subjects who experienced it discontinued the treatment, and the study was continued by dose reduction or interruption of lenvatinib in such subjects, most of whom recovered later. Therefore, palmar-plantar erythrodysaesthesia syndrome is manageable with appropriate measures including dose reduction of lenvatinib. Information on the incidence of palmar-plantar erythrodysaesthesia syndrome in clinical studies, however, should be appropriately provided to healthcare providers in the clinical settings.

4.(iii).B.(3).7) Haematotoxicity
The applicant explained haematotoxicity associated with lenvatinib as follows:
The incidence of events related to haematotoxicity in Study 303 was as shown in the table below.

Incidence of events related to haematotoxicity (Study 303)

Preferred term (MedDRA Ver.16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Haematotoxicity	84 (32.2)	15 (5.7)	18 (13.7)	2 (1.5)
Anaemia	24 (9.2)	4 (1.5)	6 (4.6)	1 (0.8)
Thrombocytopenia	23 (8.8)	4 (1.5)	3 (2.3)	0
Lymphopenia	19 (7.3)	3 (1.1)	2 (1.5)	0
Platelet count decreased	17 (6.5)	1 (0.4)	0	0
White blood cell count decreased	14 (5.4)	2 (0.8)	4 (3.1)	0
Leukopenia	11 (4.2)	0	1 (0.8)	0
Lymphocyte count decreased	9 (3.4)	3 (1.1)	4 (3.1)	1 (0.8)
Neutropenia	9 (3.4)	3 (1.1)	0	0
Platelet count increased	4 (1.5)	0	1 (0.8)	0
Neutrophil count decreased	3 (1.1)	1 (0.4)	1 (0.8)	0
White blood cell count increased	3 (1.1)	0	1 (0.8)	0
Haematocrit increased	2 (0.8)	0	0	0
Haemoglobin decreased	2 (0.8)	0	0	0
Haematocrit decreased	1 (0.4)	0	0	0
Red blood cell count decreased	1 (0.4)	0	0	0
Mean cell haemoglobin decreased	1 (0.4)	0	0	0
Thrombocytosis	1 (0.4)	0	1 (0.8)	0
Eosinophilia	1 (0.4)	0	0	0
Anaemia macrocytic	1 (0.4)	0	0	0
Leukocytosis	1 (0.4)	0	0	0
Neutrophil count increased	0	0	1 (0.8)	0
Eosinophilia	0	0	1 (0.8)	0

Grade ≥4 haematotoxicity was not reported. Serious adverse events of anaemia, platelet count decreased, and neutropenia/thrombocytopenia occurred (1 subject each) in the lenvatinib group, and no serious adverse events occurred in the placebo group. Treatment interruption, dose reduction, or treatment discontinuation due to haematotoxicity occurred in 21 of 261 subjects (8.0%), 11 of 261 subjects (4.2%), and 0 of 261 subjects (0%), respectively, in the lenvatinib group and in 1 subject (0.8%) each in the placebo group. Of them in the lenvatinib group, adverse events in 3 subjects (anaemia, platelet count decreased, neutropenia/thrombocytopenia in 1 subject each) were serious, and a causal relationship to the study drug could not be ruled out for platelet count decreased in 1 subject.

The time of onset of haematotoxicity (median) was 8.2 weeks in the lenvatinib group.

PMDA considers as follows:
In Study 303, the incidence of haematotoxicity was higher in the lenvatinib group than in the placebo group, and serious haematotoxicity occurred in the lenvatinib group. Therefore, attention should be paid to haematotoxicity during the treatment with lenvatinib. Also it is necessary to provide information on the incidence of haematotoxicity to healthcare providers in the clinical settings appropriately, and to include appropriate caution in the package insert etc., to ensure measures such as periodic blood tests and dose reduction of lenvatinib corresponding to the patient's condition.

4.(iii).B.(3).8) Liver disorder
The applicant explained liver disorder associated with lenvatinib as follows:
The incidence of events related to liver disorder in Study 303 was as shown in the table below.

Incidence of events related to liver disorder (Study 303)

Preferred term (MedDRA Ver.16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Liver disorder	69 (26.4)	15 (5.7)	5 (3.8)	1 (0.8)
Hypoalbuminaemia	25 (9.6)	1 (0.4)	2 (1.5)	0
ALT increased	20 (7.7)	4 (1.5)	0	0
AST increased	18 (6.9)	5 (1.9)	2 (1.5)	0
Blood ALP increased	16 (6.1)	2 (0.8)	3 (2.3)	1 (0.8)
Blood albumin decreased	8 (3.1)	1 (0.4)	1 (0.8)	0
Hepatic function abnormal	6 (2.3)	1 (0.4)	0	0
Blood bilirubin increased	5 (1.9)	0	0	0
γ-GTP increased	4 (1.5)	2 (0.8)	1 (0.8)	0
Transaminases increased	2 (0.8)	0	0	0
Blood ALP abnormal	1 (0.4)	1 (0.4)	0	0
Cholestatic liver injury	1 (0.4)	1 (0.4)	0	0
Drug-induced liver injury	1 (0.4)	1 (0.4)	0	0
Hepatic failure	1 (0.4)	1 (0.4)	0	0
Ascites	1 (0.4)	0	0	0
Hepatic enzyme increased	1 (0.4)	0	0	0
Hepatic steatosis	1 (0.4)	0	0	0
Jaundice	1 (0.4)	0	0	0
Liver injury	1 (0.4)	0	0	0

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; γ-GTP, gamma-glutamyltransferase

In Study 303, serious liver disorder occurred in 5 of 261 subjects (1.9%) in the lenvatinib group and did not in the placebo group. Grade 5 liver disorder occurred in 1 subject (hepatic failure) in the lenvatinib group, for which a causal relationship to lenvatinib was ruled out. Treatment interruption, dose reduction, or treatment discontinuation due to liver disorder occurred in 7 of 261 subjects (2.7%), 13 of 261 subjects (5.0%), and 1 of 261 subjects (0.4%), respectively, in the lenvatinib group and no such events occurred in the placebo group.

The time of onset of liver disorder (median) was 12.0 weeks in the lenvatinib group.

Liver disorder classified as Hy's law (defined according to the Guidance for industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009) did not occur.

PMDA considers as follows:
Attention needs to be paid to liver disorder during the treatment with lenvatinib, because liver disorder frequently occurred following administration of lenvatinib and some events were serious. Therefore, it is necessary to provide information on the incidence of liver disorder in clinical studies appropriately to healthcare providers in the clinical settings, and the following caution statement should be included in the package insert etc.,: patients should be monitored periodically through liver function tests during the treatment with lenvatinib, and if abnormalities are observed, appropriate measures such as treatment discontinuation should be taken.

4.(iii).B.(3).9) Arrhythmia

The applicant explained arrhythmia associated with lenvatinib as follows:
The incidence of events related to arrhythmia in Study 303 was as shown in the table below.

Incidence of events related to arrhythmia (Study 303)

Preferred term (MedDRA Ver.16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Arrhythmia	59 (22.6)	12 (4.6)	11 (8.4)	1 (0.8)
Electrocardiogram QT prolonged	23 (8.8)	4 (1.5)	2 (1.5)	0
Tachycardia	10 (3.8)	1 (0.4)	3 (2.3)	0
Atrial fibrillation	9 (3.4)	1 (0.4)	1 (0.8)	0
Palpitations	6 (2.3)	0	1 (0.8)	0
Sinus tachycardia	5 (1.9)	0	1 (0.8)	0
Sinus bradycardia	4 (1.5)	0	0	0
Syncope	3 (1.1)	2 (0.8)	0	0
Atrial flutter	3 (1.1)	0	0	0
Atrioventricular block first degree	3 (1.1)	0	0	0
Electrocardiogram ST-T segment abnormal	2 (0.8)	0	0	0
Bundle branch block right	2 (0.8)	0	0	0
Bradycardia	2 (0.8)	0	0	0
Cardio-respiratory arrest	2 (0.8)	2 (0.8)	0	0
Sudden death	1 (0.4)	1 (0.4)	1 (0.8)	1 (0.8)
Electrocardiogram abnormal	1 (0.4)	0	0	0
Electrocardiogram T wave abnormal	1 (0.4)	0	0	0
Electrocardiogram repolarisation abnormality	1 (0.4)	0	0	0
Heart rate decreased	1 (0.4)	0	0	0
Loss of consciousness	1 (0.4)	1 (0.4)	0	0
Extrasystoles	1 (0.4)	0	0	0
Bundle branch block left	1 (0.4)	0	0	0
Ventricular extrasystoles	1 (0.4)	0	0	0
Electrocardiogram T wave inversion	0	0	1 (0.8)	0
Heart rate increased	0	0	1 (0.8)	0
Supraventricular extrasystoles	0	0	1 (0.8)	0

Grade 5 events related to arrhythmia included cardio-respiratory arrest (2 subjects) and sudden death (1 subject) in the lenvatinib group as well as sudden death (1 subject) in the placebo group. Of these, a causal relationship to lenvatinib could not be ruled out for sudden death (1 subject) in the lenvatinib group. Serious adverse events related to arrhythmia included cardio-respiratory arrest (2 subjects) and atrial fibrillation/atrial flutter, atrial fibrillation, syncope, bundle branch block right, sudden death, and loss of consciousness (1 subject each) in the lenvatinib group as well as sinus tachycardia/sudden death (1 subject) in the placebo group.

The results from Study E7080-A001-002 [see "4.(ii).A.(5) Foreign phase I study"] showed that lenvatinib is unlikely to prolong QT/QTc directly. The incidence of electrolyte abnormality including hypocalcaemia and hypokalaemia was, on the other hand, higher in the lenvatinib group than in the placebo group and electrolyte abnormality possibly induced QT/QTc prolonged.

PMDA considers as follows:
Although lenvatinib has not been demonstrated to prolong QT/QTc, adverse events related to arrhythmia including QT/QTc prolonged occurred more frequently in the lenvatinib group than in the placebo group, and death due to arrhythmia also occurred. During the treatment with lenvatinib, thus, attention should be paid to arrhythmia. It is therefore necessary to include the following caution statement in the package insert etc.,: (i) electrolyte test and electrocardiography should be performed before the start of treatment with lenvatinib and periodically during the treatment, (ii) electrolyte abnormalities should be corrected if found before the start of treatment with lenvatinib, and (iii) if QT/QTc interval prolonged or arrhythmia is observed, appropriate measures such as treatment interruption should be taken.

4.(iii).B.(3).10) Cardiac function disturbance

The applicant explained cardiac function disturbance associated with lenvatinib as described in the subsequent paragraphs.

Adverse events of ejection fraction decreased, cardiac failure, pulmonary oedema, and right ventricular failure were included in the tabulation as those indicating cardiac function disturbance.

In Study 303, cardiac function disturbance occurred in 17 of 261 subjects (6.5%) in the lenvatinib group and in 3 of 131 subjects (2.3%) in the placebo group. Grade 3 events occurred in 4 of 261 subjects (1.5%) in the lenvatinib group, but did not occur in the placebo group. Treatment discontinuation due to cardiac function disturbance occurred only in 1 subject in the lenvatinib group. No serious adverse events occurred.

In Study 303, echocardiography was scheduled before the first dose of lenvatinib and every 16 weeks after the first dose. As a result, the change rate (mean) of the left ventricular ejection fraction (LVEF) from baseline to the minimum value was -5.6% in the lenvatinib group and -1.6% in the placebo group. In the lenvatinib group, deterioration from mild dysfunction (LVEF, 40%-49%) to severe dysfunction (LVEF, <30%) occurred in 1 subject.

PMDA considers as follows:

In Study 303, patients who discontinued the treatment due to cardiac function disturbance associated with lenvatinib were limited and no serious adverse events occurred. Cardiac function disturbance is therefore considered to be manageable with measures such as treatment interruption. It is therefore necessary to appropriately provide information on the incidence of cardiac function disturbance in clinical studies to healthcare providers in meical settings, and caution should be included in the package insert etc., to ensure appropriate measures such as dose reduction of lenvatinib according to the patient's condition are taken.

The criteria for echocardiography established in Study 303 should be provided appropriately to healthcare providers in meical settings using information leaflets.

4.(iii).B.(3).11) Hypocalcaemia

The applicant explained hypocalcaemia associated with lenvatinib as follows:

In Study 303, hypocalcaemia occurred in 33 of 261 subjects (12.6%) in the lenvatinib group, but did not occur in the placebo group. Grade ≥3 events occurred in 13 of 261 subjects (5.0%) in the lenvatinib group. Hypocalcaemia leading to treatment interruption or dose reduction of lenvatinib occurred in 4 of 261 subjects (1.5%) and 3 of 261 subjects (1.1%), respectively, in the lenvatinib group but no events leading to the treatment discontinuation occurred.

As hypoparathyroidism potentially occurs following parathyroidectomy associated with the treatment for thyroid cancer, the incidence of hypocalcaemia was compared between presence and absence of history of hypoparathyroidism in the lenvatinib group in Study 303. In the subgroup without history of hypoparathyroidism, hypocalcaemia occurred in 29 of 246 subjects (11.8%), and of them, Grade ≥3 events occurred in 10 of 246 subjects (4.1%) and serious events in 2 of 246 subjects (0.8%). On the other hand, in the subgroup with history of hypoparathyroidism, hypocalcaemia occurred in 4 of 15 subjects (26.7%), and Grade ≥3 events occurred in 3 of 15 subjects (20.0%) and serious events in 2 of 15 subjects (13.3%).

PMDA considers as follows:

Hypocalcaemia frequently occurred during the treatment with lenvatinib, especially in patients with hypoparathyroidism. It is therefore necessary to monitor blood calcium periodically during the treatment with lenvatinib and to provide appropriate treatment for hypocalcaemia such as supplementing calcium in the event of blood calcium value decrease. In addition, information on the incidence of hypocalcaemia in clinical studies including the frequent occurrence in patients with history of hypoparathyroidism should be appropriately included in the package insert etc., to raise caution.

4.(iii).B.(3).12) Thromboembolism

The applicant explained thromboembolism associated with lenvatinib as follows:

The incidence of events related to arterial thromboembolism in Study 303 was as shown in the table below.

Incidence of events related to arterial thromboembolism (Study 303)

Preferred term (MedDRA Ver.16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Arterial thromboembolism	14 (5.4)	7 (2.7)	3 (2.3)	1 (0.8)
Monoparesis	3 (1.1)	2 (0.8)	0	0
Myocardial infarction	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)
Cerebrovascular accident	2 (0.8)	1 (0.4)	0	0
Splenic infarction	2 (0.8)	0	0	0
Transient ischaemic attack	2 (0.8)	0	0	0
Acute myocardial infarction	1 (0.4)	1 (0.4)	0	0
Cerebral ischaemia	1 (0.4)	1 (0.4)	0	0
Haemorrhagic stroke	1 (0.4)	1 (0.4)	0	0
Hemiparesis	1 (0.4)	0	0	0
Ischaemic stroke	1 (0.4)	0	0	0
Peripheral arterial occlusive disease	1 (0.4)	0	0	0
Coronary artery occlusion	0	0	1 (0.8)	0
Monoplegia	0	0	1 (0.8)	0

Grade 5 events related to arterial thromboembolism included myocardial infarction and haemorrhagic stroke (1 subject each) in the lenvatinib group and myocardial infarction (1 subject) in the placebo group. Of these, a causal relationship to lenvatinib could not be ruled out for haemorrhagic stroke (1 subject) in the lenvatinib group. Serious events related to arterial thromboembolism included monoparesis (2 subjects) and myocardial infarction/cerebrovascular accident, myocardial infarction, cerebrovascular accident, transient ischaemic attack, acute myocardial infarction, cerebral ischaemia, haemorrhagic stroke, and ischaemic stroke (1 subject each) in the lenvatinib group as well as myocardial infarction and coronary artery occlusion (1 subject each) in the placebo group. Arterial thromboembolism leading to the study drug discontinuation occurred in 4 subjects in the lenvatinib group, but did not occur in the placebo group.

The time of onset of arterial thromboembolism (median) was 12.0 weeks in the lenvatinib group.

Relationships between the occurrence of arterial thromboembolism and presence or absence of related history or risk factors* of arterial thromboembolism were investigated. The results showed that arterial thromboembolism occurred only in the subjects with a related history or risk factors, and the incidence of arterial thromboembolism tended to be higher in the lenvatinib group than in the placebo group. In the patients with a related history or risk factors, lenvatinib potentially increases the incidence of arterial thromboembolism.

*: Risk factors investigated include age (≥65 years), BMI ≥25, concomitant use with an anticoagulant agent or antiplatelet agent; history of antihypertensive treatment; comorbidity or history of diabetes mellitus, hypertension, hyperlipidaemia, dyslipidaemia, hypercholesterolaemia, atrial fibrillation, or mitral valve incompetence; hypertension at the screening (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), as well as hypercholesterolaemia or hypertriglyceridaemia at baseline (exceeded the reference value).

The incidence of events related to venous thromboembolism in Study 303 was as shown in the table below.

Incidence of events related to venous thromboembolism (Study 303)

Preferred term (MedDRA Ver.16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism	14 (5.4)	10 (3.8)	6 (4.6)	2 (1.5)
Pulmonary embolism	8 (3.1)	8 (3.1)	2 (1.5)	2 (1.5)
Pelvic venous thrombosis	1 (0.4)	1 (0.4)	0	0
Retinal vein thrombosis	1 (0.4)	1 (0.4)	0	0
Jugular vein thrombosis	1 (0.4)	0	2 (1.5)	0
Deep vein thrombosis	1 (0.4)	0	0	0
Thrombophlebitis superficial	1 (0.4)	0	0	0
Vena cava thrombosis	1 (0.4)	0	0	0
Venous thrombosis	1 (0.4)	0	0	0
Subclavian vein thrombosis	0	0	2 (1.5)	0

Grade 5 events related to venous thromboembolism occurred only in 2 subjects (pulmonary embolism in both) in the lenvatinib group, and of them, a causal relationship to lenvatinib could not be ruled out in 1 subject. Serious events related to venous thromboembolism included pulmonary embolism (4 subjects) and pulmonary embolism/deep vein thrombosis and retinal vein thrombosis (1 subject each) in the lenvatinib group as well as pulmonary embolism (2 subjects) in the placebo group. Venous thromboembolism leading to the study drug discontinuation occurred in 1 subject in the lenvatinib group but did not occur in the placebo group.

The time of onset of venous thromboembolism (median) was 22.0 weeks in the lenvatinib group.

Relationships between the occurrence of venous thromboembolism and presence or absence of related history or risk factors* of venous thromboembolism were investigated. The results showed that venous thromboembolism occurred only in the subjects with a related history or risk factors, and the incidence of venous thromboembolism tended to be higher in the lenvatinib group than in the placebo group. In the patients with a related history or risk factors, lenvatinib potentially increases the incidence of venous thromboembolism.

*: Risk factors investigated include age (≥65 years), BMI ≥25, concomitant use with an anticoagulant agent or antiplatelet agent, history of antihypertensive treatment, use of an oral contraceptive agent; comorbidity or history of diabetes mellitus, hypertension, hyperlipidaemia, dyslipidaemia, hypercholesterolaemia; hypertension at the screening (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg); hypercholesterolaemia or hypertriglyceridaemia at baseline (exceeded the reference value), as well as history of surgery within 1 month before the time of baseline.

PMDA considers as follows:
Attention should be paid to thromboembolism during the treatment with lenvatinib, because thromboembolism occurred following administration of lenvatinib and some subjects died consequently. It is therefore necessary to provide the following information to healthcare providers in clinical settings: the incidences of events related to thromboembolism and the characteristics of the patients who experienced the events in clinical studies; patients with a history of cardiovascular diseases in the past 6 months, patients with haemorrhagic or thrombotic diseases, and patients receiving anticoagulant agents were excluded in Study 303. In addition, it should be cautioned in the package insert etc., that appropriate measures be taken if thromboembolism occurs.

4.(iii).B.(3).13) Others
Based on the mechanism of action of lenvatinib and adverse events of similar drugs, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, and wound healing delayed as well as blood TSH increased are considered to be possible adverse events of lenvatinib.

The applicant explained these events as follows:

(a) Gastrointestinal perforation and gastrointestinal fistulae
In the pooled analysis of Study 303, Study 201, and Study 208, gastrointestinal perforation and gastrointestinal fistulae were found in 14 of 532 subjects (2.6%). Serious adverse events included perineal abscess (2 subjects) and anal fistula/anal abscess, abscess intestinal/diverticular perforation, oesophageal perforation/oesophagobronchial fistula, anal fistula, colonic abscess, oesophageal fistula, tracheal fistula, and tracheo-oesophageal fistula (1 subject each). Of the serious adverse events, a causal relationship to lenvatinib could not be ruled out in 7 subjects (anal fistula/anal abscess, oesophageal perforation/oesophagobronchial fistula, anal fistula, oesophageal fistula, perineal abscess, tracheal fistula, and tracheo-oesophageal fistula in 1 subject each). No death occurred.

(b) Posterior reversible encephalopathy syndrome
In Study 303, Study E7080-A001-102, and Study E7080-G000-203, posterior reversible encephalopathy syndrome occurred in 1 subject each. All the events were deemed as serious adverse events.

(c) Wound healing delayed
In Study 303, wound healing delayed occurred in 5 of 261 subjects (1.9%) in the lenvatinib group, but did not occur in the placebo group. In the lenvatinib group, Grade ≥3 wound healing delayed occurred in 2 subjects. In addition, serious wound healing delayed occurred in 3 subjects, in 2 subjects of which a causal relationship to lenvatinib could not be ruled out.

Although no clear criteria for surgery-related treatment interruption and resumption of lenvatinib were included in the protocol of Study 303, the following cautions were provided in response to inquiries from study sites.

- Perform the surgery after treatment interruption of 7 days, which corresponds to 5 times the half-life of lenvatinib.

- Resume the treatment with lenvatinib after thoroughly confirming that the surgical site has been adequately healed so that anti-angiogenic lenvatinib will not affect the site.

- When performing a minor surgery, interrupt the treatment for 2 days before and after the surgery.

(d) Blood TSH increased
Patients with blood TSH ≤5.50 μIU/mL were enrolled in Study 303 to exclude patients with hypothyroidism.

In Study 303, blood TSH increased occurred in 17 of 261 subjects (6.5%) in the lenvatinib group, but did not occur in the placebo group. All the events were Grade ≤2 and serious adverse events or events leading to dose reduction, interruption, or discontinuation of lenvatinib treatment were not reported. At the occurrence of blood TSH increased, the dose of a thyroid hormone preparation was increased. Consequently, the blood TSH level returned to the baseline.

PMDA considers as follows:
Concerning (a), serious gastrointestinal perforation and gastrointestinal fistulae occurred during the treatment with lenvatinib and thus attention should be paid to gastrointestinal perforation and gastrointestinal fistulae. It is therefore necessary to appropriately provide information on the incidence of gastrointestinal perforation and gastrointestinal fistulae in clinical studies to healthcare providers in the clinical settings, and to provide a caution in the package insert etc., that appropriate measures be taken if gastrointestinal perforation and gastrointestinal fistulae occur.

Concerning (b), the incidence was low, but serious adverse events occurred. It is, therefore, necessary to include caution about the onset of such an event in the package insert etc.

Concerning (c), it is necessary to discontinue lenvatinib before major surgery and to make a careful decision whether to resume lenvatinib or not, in consideration of the points below. It is, therefore,

necessary to include information on the incidence of wound healing delayed and a caution statement applied in clinical studies in the package insert etc., to raise caution.

- Lenvatinib has an anti-angiogenic effect, and wound healing delayed has been reported for the other antineoplastic drugs having the same anti-angiogenic effect as lenvatinib.

- In Study 303, "patients who underwent major surgery within 3 weeks before the start of the study treatment" were excluded. The safety of lenvatinib in such patients, therefore, remains unclear.

- Instructions for interruption and resumption of treatment with lenvatinib in relation to surgery had been provided to raise attention to them.

Concerning (d), the incidence of blood TSH increased was higher in the lenvatinib group than in the placebo group in Study 303, and Japanese patients frequently experienced this event [see "4.(iii).B.(3).1) Safety profile and its differences between Japanese and non-Japanese patients"]. Therefore, a caution should be provided in the package insert etc., that the blood TSH value be monitored periodically during the treatment with lenvatinib to take appropriate measures such as dose increase of a thyroid hormone preparation when necessary.

4.(iii).B.(4) Clinical positioning and indication

The proposed indication of lenvatinib was "thyroid cancer." The applicant explained that the following cautions will be included under the Precautions for indications section in the package insert: (a) RAI therapy should precede other therapies for the treatment of DTC, (b) eligible patients should be selected based on the understanding of the "Clinical Studies" section in terms of histopathological type etc., of the patients included in the clinical studies, and (c) the efficacy and safety of lenvatinib in postoperative adjuvant chemotherapy have not been established.

Based on the review described below in addition to the results of reviews in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety," PMDA has concluded that it is appropriate to set the indication of lenvatinib as "unresectable thyroid cancer" and that the Clinical Studies section in the package insert should include that the patients with RAI-refractory DTC were included in Study 303 and then the Precautions for indications section should provide the following caution.

- The efficacy and safety of lenvatinib in radioactive iodine-naïve patients with DTC have not been established.

- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the "Clinical Studies" section in terms of histopathological type etc., of the patients included in the clinical studies.

4.(iii).B.(4).1) Patients to be treated with lenvatinib

PMDA confirmed that various clinical practice guidelines in and out of Japan and DeVita VT, Lawrence TS, Rosenberg SA. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* 9th ed. PA, USA: Lippincott Williams & Wilkins; 2011, one of the internationally known oncology textbooks, etc., do not mention lenvatinib.

PMDA asked the applicant to explain the clinical positioning of lenvatinib in treatment of thyroid cancer.

The applicant responded as follows:
Lenvatinib is considered to be positioned as a therapeutic option for patients with locally advanced or metastatic RAI-refractory DTC, a type of thyroid cancer, in whom the efficacy and safety of lenvatinib have been demonstrated in Study 303.

In addition, the efficacy of lenvatinib in patients with MTC and ATC can be expected because of the following reasons: in Study 201, the response rate [95% CI] (%) of lenvatinib in patients with locally advanced or metastatic MTC was 35.6 [23.6, 49.1] [see "4.(iii).A. *Evaluation data* (4).2) Foreign

phase II study"]; in Study 208, the response rates [95% CI] (%) of lenvatinib in patients with locally advanced or metastatic MTC and ATC were 12.5 [0.3, 52.7] and 27.3 [6.0, 61.0], respectively [see "4.(iii).A. *Evaluation data* (2).3) Japanese phase II study"]; and these studies have shown that lenvatinib reduces the tumor size of MTC and ATC. Both Study 201 and Study 208 were, however, conducted in an exploratory manner, and thus caution will be provided under the Precautions for indications section of the package insert that eligible patients should be selected by reviewing the cell type etc., of the patients included in the clinical studies.

In addition to the above, it is almost unnecessary to define the indication of lenvatinib as unresectable thyroid cancer because surgical resection is the first-line treatment for the patients with resectable thyroid cancer.

Based on the above, the proposed indication of lenvatinib was determined to be "thyroid cancer."

PMDA considers as follows:
PMDA accepted the above applicant's explanation on clinical positioning of lenvatinib in patients with locally advanced or metastatic RAI-refractory DTC. Although the number of patients with locally advanced or metastatic MTC and ATC enrolled was small, thus limiting thorough evaluation, lenvatinib is potentially positioned as one of therapeutic options for MTC and ATC patients, in consideration that lenvatinib is a drug to be used by physicians with sufficient knowledge and experience in cancer chemotherapy and that the standard therapeutic procedure for locally advanced or metastatic MTC and ATC has not been established.

Based on the above, the indication needs to include "unresectable" to clarify that the target disease of the clinical studies was locally advanced or metastatic thyroid cancer for which surgical resection was not indicated while it is considered acceptable to include patients with MTC and ATC in the patients with unresectable thyroid cancer. Patients to be treated with lenvatinib should be selected based on the understanding of the study population and the results of the clinical studies. It has been thus concluded that the Precautions for indications section of the package insert should include the above content to raise caution.

4.(iii).B.(4).2) RAI-naïve patients
PMDA asked the applicant to explain administration of lenvatinib to RAI-naïve patients with DTC.

The applicant responded as follows:
In Study 303, lenvatinib was administered to 8 RAI-naïve patients with at least 1 measurable DTC lesion in which iodine uptake was not observed on some RAI scan. Of these, 6 patients achieved partial response (PR), and the safety was not clearly different between patients with and without RAI therapy history.

RAI should be primarily indicated for patients with unresectable DTC eligible for RAI, but for patients with a lesion in which iodine uptake is not observed and thus for which RAI cannot be indicated, lenvatinib is expected to be one of therapeutic options.

PMDA considers as follows:
The efficacy and safety of lenvatinib in RAI-naïve patients with DTC remain unclear. However, there is little need to include RAI status in the indication, provided that the Precautions for indications section includes a statement the efficacy and safety of lenvatinib in RAI-naïve patients with DTC have not been established, in consideration that lenvatinib is a drug to be used by physicians with sufficient knowledge and experience in cancer chemotherapy and there are patients with lesion in which iodine uptake is not observed on some RAI scan and thus for which RAI is not indicated.

4.(iii).B.(4).3) Efficacy and safety of lenvatinib in postoperative adjuvant chemotherapy
The applicant explained that since clinical data on the efficacy and safety of lenvatinib used in postoperative adjuvant chemotherapy have not been available at present, caution in this regard is to be provided under the Precautions for indications section in the package insert.

PMDA considers as follows:
Postoperative adjuvant chemotherapy in patients with locally advanced or metastatic DTC, MTC, and ATC has not been established, although locally advanced or metastatic thyroid cancer may possibly respond dramatically to chemotherapy and thus be considered eligible for radical resection.

Based on the above, there is little need to provide a caution statement that the efficacy and safety of lenvatinib in postoperative adjuvant chemotherapy have not been established.

4.(iii).B.(5) Dosage and administration
The proposed dosage and administration of lenvatinib was "The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition." Under the Precautions for dosage and administration section, the following contents were included.

- Criteria for dose reduction, interruption, and discontinuation of lenvatinib at the occurrence of adverse events

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs or radioiodine preparation have not been established.

- For patients with severe hepatic impairment, the starting dose of lenvatinib should be reduced to 14 mg because the blood lenvatinib concentration increases in such patients.

- The blood lenvatinib (unbound) concentration may increase in patients with severe renal impairment, and renal disorder may occur following administration of lenvatinib. During the treatment with lenvatinib in such patients, careful attention should be paid to adverse events.

Based on the review in "3.(ii).B.(2) Pharmacokinetic interactions" and "4.(ii).B.(2) Use of lenvatinib in patients with severe hepatic impairment" as well as the review described below, PMDA has concluded that the proposed dosage and administration ("The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition.") can be accepted. In addition, the following precautionary statements should be included in the Precautions for indications section.

- Criteria for dose reduction, interruption, and discontinuation of lenvatinib at the occurrence of adverse events

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.

- It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse events.

4.(iii).B.(5).1) Dosage and administration at the start of lenvatinib
The applicant justified the dosage and administration at the start of treatment with lenvatinib as follows:
Based on the following study data, the dosage regimen in Study 303, Study 201, and Study 208 were selected as "24 mg once daily, every day," which demonstrated the efficacy of lenvatinib. The proposed dosage and administration of lenvatinib were therefore selected based on these 3 studies.

- In a foreign phase I study in patients with solid cancer or malignant lymphoma (Study 101), the MTD of lenvatinib was estimated to be 25 mg QD [see "4.(iii).A. *Evaluation data* (4).1) Foreign phase I study"].

- In Schedule 1 of a foreign phase I study in patients with solid cancer or malignant lymphoma (Study 102), lenvatinib was administered in 1-week on/1-week off cycles to investigate the efficacy.

In a Japanese phase I study in patients with solid cancer (Study 103), lenvatinib was administered in 2-week on/1-week off cycles to investigate the efficacy. In Study 102 and Study 103, the PR defined based on the best overall response under RECIST was observed only in 0 of 18 subjects and in 1 of 25 subjects, respectively, indicating that the efficacy of lenvatinib administered with rest was unsatisfactory.

- The results from the PPK and PK/PD analysis of Study 101 and Study 102 suggested that the efficacy increases with the increasing AUC and C_{max} of lenvatinib. The proposed dosage and administration were therefore 24 mg QD, which was a feasible dose with the to-be-marketed formulation of lenvatinib and closest to but below the acceptably highest daily dose, the MTD of 25 mg QD in Study 101.

- A Japanese phase I study in patients with solid cancer (Study 105) demonstrated that the dosage regimen of 24 mg QD is tolerated in Japanese patients [see "4.(iii).A. *Evaluation data* (2).2) Japanese phase I study"].

PMDA accepted the applicant's explanation.

4.(iii).B.(5).2) Criteria for dose reduction, interruption, and discontinuation of lenvatinib

The applicant explained the criteria for dose reduction, interruption, discontinuation, and resumption of lenvatinib treatment as follows:

In Study 303 and Study 208, the criteria for dose reduction, interruption, and discontinuation were specified, and by applying the criteria, the tolerability of lenvatinib was confirmed. The following criteria were established based on those for dose reduction and treatment interruption employed in Study 303 and Study 208 and included in the Precautions for dosage and administration section.

- If any adverse drug reaction is observed, dose of lenvatinib should be reduced, interrupted or discontinued according to the severity, taking the following criteria into account. When treatment is continued at a reduced dose, the dose should be reduced to 20 mg, 14 mg, 10 mg, 8 mg, or 4 mg QD.

Criteria for dose reduction, interruption, and discontinuation of lenvatinib

Adverse drug reaction	Measure
Hypertension	Initiate antihypertensive drug or increase its dose to control blood pressure. If control fails, interrupt lenvatinib. When the control of blood pressure succeeds following interruption of lenvatinib, resume lenvatinib at a one-level lower dose. When a Grade 4* adverse drug reaction occurs, discontinue lenvatinib.
Other adverse drug reactions	When an intolerable Grade 2* or Grade 3* adverse drug reaction occurs, interrupt lenvatinib untilthe condition resolves to the baseline level or ≤Grade 1.* (For nausea, vomiting, and diarrhoea, provide appropriate treatments to control reaction before interruption of lenvatinib. If control fails, interrupt lenvatinib.) After recovery, resume lenvatinib at a one-level lower dose. When a Grade 4* adverse drug reaction occurs, discontinue lenvatinib. (For a non-life-threatening laboratory abnormality, treat it in the same manner as for a Grade 3* adverse drug reaction.)

*, Based on the CTCAE (Common Terminology Criteria for Adverse Events)

Although the protocols for Study 303 and Study 208 specified that the lowest allowable dose was to be 10mg, some patients in Study 101 and Study 201 achieved PR at the reduced dose of 8 mg or 4 mg. In response to that, the protocols for Study 303 and Study 208 also specified that the dose reduction to <10 mg should be subjected to prior consultation with the sponsor. In the following cases, dose reduction to 8 mg or 4 mg was allowed: (a) neither disease progression nor its suggestive findings was observed and (b) the investigator assessed that the efficacy of lenvatinib would be expected in continuing the treatment at a reduced dose.

The results from Study 303 showed (a) the duration of the treatment at the doses of 8 mg and 4 mg (median) was 172 and 101 days, respectively, and (b) of the adverse events observed at the dose of 10 mg, the incidence was lower at the doses of ≤8 mg. The dose reduction of lenvatinib to <10 mg was thus considered allowable.

PMDA considers as follows:
In consideration that lenvatinib is a drug to be used by physicians with sufficient knowledge and experience in cancer chemotherapy, the applicant's explanation is acceptable. It is therefore appropriate to modify the proposed criteria for dose reduction and treatment interruption as shown below and to include them in the Precautions for dosage and administration.

- If any adverse drug reaction is observed, the dose should be reduced or the treatment should be interrupted or discontinued according to the symptoms and severity, taking the following criteria into account. When treatment is continued at a reduced dose, the dose should be reduced to 20 mg, 14 mg, 10 mg, 8 mg, or 4 mg QD.

Criteria for dose reduction, interruption, and discontinuation of lenvatinib

Adverse drug reaction	Severity	Measure
Hypertension	Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg	Continue lenvatinib and initiate antihypertensive drug.
	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite antihypertensive treatment	Interrupt lenvatinib until systolic blood pressure decreases to ≤150 mmHg and diastolic blood pressure to ≤95 mmHg, and initiate antihypertensive drug. If lenvatinib treatment is resumed, reduce the dose to one-level lower.
	Grade 4* adverse drug reaction	Discontinue lenvatinib.
Other adverse drug reactions	Intolerable Grade 2* or Grade 3* adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline level or ≤Grade 1.* (For nausea, vomiting, and diarrhoea, provide appropriate treatments to control reaction before interruption of lenvatinib. If control fails, interrupt lenvatinib.) If lenvatinib treatment is resumed, reduce the dose to one-level lower.
	Grade 4* adverse drug reaction (For non-life-threatening laboratory abnormality, take measures as done for a Grade 3* adverse drug reaction.)	Discontinue lenvatinib.

*, Based on the CTCAE version 4.0

4.(iii).B.(5).3) Concomitant use with other antineoplastic drugs or radioiodine preparation
PMDA asked the applicant to explain the possibility of concomitant use of lenvatinib with other antineoplastic drugs or radioiodine preparation.

The applicant explained as follows:
In a foreign phase I study (Study 102), a Japanese phase Ib study (Study E7080-J081-110), and foreign phase II studies (Study E7080-701, Study E7080-702) of lenvatinib, the concomitant use with the other antineoplastic drugs was investigated. There were no patients who received lenvatinib concomitantly with radioiodine preparation. Therefore, concomitant use of lenvatinib with other antineoplastic drugs or radioiodine preparation has not been extensively investigated, leaving the efficacy and safety of such use unclear. Therefore, a caution in this regard will be included in the Precautions for dosage and administration section to raise caution.

PMDA considers as follows:
PMDA largely accepted the applicant's explanation. However, there is little need to provide additional caution that the efficacy and safety of concomitant use of lenvatinib with radioiodine preparation have not been established, because lenvatinib is a drug to be used by physicians with sufficient knowledge and experience in cancer chemotherapy and the efficacy and safety of lenvatinib have been demonstrated in patients with RAI-refractory DTC, for which RAI is not indicated.

4.(iii).B.(5).4) Use in patients with renal impairment
The applicant explained the use of lenvatinib in patients with renal impairment as follows:
The proposed Precautions for the dosage and administration section included a caution statement that blood lenvatinib concentrations (unbound form) possibly increase in patients with renal impairment, based on the data from Study 005. However, such information proved unfounded after the data were scrutinized again. The above caution statement was therefore unnecessary to be included.

PMDA accepted the applicant's explanation.

4.(iii).B.(6) Post-marketing investigations

The applicant explained the post-marketing surveillance plan as follows:

The applicant plans to conduct all case post-marketing surveillance, which is to include all the patients with thyroid cancer treated with lenvatinib in order to investigate the safety of lenvatinib in routine clinical use after market launch.

The priority investigation items of this surveillance were hypertension, arterial thromboembolism, venous thromboembolism, proteinuria, renal disorder, and palmar-plantar erythrodysaesthesia syndrome based on the adverse events reported in Study 303.

The target sample size was set as 100, based on the incidence of Grade ≥3 adverse events in Study 303 included in the priority investigation items.

The follow-up period was set as 2 years, because the median PFS in Study 303 was 18.3 and 16.5 months in the overall population and Japanese population, respectively, and some events occurred more than 1 year after the start of lenvatinib treatment.

PMDA considers as follows:

Since the safety information of lenvatinib in Japanese patients with thyroid cancer is limited, the applicant plans to collect the post-marketing information for a certain period through the all case surveillance promptly without bias and then provide the obtained safety information to healthcare providers in clinical settings immediately. The applicant's plan is considered appropriate.

In addition to those specified by the applicant, the primary investigation items of this surveillance need to include the following adverse events that require attention during the treatment with lenvatinib: haemorrhage-related events, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood TSH increased. The follow-up period needs to be set based on the time of onset in the clinical studies for each of the events included in the priority investigation items. Furthermore, the target sample size needs to be re-examined based on the estimated number of patients for whom lenvatinib is to be indicated during a certain period of time.

4.(iv) Adverse events etc., observed in clinical studies

Deaths reported in clinical studies submitted are described in "4.(iii) Summary of clinical efficacy and safety." Major adverse events other than deaths were as shown below.

4.(iv).(1) Japanese phase I study (Study E7080-J081-103)

Adverse events were observed in all subjects in all the dose groups (0.5, 1, 2, 4, 6, 9, 13, 16, 20 mg). Adverse events for which a causal relationship to the study drug could not be ruled out were also observed in all subjects in all the dose groups.

Adverse events with an incidence of ≥60% included hypertension, nausea, blood urine present, AST increased, blood lactate dehydrogenase increased, and glucose urine present (2 subjects [66.7%] each) in the 0.5 mg BID group; inappetence, hyperlipidaemia, hypertension, nausea, fatigue, AST increased, ALT increased, and blood ALP increased (2 subjects [66.7%] each) in the 1 mg BID group; headache, blood urine present, and blood ALP increased (2 subjects [66.7%] each) in the 2 mg BID group; nasopharyngitis, headache, diarrhoea, protein urine present, and blood ALP increased (3 subjects [100%] each), and dizziness, hypertension, fatigue, blood urine present, AST increased, ALT increased, blood lactate dehydrogenase increased, and blood bilirubin increased (2 subjects each [66.7%]) in the 4 mg BID group; fatigue and blood urine present (3 subjects [75.0%] each) in the 6 mg BID group; blood urine present, protein urine present, and blood albumin decreased (3 subjects [100%] each), and anaemia, inappetence, headache, hypertension, dyspnoea, diarrhoea, back pain, fatigue, AST increased, ALT increased, blood lactate dehydrogenase increased, platelet count decreased, blood fibrinogen increased, total protein decreased, blood urea increased, and electrocardiogram T wave amplitude

decreased (2 subjects [66.7%] each) in the 9 mg BID group; hypertension, vomiting, fatigue, blood urine present, and blood albumin decreased (3 subjects [100%] each), and inappetence, headache, diarrhoea, nausea, constipation, stomach discomfort, dermatitis acneiform, protein urine present, blood lactate dehydrogenase increased, platelet count decreased, blood fibrinogen increased, and blood TSH increased (2 subjects [66.7%] each) in the 13 mg BID group; inappetence, headache, hypertension, dysphonia, diarrhoea, nausea, fatigue, oedema peripheral, blood urine present, AST increased, protein urine present, blood albumin decreased, platelet count decreased, total protein decreased, blood creatinine increased, blood TSH increased, and white blood cell count decreased (3 subjects [100%] each), and constipation, face oedema, ALT increased, blood lactate dehydrogenase increased, blood ALP increased, gamma-glutamyltransferase (γ-GTP) increased, blood fibrinogen increased, and neutrophil count decreased (2 subjects [66.7%] each) in the 16 mg BID group; and anaemia, headache, hypertension, fatigue, oedema peripheral, blood urine present, AST increased, protein urine present, ALT increased, blood albumin decreased, blood ALP increased, γ-GTP increased, platelet count decreased, total protein decreased, blood urea increased, leucine aminopeptidase increased, and weight increased (2 subjects [100%] each) in the 20 mg BID group. Of these, adverse events assessed as Grade ≥3 included blood lactate dehydrogenase increased (1 subject) in the 0.5 mg BID group; AST increased and ALT increased (1 subject each) in the 4 mg BID group; dyspnoea (2 subjects), and anaemia, AST increased, blood lactate dehydrogenase increased, and platelet count decreased (1 subject each) in the 9 mg BID group; inappetence, hypertension, diarrhoea, nausea, and vomiting (1 subject each) in the 13 mg BID group; hypertension, fatigue, AST increased, protein urine present, ALT increased, and blood ALP increased (1 subject each) in the 16 mg BID group; and hypertension and platelet count decreased (2 subjects each), and anaemia and γ-GTP increased (1 subject each) in the 20 mg BID group.

Serious adverse events were observed in 1 of 3 subjects (33.3%) in the 0.5 mg BID group; 0 of 3 subjects (0%) in the 1 mg BID group; 0 of 3 subjects (0%) in the 2 mg BID group; 0 of 3 subjects (0%) in the 4 mg BID group; 3 of 4 subjects (75.0%) in the 6 mg BID group; 2 of 3 subjects (66.7%) in the 9 mg BID group; 0 of 3 subjects (0%) in the 13 mg BID group; 0 of 3 subjects (0%) in the 16 mg BID group; and 1 of 2 subjects (50.0%) in the 20 mg BID group. These were hypertension (1 subject [33.3%]) in the 0.5 mg BID group; hypertension, postrenal failure, and haemorrhage (1 subject [25.0%] each) in the 6 mg BID group; pneumonia, dyspnoea, and platelet count decreased (1 subject [33.3%] each) in the 9 mg BID group; and humerus fracture (1 subject [50.0%]) in the 20 mg BID group. Of these, serious adverse events for which a causal relationship to the study drug could not be ruled out were hypertension (1 subject) in the 0.5 mg BID group, hypertension and haemorrhage (1 subject each) in the 6 mg BID group, and pneumonia, dyspnoea, and platelet count decreased (1 subject each) in the 9 mg BID group.

Adverse events leading to study drug discontinuation were reported by 0 of 3 subjects (0%) in the 0.5 mg BID group; 0 of 3 subjects (0%) in the 1 mg BID group; 0 of 3 subjects (0%) in the 2 mg BID group; 0 of 3 subjects (0%) in the 4 mg BID group; 0 of 4 subjects (0%) in the 6 mg BID group; 1 of 3 subjects (33.3%) in the 9 mg BID group; 0 of 3 subjects (0%) in the 13 mg BID group; 0 of 3 subjects (0%) in the 16 mg BID group; and 2 of 2 subjects (100%) in the 20 mg BID group. These were pneumonia and dyspnoea (1 subject [33.3%] each) in the 9 mg BID group and γ-GTP increased and humerus fracture (1 subject [50.0%] each) in the 20 mg BID group. Of these, a causal relationship to the study drug could not be ruled out for pneumonia or dyspnoea (1 subject each) in the 9 mg BID group or γ-GTP increased (1 subject) in the 20 mg BID group.

4.(iv).(2) Japanese phase I study (Study E7080-J081-105)

Adverse events were observed in 3 of 3 subjects (100%) in the 20 mg group and in 6 of 6 subjects (100%) in the 24 mg group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 3 subjects (100%) in the 20 mg group and in 6 of 6 subjects (100%) in the 24 mg group.

Adverse events with an incidence of ≥40% in either group were as shown in the following table.

Adverse events with an incidence of ≥40% in either group

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)			
	20 mg group N = 3		24 mg group N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	6 (100)	3 (50.0)
Gastrointestinal disorders				
Nausea	2 (66.7)	0	4 (66.7)	0
Diarrhoea	0	0	5 (83.3)	1 (16.7)
Abdominal discomfort	1 (33.3)	0	3 (50.0)	0
Abdominal pain upper	0	0	3 (50.0)	0
Vomiting	2 (66.7)	0	1 (16.7)	0
General disorders and administration site conditions				
Malaise	2 (66.7)	0	4 (66.7)	0
Oedema peripheral	2 (66.7)	0	2 (33.3)	0
Eye disorders				
Eyelid oedema	2 (66.7)	0	0	0
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (33.3)	0	4 (66.7)	0
Myalgia	0	0	5 (83.3)	0
Blood and lymphatic system disorders				
Thrombocytopenia	2 (66.7)	0	6 (100)	0
Leukopenia	2 (66.7)	1 (33.3)	5 (83.3)	0
Neutropenia	2 (66.7)	2 (66.7)	3 (50.0)	1 (16.7)
Vascular disorders				
Hypertension	2 (66.7)	0	6 (100)	1 (16.7)
Respiratory, thoracic and mediastinal disorders				
Dysphonia	1 (33.3)	0	4 (66.7)	0
Nervous system disorders				
Headache	3 (100)	0	4 (66.7)	0
Renal and urinary disorders				
Proteinuria	2 (66.7)	1 (33.3)	5 (83.3)	0
Haematuria	3 (100)	0	0	0
Metabolism and nutrition disorders				
Hypertriglyceridaemia	1 (33.3)	0	5 (83.3)	1 (16.7)
Decreased appetite	0	0	4 (66.7)	0
Hypoalbuminaemia	2 (66.7)	0	2 (33.3)	0
Endocrine disorders				
Hypothyroidism	0	0	3 (50.0)	0
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	2 (66.7)	0	4 (66.7)	0
Rash	1 (33.3)	0	3 (50.0)	0
Investigations				
Blood TSH increased	3 (100)	0	5 (83.3)	0
AST increased	3 (100)	0	3 (50.0)	0
Blood cholesterol increased	2 (66.7)	0	4 (66.7)	2 (33.3)
ALT increased	3 (100)	0	2 (33.3)	0
Blood lactate dehydrogenase increased	2 (66.7)	0	2 (33.3)	0
Electrocardiogram T wave inversion	0	0	4 (66.7)	0
Blood ALP increased	0	0	3 (50.0)	0

TSH, Thyroid stimulating hormone; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase

Serious adverse events were observed in 0 of 3 subjects (0%) in the 20 mg group and in 1 of 6 subjects (16.7%) in the 24 mg group. Serious adverse event observed in the 24 mg group was diarrhoea (1 subject [16.7%]) and a causal relationship to the study drug could not be ruled out for the event.

Adverse events leading to study drug discontinuation were reported by 0 of 3 subjects (0%) in the 20 mg group and by 1 of 6 subjects (16.7%) in the 24 mg group. Adverse events leading to study drug discontinuation observed in the 24 mg group were arthralgia and palmar-plantar erythrodysaesthesia syndrome (1 subject [16.7%] each) and a causal relationship of either event to the study drug could not be ruled out.

4.(iv).(3) Japanese phase II study (Study E7080-J081-208)

Adverse events were observed in 23 of 23 subjects (100%) in the DTC group, in 9 of 9 subjects (100%) in the MTC group, and in 11 of 11 subjects (100%) in the ATC group. Adverse events for

which a causal relationship to the study drug could not be ruled out were observed in 23 of 23 subjects (100%) in the DTC group, in 9 of 9 subjects (100%) in the MTC group, and in 11 of 11 subjects (100%) in the ATC group.

Adverse events with an incidence of ≥20% in either group were as shown in the following table.

Adverse events with an incidence of ≥20% in any group

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)					
	DTC group N = 23		MTC group N = 9		ATC group N = 11	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	23 (100)	16 (69.6)	9 (100)	7 (77.8)	11 (100)	8 (72.7)
Gastrointestinal disorders						
Stomatitis	14 (60.9)	0	4 (44.4)	0	6 (54.5)	0
Diarrhoea	12 (52.2)	3 (13.0)	6 (66.7)	2 (22.2)	4 (36.4)	0
Nausea	8 (34.8)	1 (4.3)	2 (22.2)	1 (11.1)	9 (81.8)	0
Abdominal pain upper	5 (21.7)	0	3 (33.3)	0	2 (18.2)	0
Vomiting	4 (17.4)	0	1 (11.1)	0	5 (45.5)	0
Constipation	2 (8.7)	0	3 (33.3)	1 (11.1)	3 (27.3)	0
Abdominal pain	1 (4.3)	0	0	0	3 (27.3)	0
General disorders and administration site conditions						
Fatigue	19 (82.6)	0	7 (77.8)	0	7 (63.6)	1 (9.1)
Oedema peripheral	2 (8.7)	0	4 (44.4)	1 (11.1)	1 (9.1)	0
Malaise	1 (4.3)	0	3 (33.3)	1 (11.1)	1 (9.1)	0
Pyrexia	1 (4.3)	0	0	0	3 (27.3)	0
Infections and infestations						
Nasopharyngitis	8 (34.8)	0	1 (11.1)	0	1 (9.1)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	12 (52.2)	0	1 (11.1)	0	4 (36.4)	0
Myalgia	6 (26.1)	0	1 (11.1)	0	1 (9.1)	0
Blood and lymphatic system disorders						
Thrombocytopenia	4 (17.4)	0	2 (22.2)	0	4 (36.4)	2 (18.2)
Anaemia	0	0	3 (33.3)	1 (11.1)	2 (18.2)	1 (9.1)
Vascular disorders						
Hypertension	21 (91.3)	13 (56.5)	7 (77.8)	1 (11.1)	9 (81.8)	2 (18.2)
Respiratory, thoracic and mediastinal disorders						
Dysphonia	9 (39.1)	0	4 (44.4)	0	5 (45.5)	0
Epistaxis	4 (17.4)	0	2 (22.2)	0	3 (27.3)	0
Dyspnoea	0	0	1 (11.1)	1 (11.1)	4 (36.4)	0
Nervous system disorders						
Headache	3 (13.0)	0	3 (33.3)	0	3 (27.3)	0
Renal and urinary disorders						
Proteinuria	14 (60.9)	2 (8.7)	6 (66.7)	1 (11.1)	5 (45.5)	0
Psychiatric disorders						
Insomnia	1 (4.3)	0	5 (55.6)	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	17 (73.9)	1 (4.3)	9 (100)	2 (22.2)	10 (90.9)	1 (9.1)
Hypocalcaemia	3 (13.0)	3 (13.0)	2 (22.2)	0	1 (9.1)	1 (9.1)
Dehydration	1 (4.3)	0	0	0	3 (27.3)	0
Hypoalbuminaemia	0	0	2 (22.2)	0	1 (9.1)	0
Endocrine disorders						
Hypothyroidism	0	0	2 (22.2)	0	3 (27.3)	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysaesthesia syndrome	20 (87.0)	2 (8.7)	8 (88.9)	0	7 (63.6)	0
Rash	6 (26.1)	0	2 (22.2)	0	2 (18.2)	0
Alopecia	6 (26.1)	0	0	0	3 (27.3)	0
Dermatitis acneiform	5 (21.7)	0	0	0	2 (18.2)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)						
Cancer pain	2 (8.7)	0	2 (22.2)	0	1 (9.1)	0
Investigations						
Weight decreased	2 (8.7)	0	2 (22.2)	0	5 (45.5)	0
AST increased	0	0	1 (11.1)	1 (11.1)	4 (36.4)	0
Blood bilirubin increased	1 (4.3)	0	3 (33.3)	1 (11.1)	1 (9.1)	0
ALT increased	0	0	0	0	4 (36.4)	0
Electrocardiogram QT prolonged	1 (4.3)	0	0	0	3 (27.3)	0

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase

Serious adverse events were observed in 7 of 23 subjects (30.4%) in the DTC group; in 5 of 9 subjects (55.6%) in the MTC group; and in 7 of 11 subjects (63.6%) in the ATC group. These were decreased appetite, nausea, cholecystitis, diverticulitis, gastroenteritis, malignant pleural effusion, pneumothorax, respiratory tract infection, and tracheal stenosis (1 subject [4.3%] each) in the DTC group; decreased appetite (2 subjects [22.2%]), and nausea, diarrhoea, gastric cancer, gastric ulcer, hepatic failure, hypoglycaemia, and oedema peripheral (1 subject [11.1%] each) in the MTC group; and decreased appetite, malignant neoplasm progression, and pneumonia (2 subjects [18.2%] each), and fatigue, haemorrhoidal haemorrhage, lung infection, pleural effusion, sepsis, and vagus nerve disorder (1 subject [9.1%] each) in the ATC group. Of these, serious adverse events for which a causal relationship to the study drug could not be ruled out were decreased appetite, nausea, cholecystitis, diverticulitis, gastroenteritis, malignant pleural effusion, and respiratory tract infection (1 subject each) in the DTC group; decreased appetite, nausea, diarrhoea, gastric ulcer, and oedema peripheral (1 subject each) in the MTC group; and decreased appetite and pneumonia (2 subjects each), and fatigue, haemorrhoidal haemorrhage, lung infection, and sepsis (1 subject each) in the ATC group.

No adverse events leading to study drug discontinuation occurred.

4.(iv).(4) Global phase III study (Study E7080-G000-303)

4.(iv).(4).1) Randomized period

Adverse events were observed in 260 of 261 subjects (99.6%) in the lenvatinib group and in 118 of 131 subjects (90.1%) in the placebo group. Adverse events for which a causal relationship could not be ruled out were observed in 254 of 261 subjects (97.3%) in the lenvatinib group and in 80 of 131 subjects (61.1%) in the placebo group.

Adverse events with an incidence of ≥10% in either group were as shown in the following table.

Adverse events with an incidence of ≥10% in either group

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	260 (99.6)	227 (87.0)	118 (90.1)	39 (29.8)
Gastrointestinal disorders				
Diarrhoea	176 (67.4)	24 (9.2)	22 (16.8)	0
Nausea	122 (46.7)	6 (2.3)	33 (25.2)	1 (0.8)
Stomatitis	96 (36.8)	11 (4.2)	9 (6.9)	0
Vomiting	93 (35.6)	5 (1.9)	19 (14.5)	0
Constipation	75 (28.7)	1 (0.4)	20 (15.3)	1 (0.8)
Dry mouth	44 (16.9)	1 (0.4)	11 (8.4)	0
Abdominal pain	43 (16.5)	4 (1.5)	5 (3.8)	1 (0.8)
Abdominal pain upper	41 (15.7)	2 (0.8)	10 (7.6)	0
Dyspepsia	34 (13.0)	1 (0.4)	5 (3.8)	0
Dysphagia	29 (11.1)	5 (1.9)	11 (8.4)	4 (3.1)
General disorders and administration site conditions				
Fatigue	111 (42.5)	12 (4.6)	32 (24.4)	2 (1.5)
Asthenia	66 (25.3)	16 (6.1)	17 (13.0)	3 (2.3)
Oedema peripheral	54 (20.7)	1 (0.4)	10 (7.6)	0
Pyrexia	38 (14.6)	1 (0.4)	15 (11.5)	1 (0.8)
Infections and infestations				
Urinary tract infection	30 (11.5)	3 (1.1)	7 (5.3)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	68 (26.1)	1 (0.4)	9 (6.9)	1 (0.8)
Myalgia	50 (19.2)	4 (1.5)	6 (4.6)	0
Back pain	46 (17.6)	5 (1.9)	12 (9.2)	0
Musculoskeletal pain	42 (16.1)	1 (0.4)	11 (8.4)	1 (0.8)
Pain in extremity	40 (15.3)	3 (1.1)	9 (6.9)	2 (1.5)
Musculoskeletal chest pain	29 (11.1)	0	13 (9.9)	0
Neck pain	20 (7.7)	2 (0.8)	15 (11.5)	1 (0.8)
Vascular disorders				
Hypertension	181 (69.3)	112 (42.9)	20 (15.3)	5 (3.8)

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)			
	Lenvatinib group N = 261		Placebo group N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Respiratory, thoracic and mediastinal disorders				
Dysphonia	82 (31.4)	3 (1.1)	7 (5.3)	0
Cough	62 (23.8)	0	23 (17.6)	0
Oropharyngeal pain	41 (15.7)	1 (0.4)	2 (1.5)	0
Dyspnoea	40 (15.3)	5 (1.9)	25 (19.1)	4 (3.1)
Epistaxis	31 (11.9)	0	1 (0.8)	0
Nervous system disorders				
Headache	100 (38.3)	8 (3.1)	15 (11.5)	1 (0.8)
Dysgeusia	47 (18.0)	0	4 (3.1)	0
Dizziness	40 (15.3)	1 (0.4)	12 (9.2)	0
Renal and urinary disorders				
Proteinuria	88 (33.7)	28 (10.7)	4 (3.1)	0
Psychiatric disorders				
Insomnia	31 (11.9)	0	4 (3.1)	0
Metabolism and nutrition disorders				
Decreased appetite	142 (54.4)	18 (6.9)	24 (18.3)	1 (0.8)
Hypokalaemia	36 (13.8)	9 (3.4)	5 (3.8)	0
Hypocalcaemia	33 (12.6)	13 (5.0)	0	0
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	84 (32.2)	9 (3.4)	1 (0.8)	0
Rash	49 (18.8)	1 (0.4)	2 (1.5)	0
Alopecia	32 (12.3)	0	7 (5.3)	0
Dry skin	28 (10.7)	0	8 (6.1)	0
Investigations				
Weight decreased	134 (51.3)	35 (13.4)	19 (14.5)	1 (0.8)

Serious adverse events were reported by 139 of 261 subjects (53.3%) in the lenvatinib group and by 31 of 131 subjects (23.7%) in the placebo group. Serious adverse events reported by ≥2 subjects in either group included pneumonia (10 subjects [3.8%]), hypertension (9 subjects [3.4%]), dehydration and general physical health deterioration (7 subjects [2.7%] each), sepsis, pulmonary embolism, and renal failure acute (5 subjects [1.9%] each), lower respiratory tract infection, hypocalcaemia, headache, vomiting, and hypotension (4 subjects [1.5%] each), dysphagia, malignant pleural effusion, spinal cord compression, pyrexia, cancer pain, urinary tract infection, back pain, lung infection, convulsion, osteoarthritis, and dyspnoea (3 subjects [1.1%] each), blood uric acid increased, hypercalcaemia, myocardial infarction, weight decreased, death, AST increased, ALT increased, gastroenteritis, diarrhoea, perineal abscess, bronchitis, bacteraemia, abdominal pain upper, cardio-respiratory arrest, atrial fibrillation, vocal cord paralysis, cholecystitis, pneumatosis intestinalis, intracranial tumour haemorrhage, cerebrovascular accident, dizziness, asthenia, pancreatitis, decreased appetite, monoparesis, confusional state, acute respiratory failure, and coronary artery stenosis (2 subjects [0.8%] each) in the lenvatinib group; and dyspnoea (5 subjects [3.8%]), pneumonia, dysphagia, and haemoptysis (3 subjects [2.3%] each), and respiratory failure, pulmonary embolism, and sepsis (2 subjects [1.5%] each) in the placebo group. Of these, the serious adverse events for which a causal relationship to the study drug could not be ruled out were hypertension (9 subjects), pneumonia (6 subjects), pulmonary embolism, headache, and vomiting (4 subjects each), lower respiratory tract infection, general physical health deterioration, dehydration, and hypotension (3 subjects each), gastroenteritis, diarrhoea, renal failure acute, death, decreased appetite, and sepsis (2 subjects each), and urinary tract infection, convulsion, hypercalcaemia, weight decreased, AST increased, ALT increased, perineal abscess, bronchitis, bacteraemia, abdominal pain upper, vocal cord paralysis, pneumatosis intestinalis, intracranial tumour haemorrhage, cerebrovascular accident, asthenia, pancreatitis, confusional state, hypocalcaemia, and coronary artery stenosis (1 subject each) in the lenvatinib group; and haemoptysis (3 subjects) and pulmonary embolism (2 subjects) in the placebo group.

Adverse events leading to study drug discontinuation were reported by 46 of 261 subjects (17.6%) in the lenvatinib group and by 6 of 131 subjects (4.6%) in the placebo group. Adverse events leading to study drug discontinuation reported by ≥2 subjects in either group were hypertension and asthenia (3 subjects [1.1%] each), renal failure acute, death, proteinuria, sepsis, and general physical health

deterioration (2 subjects [0.8%] each) in the lenvatinib group and no such events were reported in the placebo group. Of these, the events for which a causal relationship to the study drug could not be ruled out were hypertension and asthenia (3 subjects each), death and proteinuria (2 subjects each), and sepsis and renal failure acute (1 subject each).

4.(iv).(4).2) Open-label period

Adverse events were observed in 82 of 82 subjects (100%) in the 24 mg group and in 29 of 29 subjects (100%) in the 20 mg group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 77 of 82 subjects (93.9%) in the 24 mg group and in 28 of 29 subjects (96.6%) in the 20 mg group.

Adverse events with an incidence of ≥10% in either group were as shown in the following table.

Adverse events with an incidence of ≥10% in either group

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)			
	24 mg group N = 82		20 mg group N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	82 (100)	71 (86.6)	29 (100)	19 (65.5)
Gastrointestinal disorders				
Diarrhoea	51 (62.2)	5 (6.1)	9 (31.0)	0
Nausea	33 (40.2)	2 (2.4)	10 (34.5)	0
Vomiting	32 (39.0)	3 (3.7)	6 (20.7)	0
Stomatitis	26 (31.7)	0	10 (34.5)	0
Constipation	20 (24.4)	0	4 (13.8)	0
Abdominal pain	19 (23.2)	2 (2.4)	4 (13.8)	0
Dysphagia	15 (18.3)	0	3 (10.3)	0
Abdominal pain upper	9 (11.0)	0	5 (17.2)	0
Dyspepsia	10 (12.2)	0	3 (10.3)	0
General disorders and administration site conditions				
Fatigue	33 (40.2)	5 (6.1)	11 (37.9)	1 (3.4)
Asthenia	21 (25.6)	9 (11.0)	8 (27.6)	1 (3.4)
Oedema peripheral	12 (14.6)	0	1 (3.4)	0
Pyrexia	8 (9.8)	0	3 (10.3)	0
Infections and infestations				
Nasopharyngitis	4 (4.9)	0	3 (10.3)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	19 (23.2)	0	6 (20.7)	1 (3.4)
Myalgia	9 (11.0)	0	7 (24.1)	0
Pain in extremity	11 (13.4)	1 (1.2)	5 (17.2)	0
Musculoskeletal pain	14 (17.1)	0	1 (3.4)	0
Back pain	12 (14.6)	2 (2.4)	3 (10.3)	0
Musculoskeletal chest pain	11 (13.4)	0	1 (3.4)	0
Vascular disorders				
Hypertension	48 (58.5)	23 (28.0)	18 (62.1)	11 (37.9)
Respiratory, thoracic and mediastinal disorders				
Dysphonia	32 (39.0)	1 (1.2)	8 (27.6)	0
Cough	21 (25.6)	0	3 (10.3)	0
Epistaxis	12 (14.6)	0	5 (17.2)	0
Dyspnoea	9 (11.0)	3 (3.7)	5 (17.2)	1 (3.4)
Haemoptysis	9 (11.0)	0	3 (10.3)	0
Oropharyngeal pain	9 (11.0)	0	0	0
Nervous system disorders				
Headache	18 (22.0)	1 (1.2)	6 (20.7)	1 (3.4)
Dizziness	11 (13.4)	0	6 (20.7)	0
Dysgeusia	9 (11.0)	0	4 (13.8)	0
Renal and urinary disorders				
Proteinuria	20 (24.4)	6 (7.3)	7 (24.1)	1 (3.4)
Reproductive system and breast disorders				
Pelvic pain	0	0	3 (10.3)	0
Psychiatric disorders				
Insomnia	9 (11.0)	0	2 (6.9)	0
Metabolism and nutrition disorders				
Decreased appetite	39 (47.6)	3 (3.7)	7 (24.1)	2 (6.9)
Hypoalbuminaemia	11 (13.4)	2 (2.4)	1 (3.4)	1 (3.4)

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)			
	24 mg group N = 82		20 mg group N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	22 (26.8)	1 (1.2)	9 (31.0)	0
Rash	12 (14.6)	0	3 (10.3)	0
Dry skin	10 (12.2)	0	2 (6.9)	0
Alopecia	8 (9.8)	0	3 (10.3)	0
Investigations				
Weight decreased	41 (50.0)	7 (8.5)	7 (24.1)	1 (3.4)
Platelet count decreased	2 (2.4)	0	4 (13.8)	0

Serious adverse events were reported by 52 of 82 subjects (63.4%) in the 24 mg group and by 8 of 29 subjects (27.6%) in the 20 mg group. Serious adverse events reported by ≥2 subjects in the 24 mg group were abdominal pain and pneumonia (4 subjects [4.9%] each), atrial fibrillation and malignant pleural effusion (3 subjects [3.7%] each), and cerebrovascular accident, dehydration, asthenia, death, haemoptysis, hypertensive crisis, metastatic pain, respiratory distress, and respiratory failure (2 subjects [2.4%] each) and no such events were observed in the 20 mg group. Of these, a causal relationship to the study drug could not be ruled out for abdominal pain, cerebrovascular accident, or malignant pleural effusion (2 subjects each) or atrial fibrillation, asthenia, death, respiratory distress, or respiratory failure (1 subject each) in the 24 mg group.

Adverse events leading to study drug discontinuation were reported by 21 of 82 subjects (25.6%) in the 24 mg group and by 3 of 29 subjects (10.3%) in the 20 mg group. Adverse events leading to study drug discontinuation reported by ≥2 subjects in either group included asthenia, death, and general physical health deterioration (2 subjects [2.4%] each) in the 24 mg group. Of these, a causal relationship to the study drug could not be ruled out for asthenia, death, or general physical health deterioration (1 subject each) in the 24 mg group.

4.(iv).(5) Foreign phase I study (Study E7080-E044-101)

Adverse events were observed in 4 of 4 subjects (100%) in the 0.2 mg group; 4 of 4 subjects (100%) in the 0.4 mg group; 4 of 4 subjects (100%) in the 0.8 mg group; 3 of 3 subjects (100%) in the 1.6 mg group; 3 of 3 subjects (100%) in the 3.2 mg group; 3 of 3 subjects (100%) in the 6.4 mg group; 12 of 12 subjects (100%) in the 12 mg group; 9 of 9 subjects (100%) in the 12.5 mg group; 6 of 6 subjects (100%) in the 16 mg group; 3 of 3 subjects (100%) in the 20 mg group; 24 of 24 subjects (100%) in the 25 mg group; and 7 of 7 subjects (100%) in the 32 mg group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 4 subjects (75.0%) in the 0.2 mg group, 3 of 4 subjects (75.0%) in the 0.4 mg group, 2 of 4 subjects (50.0%) in the 0.8 mg group, 2 of 3 subjects (66.7%) in the 1.6 mg group, 3 of 3 subjects (100%) in the 3.2 mg group, 3 of 3 subjects (100%) in the 6.4 mg group, 11 of 12 subjects (91.7%) in the 12 mg group, 9 of 9 subjects (100%) in the 12.5 mg group, 6 of 6 subjects (100%) in the 16 mg group, 3 of 3 subjects (100%) in the 20 mg group, 24 of 24 subjects (100%) in the 25 mg group, and 6 of 7 subjects (85.7%) in the 32 mg group.

Adverse events with an incidence of ≥40% in each group included nausea (3 subjects [75.0%]) and diarrhoea, vomiting, and abdominal pain (2 subjects [50.0%] each) in the 0.4 mg group; dyspnoea (3 subjects [75.0%]) and nausea (2 subjects [50.0%]) in the 0.8 mg group; nausea (2 subjects [66.7%]) in the 1.6 mg group; nausea and vomiting (3 subjects [100%] each), and diarrhoea, pyrexia, urinary tract infection, arthralgia, lethargy, and decreased appetite (2 subjects [66.7%] each) in the 3.2 mg group; nausea, toothache, and musculoskeletal pain (2 subjects [66.7%] each) in the 6.4 mg group; constipation (6 subjects [50.0%]) and hypertension (5 subjects [41.7%]) in the 12 mg group; vomiting and decreased appetite (4 subjects [44.4%]) in the 12.5 mg group; hypertension and cough (4 subjects [66.7%] each) and diarrhoea, stomatitis, and proteinuria (3 subjects [50.0%] each) in the 16 mg group; nausea and diarrhoea (3 subjects [100%] each), vomiting, dyspepsia, pyrexia, pain, proteinuria, and decreased appetite (2 subjects [66.7%] each) in the 20 mg group; nausea (17 subjects [70.8%]), diarrhoea (16 subjects [66.7%]), stomatitis and hypertension (15 subjects [62.5%] each), vomiting (14 subjects [58.3%]), constipation (13 subjects [54.2%]), dysphonia and decreased appetite (12 subjects

[50.0%] each), abdominal pain and dry skin (11 subjects [45.8%] each), back pain, lethargy, and headache (10 subjects [41.7%] each) in the 25 mg group; and diarrhoea, stomatitis, hypertension, and headache (4 subjects [57.1% each]), nausea, fatigue, nasopharyngitis, dyspnoea, dysphonia, proteinuria, and decreased appetite (3 subjects [42.9%] each) in the 32 mg group. Of these, events assessed as Grade ≥3 included nausea (1 subject) in the 0.4 mg group; dyspnoea (1 subject) in the 0.8 mg group; musculoskeletal pain (1 subject) in the 6.4 mg group; hypertension (1 subject) in the 12 mg group; hypertension (1 subject) in the 16 mg group; nausea, diarrhoea, vomiting, pyrexia, and pain (1 subject each) in the 20 mg group; abdominal pain and hypertension (3 subjects each), diarrhoea (2 subjects), and nausea, vomiting, constipation, headache, and decreased appetite (1 subject each) in the 25 mg group; and hypertension and proteinuria (2 subjects each), and dyspnoea (1 subject) in the 32 mg group.

Serious adverse events were reported by 2 of 4 subjects (50.0%) in the 0.2 mg group; 2 of 4 subjects (50.0%) in the 0.4 mg group; 1 of 4 subjects (25.0%) in the 0.8 mg group; 1 of 3 subjects (33.3%) in the 1.6 mg group; 0 of 3 subjects (0%) in the 3.2 mg group; 3 of 3 subjects (100%) in the 6.4 mg group; 5 of 12 subjects (41.7%) in the 12 mg group; 4 of 9 subjects (44.4%) in the 12.5 mg group; 2 of 6 subjects (33.3%) in the 16 mg group; 3 of 3 subjects (100%) in the 20 mg group; 15 of 24 subjects (62.5%) in the 25 mg group; and 3 of 7 subjects (42.9%) in the 32 mg group. Serious adverse events reported by ≥2 subjects in each group were abdominal pain and vomiting (3 subjects [12.5%] each) and hypertension, nausea, and pneumonia (2 subjects [8.3%] each) in the 25 mg group; and dyspnoea (2 subjects [28.6%]) in the 32 mg group. Of these, a causal relationship to the study drug could not be ruled out for hypertension (2 subjects [8.3%]) or abdominal pain, nausea, or vomiting (1 subject [4.2%] each) in the 25 mg group.

Adverse events leading to study drug discontinuation were reported by 1 of 4 subjects (25.0%) in the 0.2 mg group; 1 of 4 subjects (25.0%) in the 0.4 mg group; 1 of 4 subjects (25.0%) in the 0.8 mg group; 0 of 3 subjects (0%) in the 1.6 mg group; 0 of 3 subjects (0%) in the 3.2 mg group; 2 of 3 subjects (66.7%) in the 6.4 mg group; 3 of 12 subjects (25.0%) in the 12 mg group; 2 of 9 subjects (22.2%) in the 12.5 mg group; 1 of 6 subjects (16.7%) in the 16 mg group; 1 of 3 subjects (33.3%) in the 20 mg group; 6 of 24 subjects (25.0%) in the 25 mg group; and 0 of 7 subjects (0%) in the 32 mg group. Adverse events leading to study drug discontinuation reported by ≥2 subjects in each group included proteinuria (3 subjects [12.5%]) in the 25 mg group, for which a causal relationship could not be ruled out.

4.(iv).(6) Foreign phase II study (Study E7080-G000-201)

Adverse events were observed in 58 of 58 subjects (100%) in the differentiated thyroid cancer (DTC) group and in 59 of 59 subjects (100%) in the medullary thyroid cancer (MTC) group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 58 of 58 subjects (100%) in the DTC group and in 59 of 59 subjects (100%) in the MTC group.

Adverse events with an incidence of ≥20% in either group were as shown in the following table.

Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)			
	DTC group N = 58		MTC group N = 59	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	58 (100)	45 (77.6)	59 (100)	47 (79.7)
Gastrointestinal disorders				
Diarrhoea	40 (69.0)	9 (15.5)	45 (76.3)	9 (15.3)
Nausea	30 (51.7)	0	29 (49.2)	1 (1.7)
Vomiting	23 (39.7)	2 (3.4)	25 (42.4)	1 (1.7)
Abdominal pain	20 (34.5)	1 (1.7)	18 (30.5)	3 (5.1)
Abdominal pain upper	18 (31.0)	1 (1.7)	18 (30.5)	1 (1.7)
Stomatitis	19 (32.8)	1 (1.7)	15 (25.4)	0
Constipation	16 (27.6)	0	16 (27.1)	1 (1.7)
Dry mouth	21 (36.2)	0	10 (16.9)	0
Dysphagia	13 (22.4)	1 (1.7)	11 (18.6)	3 (5.1)
Glossodynia	9 (15.5)	0	12 (20.3)	0

System organ class Preferred term (MedDRA Ver. 16.1)	Number of subjects (%)			
	DTC group N = 58		MTC group N = 59	
	All Grades	Grade ≥3	All Grades	Grade ≥3
General disorders and administration site conditions				
Fatigue	35 (60.3)	5 (8.6)	32 (54.2)	3 (5.1)
Pyrexia	15 (25.9)	0	12 (20.3)	0
Oedema peripheral	14 (24.1)	1 (1.7)	9 (15.3)	0
Asthenia	13 (22.4)	3 (5.2)	6 (10.2)	3 (5.1)
Infections and infestations				
Upper respiratory tract infection	12 (20.7)	0	11 (18.6)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	21 (36.2)	3 (5.2)	20 (33.9)	1 (1.7)
Musculoskeletal pain	20 (34.5)	2 (3.4)	16 (27.1)	0
Back pain	23 (39.7)	3 (5.2)	13 (22.0)	1 (1.7)
Pain in extremity	18 (31.0)	0	17 (28.8)	2 (3.4)
Musculoskeletal chest pain	14 (24.1)	1 (1.7)	14 (23.7)	1 (1.7)
Myalgia	14 (24.1)	0	14 (23.7)	0
Muscle spasms	13 (22.4)	0	6 (10.2)	0
Vascular disorders				
Hypertension	45 (77.6)	6 (10.3)	31 (52.5)	6 (10.2)
Hypotension	16 (27.6)	3 (5.2)	10 (16.9)	1 (1.7)
Respiratory, thoracic and mediastinal disorders				
Cough	27 (46.6)	1 (1.7)	23 (39.0)	0
Dysphonia	25 (43.1)	0	19 (32.2)	0
Dyspnoea	20 (34.5)	0	18 (30.5)	2 (3.4)
Epistaxis	19 (32.8)	0	12 (20.3)	0
Oropharyngeal pain	14 (24.1)	0	13 (22.0)	1 (1.7)
Nervous system disorders				
Headache	27 (46.6)	1 (1.7)	26 (44.1)	1 (1.7)
Dizziness	10 (17.2)	0	13 (22.0)	0
Dysgeusia	12 (20.7)	0	9 (15.3)	0
Renal and urinary disorders				
Proteinuria	41 (70.7)	6 (10.3)	38 (64.4)	1 (1.7)
Psychiatric disorders				
Insomnia	13 (22.4)	0	7 (11.9)	0
Metabolism and nutrition disorders				
Decreased appetite	31 (53.4)	1 (1.7)	32 (54.2)	6 (10.2)
Hypocalcaemia	9 (15.5)	2 (3.4)	12 (20.3)	2 (3.4)
Dehydration	12 (20.7)	6 (10.3)	8 (13.6)	3 (5.1)
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	15 (25.9)	1 (1.7)	15 (25.4)	2 (3.4)
Rash	10 (17.2)	0	16 (27.1)	0
Investigations				
Weight decreased	40 (69.0)	7 (12.1)	29 (49.2)	3 (5.1)
Blood TSH increased	4 (6.9)	0	13 (22.0)	0

TSH, Thyroid stimulating hormone

Serious adverse events were reported by 32 of 58 subjects (55.2%) in the DTC group and by 42 of 59 subjects (71.2%) in the MTC group. Serious adverse events reported by ≥2 subjects in each group included dehydration, pulmonary embolism, and hypotension (4 subjects [6.9%] each) and hypertension, abdominal pain lower, asthenia, and cardiac failure (2 subjects [3.4%] each) in the DTC group; and pneumonia (4 subjects [6.8%]), and dehydration, pulmonary embolism, decreased appetite, and abdominal pain (3 subjects [5.1%] each) and diarrhoea, dyspnoea, lung infection, pancreatitis, and premature menopause (2 subjects each [3.4%]) in the MTC group. Of these, serious adverse events for which a causal relationship to the study drug could not be ruled out were dehydration and pulmonary embolism (3 subjects each), hypertension, asthenia, and cardiac failure (2 subjects each), and abdominal pain lower (1 subject) in the DTC group; and pneumonia, decreased appetite, and premature menopause (2 subjects each) and dehydration, pulmonary embolism, diarrhoea, and lung infection (1 subject each) in the MTC group.

Adverse events leading to study drug discontinuation were reported by 18 of 58 subjects (31.0%) in the DTC group and by 21 of 59 subjects (35.6%) in the MTC group. Adverse events leading to study drug discontinuation reported by ≥2 subjects in each group included proteinuria (4 subjects [6.9%])

and diarrhoea, deep vein thrombosis, malignant pleural effusion, and pulmonary embolism (2 subjects [3.4%] each) in the DTC group; and decreased appetite and weight decreased (3 subjects [5.1%] each) and diarrhoea (2 subjects [3.4%]) in the MTC group. Of these, adverse events for which a causal relationship to the study drug could not be ruled out were proteinuria (4 subjects) and diarrhoea, deep vein thrombosis, and pulmonary embolism (2 subjects each) in the DTC group; and decreased appetite and weight decreased (3 subjects each) and diarrhoea (2 subjects) in the MTC group.

4.(iv).(7) Foreign phase I study (Study E7080-E044-104)

Throughout the single-dose and extension periods, adverse events were reported by 6 of 6 subjects (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 6 of 6 subjects (100%) as well.

Adverse events with an incidence of ≥20% included diarrhoea, stomatitis, fatigue, and dysphonia (4 subjects [66.7%] each); nausea, vomiting, dry skin, and weight decreased (3 subjects each [50.0%]); and disease progression, feeling cold, myalgia, back pain, and blister (2 subjects each [33.3%]). Of these, events assessed as Grade ≥3 included disease progression (2 subjects) and stomatitis, nausea, vomiting, and fatigue (1 subject each).

Serious adverse events were observed in 3 of 6 subjects (50.0%). These were disease progression (2 subjects [33.3%]) and vomiting, nausea, hyponatraemia, and ileus (1 subject [16.7%] each). Of these, a causal relationship to the study drug could not be ruled out for vomiting, nausea, or hyponatraemia (1 subject each).

No adverse events leading to study drug discontinuation were reported.

4.(iv).(8) Foreign phase I study (Study E7080-A001-001)

Adverse events were reported by 3 of 20 subjects (15.0%) in the 10 mg capsule group and by 3 of 19 subjects (15.8%) in the 10 mg tablet group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 0 of 20 subjects (0%) in the 10 mg capsule group and by 1 of 19 subjects (5.3%) in the 10 mg tablet group.

There were no adverse events of which the incidences were ≥10%.

Neither serious adverse events nor adverse events leading to discontinuation of lenvatinib were observed in any group.

4.(iv).(9) Foreign phase I study (Study E7080-A001-002)

Adverse events were reported by 1 of 52 subjects (1.9%) in the placebo (Day 1) group; 12 of 50 subjects (24.0%) in the placebo (Days 2, 15, 29) group; 14 of 50 subjects (28.0%) in the moxifloxacin 400 mg group; and 13 of 51 subjects (25.5%) in the lenvatinib 32 mg group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 0 of 52 subjects (0%) in the placebo (Day 1) group; 5 of 50 subjects (10.0%) in the placebo (Days 2, 15, 29) group; 9 of 50 subjects (18.0%) in the moxifloxacin 400 mg group; and 11 of 51 subjects (21.6%) in the lenvatinib 32 mg group.

There were no adverse events of which the incidences were ≥10%.

Neither serious adverse events nor adverse events leading to study drug discontinuation were observed in any group.

4.(iv).(10) Foreign phase I study (Study E7080-A001-003)

Adverse events were reported by 2 of 15 subjects (13.3%) treated under fasted conditions and by 2 of 16 subjects (12.5%) treated after meals. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 2 of 15 subjects (13.3%) treated under fasted conditions and by 0 of 16 subjects (0%) treated after meals.

There were no adverse events of which the incidences were ≥10%.

Neither serious adverse events nor adverse events leading to discontinuation of lenvatinib were observed in any group.

4.(iv).(11) Foreign phase I study (Study E7080-A001-004)
Adverse events were reported by 10 of 17 subjects (58.8%) in the lenvatinib 5 mg + placebo group and by 8 of 18 subjects (44.4%) in the lenvatinib 5 mg + ketoconazole group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 1 of 17 subjects (5.9%) in the lenvatinib 5 mg + placebo group and by 3 of 18 subjects (16.7%) in the lenvatinib 5 mg + ketoconazole group.

There were no adverse events of which the incidences were ≥20%.

Neither serious adverse events nor adverse events leading to discontinuation of lenvatinib were observed in any group.

4.(iv).(12) Foreign phase I study (Study E7080-A001-005)
Adverse events were reported by 2 of 8 subjects (25.0%) in the normal renal function group; 4 of 6 subjects (66.7%) in the mild renal impairment group; 2 of 6 subjects (33.3%) in the moderate renal impairment group; and 1 of 6 subjects (16.7%) in the severe renal impairment group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 1 of 8 subjects (12.5%) in the normal renal function group; 3 of 6 subjects (50.0%) in the mild renal impairment group; 1 of 6 subjects (16.7%) in the moderate renal impairment group; and 0 of 6 subjects (0%) in the severe renal impairment group.

There were no adverse events of which the incidences were ≥20%.

Neither serious adverse events nor adverse events leading to discontinuation of lenvatinib were observed in any group.

4.(iv).(13) Foreign phase I study (Study E7080-A001-006)
Adverse events were reported by 3 of 8 subjects (37.5%) in the normal hepatic function group; 1 of 6 subjects (16.7%) in the mild hepatic impairment group; 3 of 6 subjects (50.0%) in the moderate hepatic impairment group; and 4 of 6 subjects (66.7%) in the severe hepatic impairment group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 1 of 8 subjects (12.5%) in the normal hepatic function group; 1 of 6 subjects (16.7%) in the mild hepatic impairment group; 2 of 6 subjects (33.3%) in the moderate hepatic impairment group; and 3 of 6 subjects (50.0%) in the severe hepatic impairment group.

There were no adverse events of which the incidences were ≥20%.

Neither serious adverse events nor adverse events leading to discontinuation of lenvatinib were observed in any group.

4.(iv).(14) Foreign phase I study (Study E7080-A001-007)
Adverse events were reported by 4 of 15 subjects (26.7%) in the lenvatinib alone group; 6 of 15 subjects (40.0%) in the lenvatinib + rifampicin single-dose group; 3 of 15 subjects (20.0%) in the rifampicin alone group; and 3 of 14 subjects (21.4%) in the lenvatinib + rifampicin multiple-dose group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 2 of 15 subjects (13.3%) in the lenvatinib alone group; 4 of 15 subjects (26.7%) in the lenvatinib + rifampicin single-dose group; 1 of 15 subjects (6.7%) in the rifampicin alone group; and 2 of 14 subjects (14.3%) in the lenvatinib + rifampicin multiple-dose group.

Adverse events reported with an incidence of ≥20% in each group included nausea (3 subjects [20.0%]) in the lenvatinib + rifampicin single-dose group, which was assessed to be mild in any of the subjects.

No serious adverse events were reported.

Adverse events leading to study drug discontinuation were reported by 0 of 15 subjects (0%) in the lenvatinib alone group; 0 of 15 subjects (0%) in the lenvatinib + rifampicin single-dose group; 1 of 15 subjects (6.7%) in the rifampicin alone group; and 0 of 14 subjects (0%) in the lenvatinib + rifampicin multiple-dose group. These were rash and lip oedema (1 subject [6.7%] each) in the rifampicin alone group, and a causal relationship to the study drug could not be ruled out for either event.

4.(iv).(15) Foreign phase I study (Study E7080-A001-008)

Adverse events were reported by 14 of 59 subjects (23.7%) in Treatment 1 (formulation with a low crystal content) group; 14 of 59 subjects (23.7%) in Treatment 2 (standard formulation) group; and 12 of 59 subjects (20.3%) in Treatment 3 (formulation with a high crystal content) group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 11 of 59 subjects (18.6%) in Treatment 1 group; 9 of 59 subjects (15.2%) in Treatment 2 group; and 10 of 59 subjects (16.9%) in Treatment 3 group.

There were no adverse events of which the incidences were ≥20%.

Serious adverse events were reported by 1 of 59 subjects (1.7%) in Treatment 1 group; 0 of 59 subjects (0%) in Treatment 2 group; and 0 of 59 subjects (0%) in Treatment 3 group. Serious adverse event observed in Treatment 1 group was abortion spontaneous (1 subject [1.7%]), and a causal relationship to the study drug could not be ruled out for the event.

No adverse events leading to discontinuation of lenvatinib were reported.

4.(iv).(16) Japanese phase Ib study (Study E7080-J081-110)

Adverse events were observed in 6 of 6 subjects (100%) in the 4 mg BID group during the recommended dose-finding period; 6 of 6 subjects (100%) in the 6 mg BID group during the recommended dose-finding period; and 16 of 16 subjects (100%) in the 4 mg BID group during the patient accrual period, and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 6 of 6 subjects (100%) in the 4 mg BID group during the recommended dose-finding period; 6 of 6 subjects (100%) in the 6 mg BID group during the recommended dose-finding period; and 16 of 16 subjects (100%) in the 4 mg BID group during the case expansion period.

Adverse events with an incidence of ≥40% in any group were as shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA Ver. 14.0)	Number of subjects (%) Recommended dose-finding period 4 mg BID group N = 6		Recommended dose-finding period 6 mg BID group N = 6		Patient accrual period 4 mg BID group 16 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	6 (100)	6 (100)	6 (100)	16 (100)	16 (100)
Blood and lymphatic system disorders						
Anaemia	4 (66.7)	0	4 (66.7)	0	13 (81.3)	3 (18.8)
Leukopenia	6 (100)	1 (16.7)	5 (83.3)	3 (50.0)	15 (93.8)	10 (62.5)
Lymphopenia	1 (16.7)	0	3 (50.0)	0	10 (62.5)	1 (6.3)
Neutropenia	6 (100)	6 (100)	5 (83.3)	5 (83.3)	15 (93.8)	15 (93.8)
Thrombocytopenia	6 (100)	1 (16.7)	4 (66.7)	0	16 (100)	5 (31.3)
Endocrine disorders						
Hypothyroidism	2 (33.3)	0	4 (66.7)	0	7 (43.8)	0
Gastrointestinal disorders						
Constipation	5 (83.3)	0	4 (66.7)	0	12 (75.0)	0
Diarrhoea	6 (100)	1 (16.7)	4 (66.7)	0	12 (75.0)	0
Nausea	5 (83.3)	0	6 (100)	0	13 (81.3)	1 (6.3)
Stomatitis	3 (50.0)	0	2 (33.3)	0	7 (43.8)	0
Vomiting	2 (33.3)	0	3 (50.0)	0	8 (50.0)	1 (6.3)
General disorders and administration site conditions						
Fatigue	5 (83.3)	0	5 (83.3)	0	10 (62.5)	0

System organ class Preferred term (MedDRA Ver. 14.0)	Number of subjects (%) Recommended dose-finding period 4 mg BID group N = 6		 6 mg BID group N = 6		 Patient accrual period 4 mg BID group 16 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatobiliary disorders						
Hyperbilirubinaemia	3 (50.0)	0	3 (50.0)	0	7 (43.8)	0
Investigations						
ALT increased	4 (66.7)	0	3 (50.0)	0	8 (50.0)	0
AST increased	4 (66.7)	0	6 (100)	0	5 (31.3)	0
Blood TSH increased	3 (50.0)	0	0	0	5 (31.3)	0
Blood urine present	2 (33.3)	0	3 (50.0)	0	5 (31.3)	0
Weight decreased	3 (50.0)	0	5 (83.3)	0	8 (50.0)	1 (6.3)
Metabolism and nutrition disorders						
Hypercholesterolaemia	4 (66.7)	0	3 (50.0)	0	8 (50.0)	0
Hypoalbuminaemia	4 (66.7)	0	3 (50.0)	0	10 (62.5)	0
Decreased appetite	4 (66.7)	1 (16.7)	4 (66.7)	0	13 (81.3)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	5 (83.3)	0	5 (83.3)	0	16 (100)	0
Myalgia	4 (66.7)	0	2 (33.3)	0	11 (68.8)	0
Nervous system disorders						
Dysgeusia	0	0	0	0	8 (50.0)	0
Headache	3 (50.0)	0	1 (16.7)	0	8 (50.0)	0
Peripheral sensory neuropathy	6 (100)	0	5 (83.3)	0	15 (93.8)	1 (6.3)
Renal and urinary disorders						
Proteinuria	6 (100)	0	3 (50.0)	0	11 (68.8)	2 (12.5)
Respiratory, thoracic and mediastinal disorders						
Epistaxis	3 (50.0)	0	3 (50.0)	0	12 (75.0)	0
Skin and subcutaneous tissue disorders						
Alopecia	6 (100)	0	5 (83.3)	0	15 (93.8)	0
Rash	4 (66.7)	0	5 (83.3)	0	12 (75.0)	0
Vascular disorders						
Hypertension	5 (83.3)	2 (33.3)	5 (83.3)	4 (66.7)	11 (68.8)	6 (37.5)

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TSH, Thyroid stimulating hormone

Serious adverse events were observed in 3 of 6 subjects (50.0%) in the 4 mg BID group during the recommended dose-finding period; 2 of 6 subjects (33.3%) in the 6 mg BID group during the recommended dose-finding period; and 6 of 16 subjects (37.5%) in the 4 mg BID group during the patient accrual period. These were pneumonia, pyelonephritis, decreased appetite, and lymphangiosis carcinomatosa (1 subject [16.7%] each) in the 4 mg BID group during the recommended dose-finding period; pneumonia, wound, syncope, and haematoma (1 subject [16.7%] each) in the 6 mg BID group during the recommended dose-finding period; febrile neutropenia (2 subjects [12.5%]), and thrombocytopenia, abdominal pain, vomiting, tumour lysis syndrome, metastases to meninges, and thrombosis (1 subject [6.3%] each) in the 4 mg BID group during the patient accrual period. Of these, serious adverse events for which a causal relationship to the study drug could not be ruled out were pneumonia, pyelonephritis, and decreased appetite (1 subject each) in the 4 mg BID group during the recommended dose-finding period; pneumonia and syncope (1 subject each) in the 6 mg BID group during the recommended dose-finding period; and febrile neutropenia (2 subjects) and thrombocytopenia, abdominal pain, vomiting, and thrombosis (1 subject each) in the 4 mg BID group during the patient accrual period.

Adverse events leading to study drug discontinuation were reported by 0 of 6 subjects (0%) in the 4 mg BID group during the recommended dose-finding period, 1 of 6 subjects (16.7%) in the 6 mg BID group during the recommended dose-finding period, and 2 of 16 subjects (12.5%) in the 4 mg BID group during the patient accrual period. These were nausea, fatigue, dehydration, and decreased appetite (1 subject [16.7%] each) in the 6 mg BID group during the recommended dose-finding period; and anal abscess, neurogenic bladder, and proteinuria (1 subject [6.3%] each) in the 4 mg BID group during the patient accrual period, a causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(17) Foreign phase I study (Study E7080-A001-102)

4.(iv).(17).1) Schedule 1 (1-week continuous treatment followed by a 1-week withdrawal)

Adverse events were observed in 3 of 3 subjects (100%) in the 0.1 mg BID group; 2 of 3 subjects (66.7%) in the 0.2 mg BID group; 3 of 3 subjects (100%) in the 0.4 mg BID group; 3 of 3 subjects (100%) in the 0.8 mg BID group; 3 of 3 subjects (100%) in the 1.6 mg BID group; and 3 of 3 subjects (100%) in the 3.2 mg BID group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 3 subjects (100%) in the 0.1 mg BID group; 0 of 3 subjects (0%) in the 0.2 mg BID group; 1 of 3 subjects (33.3%) in the 0.4 mg BID group; 3 of 3 subjects (100%) in the 0.8 mg BID group; 3 of 3 subjects (100%) in the 1.6 mg BID group; and 3 of 3 subjects (100%) in the 3.2 mg BID group.

Serious adverse events were observed in 1 of 3 subjects (33.3%) in the 0.1 mg BID group; 1 of 3 subjects (33.3%) in the 0.2 mg BID group; 1 of 3 subjects (33.3%) in the 0.4 mg BID group; 2 of 3 subjects (66.7%) in the 0.8 mg BID group; 0 of 3 subjects (0%) in the 1.6 mg BID group; and 2 of 3 subjects (66.7%) in the 3.2 mg BID group. Serious adverse events reported by ≥2 subjects in each group included dyspnoea (2 subjects [66.7%]) in the 3.2 mg BID group, for which a causal relationship to the study drug was ruled out.

Adverse events leading to study drug discontinuation were reported by 1 of 3 subjects (33.3%) in the 0.1 mg BID group; 0 of 3 subjects (0%) in the 0.2 mg BID group; 0 of 3 subjects (0%) in the 0.4 mg BID group; 2 of 3 subjects (66.7%) in the 0.8 mg BID group; 1 of 3 subjects (33.3%) in the 1.6 mg BID group; and 0 of 3 subjects (0%) in the 3.2 mg BID group. These were thrombotic thrombocytopenic purpura (1 subject [33.3%]) in the 0.1 mg BID group; cardiac failure congestive, ischaemic cardiomyopathy, pulmonary hypertension, and oesophageal varices haemorrhage (1 subject [33.3%] each) in the 0.8 mg BID group; and blood creatinine increased (1 subject [33.3%]) in the 1.6 mg BID group. Of these, a causal relationship to the study drug could not be ruled out for thrombotic thrombocytopenic purpura (1 subject) in the 0.1 mg BID group; cardiac failure congestive, ischaemic cardiomyopathy, or pulmonary hypertension (1 subject each) in the 0.8 mg BID group; or blood creatinine increased (1 subject) in the 1.6 mg BID group.

4.(iv).(17).2) Schedule 2 (continuous treatment)

Adverse events were observed in 3 of 3 subjects (100%) in the 3.2 mg BID group; 7 of 7 subjects (100%) in the 5 mg BID group; 16 of 16 subjects (100%) in the 8 mg BID group; and 7 of 7 subjects (100%) in the 12 mg BID group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 2 of 3 subjects (66.7%) in the 3.2 mg BID group; 6 of 7 subjects (85.7%) in the 5 mg BID group; 14 of 16 subjects (87.5%) in the 8 mg BID group; and 7 of 7 subjects (100%) in the 12 mg BID group.

Serious adverse events were observed in 2 of 3 subjects (66.7%) in the 3.2 mg BID group; 1 of 7 subjects (14.3%) in the 5 mg BID group; 9 of 16 subjects (56.3%) in the 8 mg BID group; and 2 of 7 subjects (28.6%) in the 12 mg BID group. Serious adverse events reported by ≥2 subjects in each group included small intestinal obstruction (2 subjects [12.5%]) in the 8 mg BID group, for which a causal relationship to the study drug was ruled out.

Adverse events leading to study drug discontinuation were reported by 0 of 3 subjects (0%) in the 3.2 mg BID group; 0 of 7 subjects (0%) in the 5 mg BID group; 6 of 16 subjects (37.5%) in the 8 mg BID group; and 2 of 7 subjects (28.6%) in the 12 mg BID group. Adverse events leading to study drug discontinuation reported by ≥2 subjects in each group included fatigue (2 subjects [12.5%]) in the 8 mg BID group, for which a causal relationship to the study drug could not be ruled out.

4.(iv).(17).3) Expanded melanoma cohort (continuous treatment)

Adverse events were observed in 26 of 26 subjects (100%), and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 26 of 26 subjects (100%).

Serious adverse events were reported by 14 of 26 subjects (53.8%). Serious adverse events reported by ≥2 subjects included dehydration (5 subjects [19.2%]), disease progression and renal failure (4 subjects [15.4%] each), diarrhoea (3 subjects [11.5%]), and cardiopulmonary failure, confusional state,

constipation, and nausea (2 subjects [7.7%] each). Of these, a causal relationship to the study drug could not be ruled out for diarrhoea (3 subjects [11.5%]), dehydration or nausea (2 subjects [7.7%] each), or confusional state (1 subject [3.8%]).

Adverse events leading to study drug discontinuation were reported by 3 of 26 subjects (11.5%). These were metastases to the central nervous system, general physical health deterioration, and malignant neoplasm progression (1 subject [3.8%] each), and a causal relationship to the study drug was ruled out for all of the events.

4.(iv).(17).4) Melanoma concomitant cohort (continuous treatment)

Adverse events were observed in 6 of 6 subjects (100%) at Level 1 (lenvatinib 20 mg + TMZ 100 mg/m^2 group); 4 of 4 subjects (100%) at Level 2 (lenvatinib 24 mg + TMZ 100 mg/m^2 group); and 22 of 22 subjects (100%) at Level 3 (lenvatinib 24 mg + TMZ 150 mg/m^2 group). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 6 of 6 subjects (100%) at Level 1; 4 of 4 subjects (100%) at Level 2; and 20 of 22 subjects (90.9%) at Level 3.

Serious adverse events were observed in 4 of 6 subjects (66.7%) at Level 1; 1 of 4 subjects (25.0%) at Level 2; and 10 of 22 subjects (45.5%) at Level 3. Serious adverse events reported by ≥2 subjects in each group included confusional state (2 subjects [33.3%]) at Level 1, for which a causal relationship to the study drug was ruled out.

Adverse events leading to study drug discontinuation were reported by 1 of 6 subjects (16.7%) at Level 1; 0 of 4 subjects (0%) at Level 2; and 0 of 22 subjects (0%) at Level 3. These were performance status decreased and general physical health deterioration (1 subject [16.7%] each) at Level 1 and a causal relationship to the study drug was ruled out for both events.

4.(iv).(18) Foreign phase Ib/II study (Study E7080-701)

Adverse events were observed in 2 of 2 subjects (100%) in Cohort 1A (lenvatinib 16 mg [Day 1-21] + CBDCA + GEM); 3 of 3 subjects (100%) in Cohort 1B (lenvatinib 16 mg [Day 2-21] + CBDCA + GEM); and 2 of 2 subjects (100%) in Cohort 1C (lenvatinib 8 mg [Day 2-21] + CBDCA + GEM). Adverse events for which a causal relationship to lenvatinib could not be ruled out were observed in 2 of 2 subjects (100%) in Cohort 1A; 2 of 3 subjects (66.7%) in Cohort 1B; and 2 of 2 subjects (100%) in Cohort 1C.

No serious adverse events were observed.

Adverse events leading to study drug discontinuation were reported by 1 of 2 subjects (50.0%) in Cohort 1A; 2 of 3 subjects (66.7%) in Cohort 1B; and 1 of 2 subjects (50.0%) in Cohort 1C. These were platelet count decreased (1 subject [50.0%]) in Cohort 1A; thrombocytopenia and proteinuria (1 subject [33.3%] each) in Cohort 1B; and pollakiuria (1 subject [50.0%]) in Cohort 1C. A causal relationship to lenvatinib could not be ruled out for any of the events.

4.(iv).(19) Foreign phase Ib/II study (Study E7080-702)

4.(iv).(19).1) Phase Ib

Adverse events were observed in 3 of 3 subjects (100%) in Cohort 1 (lenvatinib 16 mg + DTIC), 7 of 7 subjects (100%) in Cohort 2 (lenvatinib 20 mg + DTIC); and 6 of 6 subjects (100%) in Cohort 3 (lenvatinib 22 mg + DTIC). Adverse events for which a causal relationship to lenvatinib could not be ruled out were observed in 3 of 3 subjects (100%) in Cohort 1; 7 of 7 subjects (100%) in Cohort 2; and 6 of 6 subjects (100%) in Cohort 3. Adverse events for which a causal relationship to DTIC could not be ruled out were observed in 3 of 3 subjects (100%) in Cohort 1; 6 of 7 subjects (85.7%) in Cohort 2; and 5 of 6 subjects (83.3%) in Cohort 3.

Serious adverse events were observed in 2 of 3 subjects (66.7%) in Cohort 1; 4 of 7 subjects (57.1%) in Cohort 2; and 2 of 6 subjects (33.3%) in Cohort 3. These were cardiac failure congestive, ileus, asthenia, fatigue, white blood cell count increased, and dehydration (1 subject [33.3%] each) in Cohort 1; vomiting, chest pain, back pain, pulmonary embolism, and hypertension (1 subject [14.3%] each) in Cohort 2; and febrile neutropenia, thrombocytopenia, abdominal pain, and back pain (1 subject

[16.7%] each) in Cohort 3. Of these, serious adverse events for which a causal relationship to lenvatinib could not be ruled out were vomiting, pulmonary embolism, and hypertension (1 subject each) in Cohort 2; and febrile neutropenia and thrombocytopenia (1 subject each) in Cohort 3.

Adverse events leading to study drug discontinuation were reported by 0 of 3 subjects (0%) in Cohort 1; 0 of 7 subjects (0%) in Cohort 2; and 1 of 6 subjects (16.7%) in Cohort 3. These were febrile neutropenia and thrombocytopenia (1 subject ([16.7%] each) in Cohort 3, and a causal relationship to lenvatinib could not be ruled out for either event.

4.(iv).(19).2) Phase II

Adverse events were observed in 40 of 42 subjects (95.2%) in the lenvatinib + DTIC group and 31 of 39 subjects (79.5%) in the DTIC alone group. Adverse events for which a causal relationship to lenvatinib could not be ruled out were observed in 35 of 42 subjects (83.3%) in the lenvatinib + DTIC group. Adverse events for which a causal relationship to DTIC could not be ruled out were observed in 30 of 42 subjects (71.4%) in the lenvatinib + DTIC group and 26 of 39 subjects (66.7%) in the DTIC alone group.

Serious adverse events were observed in 16 of 42 subjects (38.1%) in the lenvatinib + DTIC group and 1 of 39 subjects (2.6%) in the DTIC alone group. These were leukopenia, neutropenia, polycythaemia, thrombocytopenia, myocardial infarction, abdominal pain, diarrhoea, intestinal perforation, abscess, erysipelas, intertrigo candida, pneumonia, postoperative wound infection, hyperglycaemia, epilepsy, partial seizures, haematuria, breast swelling, cough, pneumothorax, physical disability, and hypotension (1 subject [2.4%] each) in the lenvatinib + DTIC group; and pyrexia (1 subject [2.6%]) in the DTIC alone group. Of these, a causal relationship to the study drug could not be ruled out for polycythaemia, myocardial infarction, abdominal pain, diarrhoea, abscess, or haematuria (1 subject each) in the lenvatinib + DTIC group; or pyrexia (1 subject) in the DTIC alone group.

No adverse events leading to discontinuation of lenvatinib treatment were reported.

4.(iv).(20) Foreign phase II study (Study E7080-G000-203)

Adverse events were observed in 40 of 42 subjects (95.2%) in Cohort 1 (patients with bevacizumab-naïve recurrent malignant glioma [GBM] at Grade IV under WHO classification); 39 of 39 subjects (100%) in Cohort 2 (patients with bevacizumab-naïve recurrent GBM at Grade III under WHO classification); and 32 of 32 subjects (100%) in Cohort 3 (patients with recurrent GBM progressed after bevacizumab treatment). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 39 of 42 subjects (92.9%) in Cohort 1; 39 of 39 subjects (100%) in Cohort 2; and 28 of 32 subjects (87.5%) in Cohort 3.

Serious adverse events were observed in 22 of 42 subjects (52.4%) in Cohort 1; 12 of 39 subjects (30.8%) in Cohort 2; and 15 of 32 subjects (46.9%) in Cohort 3. Serious adverse events reported by ≥2 subjects in each group included convulsion (5 subjects [11.9%]) and general physical health deterioration, vomiting, cerebrovascular accident, and hypothyroidism (2 subjects [4.8%] each) in Cohort 1; headache and fatigue (2 subjects [5.1%] each) in Cohort 2; and convulsion (2 subjects [6.3%]) in Cohort 3. Of these, a causal relationship to the study drug could not be ruled out for cerebrovascular accident or hypothyroidism (2 subjects each) in Cohort 1 or fatigue (2 subjects) in Cohort 2.

Adverse events leading to study drug discontinuation were reported by 14 of 42 subjects (33.3%) in Cohort 1; 15 of 39 subjects (38.5%) in Cohort 2; and 12 of 32 subjects (37.5%) in Cohort 3. Adverse events leading to study drug discontinuation reported by ≥2 subjects in each group included fatigue and cerebrovascular accident (2 subjects [4.8%] each) in Cohort 1 and fatigue (5 subjects [12.8%]), ALT increased, hypertension, and muscular weakness (2 subjects each [5.1%]) in Cohort 2. Of these, adverse events for which a causal relationship to the study drug could not be ruled out were fatigue and cerebrovascular accident (2 subjects each) in Cohort 1 and fatigue (5 subjects) and ALT increased and hypertension (2 subjects each), and muscular weakness (1 subject) in Cohort 2.

4.(iv).(21) Foreign phase II study (Study E7080-G000-204)
Adverse events were observed in 126 of 133 subjects (94.7%) and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 116 of 133 subjects (87.2%).

Serious adverse events were observed in 64 of 133 subjects (48.1%). Serious adverse events reported by ≥2 subjects included abdominal pain (7 subjects [5.3%]), asthenia, dehydration, hypertension, and acute kidney injury (6 subjects [4.5%] each), pulmonary embolism and vomiting (5 subjects [3.8%] each), diarrhoea and hypotension (4 subjects [3.0%] each), female genital tract fistula, general physical health deterioration, mental status changes, and nausea (3 subjects [2.3%] each), and colitis, constipation, dyspnoea, hypocalcaemia, hypokalaemia, intestinal obstruction, pleural effusion, rib fracture, small intestinal obstruction, and urinary tract infection (2 subjects each [1.5%]). Of these, serious adverse events for which a causal relationship to the study drug could not be ruled out were hypertension (6 subjects), asthenia (5 subjects), abdominal pain, dehydration, and pulmonary embolism (4 subjects each), diarrhoea, nausea, and vomiting (3 subjects each), colitis and acute kidney injury (2 subjects each), and female genital tract fistula, general physical health deterioration, hypotension, mental status changes, and urinary tract infection (1 subject each).

Adverse events leading to study drug discontinuation were reported by 39 of 133 subjects (29.3%). Adverse events leading to study drug discontinuation reported by ≥2 subjects in each group included hypertension (6 subjects [4.5%]), asthenia (4 subjects [3.0%]), hypokalaemia, pulmonary embolism, and vomiting (3 subjects [2.3%] each), and fatigue, female genital tract fistula, general physical health deterioration, and mental status changes (2 subjects [1.5%] each). Of these, adverse events for which a causal relationship to the study drug could not be ruled out were hypertension (6 subjects), asthenia and pulmonary embolism (3 subjects each), fatigue and vomiting (2 subjects each), and general physical health deterioration, hypokalaemia, and mental status changes (1 subject each).

4.(iv).(22) Foreign phase II study (Study E7080-G000-206)
Adverse events were observed in 93 of 93 subjects (100%) in Cohort 1 (patients with malignant melanoma without v-raf murine sarcoma oncogene homolog B1 [BRAF] V600E mutation) and 89 of 89 subjects (100%) in Cohort 2 (patients with malignant melanoma with BRAF V600E mutation). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 91 of 93 subjects (97.8%) in Cohort 1 and 80 of 89 subjects (89.9%) in Cohort 2.

Serious adverse events were observed in 41 of 93 subjects (44.1%) in Cohort 1 and 37 of 89 subjects (41.6%) in Cohort 2. Serious adverse events reported by ≥2 subjects in each group included hypertension (5 subjects [5.4%]), nausea, pulmonary embolism, and deep vein thrombosis (3 subjects each [3.2%]), pneumonia, mental status changes, vomiting, cerebrovascular accident, hyponatraemia, pancreatitis, and pyrexia (2 subjects [2.2%] each) in Cohort 1; and nausea, abdominal pain, and fatigue (3 subjects [3.4%] each), pulmonary embolism, pneumonia, general physical health deterioration, groin pain, and metastatic pain (2 subjects [2.2%] each) in Cohort 2. Of these, serious adverse events for which a causal relationship to the study drug could not be ruled out were hypertension (5 subjects), pulmonary embolism, and deep vein thrombosis (3 subjects each), mental status changes, nausea, hyponatraemia, and pyrexia (2 subjects each), cerebrovascular accident, pancreatitis, and vomiting (1 subject each) in Cohort 1; and fatigue (3 subjects), pulmonary embolism, nausea, abdominal pain, and general physical health deterioration (1 subject each) in Cohort 2.

Adverse events leading to study drug discontinuation were reported by 19 of 93 subjects (20.4%) in Cohort 1 and 18 of 89 subjects (20.2%) in Cohort 2. Adverse events leading to study drug discontinuation reported by ≥2 subjects in each group included fatigue (4 subjects [4.3%]) and hypertension and hyponatraemia (2 subjects [2.2%] each) in Cohort 1 and fatigue (4 subjects [4.5%]) in Cohort 2. Of these, adverse events for which a causal relationship to the study drug could not be ruled out were fatigue (4 subjects) and hypertension and hyponatraemia (2 subjects each) in Cohort 1 and fatigue (4 subjects) in Cohort 2.

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

The assessment is currently ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

2. PMDA's conclusion on the results of GCP on-site inspection

The assessment is currently ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of lenvatinib in the treatment of patients with unresectable thyroid cancer has been demonstrated and the safety is acceptable in view of its observed benefits. Lenvatinib is a drug with a new active ingredient that inhibits kinases such as vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3, REarranged during Transfection proto-oncogene (RET), fibroblast growth factor receptors (FGFRs) 1, 2, 3, and 4, platelet-derived growth factor receptor (PDGFR) α, and stem cell factor receptor (KIT) and is considered to have clinical significance as one of the therapeutic options against unresectable thyroid cancer. In addition, the indication, dosage and administration, and post-marketing surveillance items will be further discussed at the Expert Discussion.

PMDA considered that lenvatinib may be approved if it can be concluded that there are no particular problems based on the comments from the Expert Discussion.

Review Report (2)

January 8, 2015

I. Product Submitted for Registration

[Brand name]	Lenvima Capsules 4 mg
	Lenvima Capsules 10 mg
[Non-proprietary name]	Lenvatinib Mesilate
[Name of applicant]	Eisai Co., Ltd.
[Date of application]	June 26, 2014

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. 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 "4.(iii).B.(2) Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of lenvatinib mesilate (hereinafter referred to as lenvatinib) in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) was demonstrated, because the global phase III study (Study E7080-G000-303 [Study 303]) showed superiority of lenvatinib to the placebo in terms of the progression-free survival assessed by the central imaging assessment institution, the primary endpoint.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

(2) Safety

As a result of the review described in the "4.(iii).B.(3) Safety" of the Review Report (1), PMDA has concluded that during the treatment with lenvatinib, attention should be paid to the following adverse events: hypertension/hypertensive crisis, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood thyroid stimulating hormone (TSH) increased.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

(3) Clinical positioning and indication

As a result of the review described in the "4.(iii).B.(4) Clinical positioning and indication" of the Review Report (1), PMDA has concluded that lenvatinib should be indicated for "unresectable thyroid cancer," with the following statement in the Precautions for indications section because lenvatinib is positioned as a drug used in patients with locally advanced or metastatic RAI-refractory DTC and as one of the therapeutic options for patients with locally advanced or metastatic medullary or anaplastic thyroid carcinoma.

- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the "Clinical Studies" section in terms of the histopathological type etc., of the patients included in the clinical studies.

- The efficacy and safety of lenvatinib in radioiodine-naïve patients have not been established.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to include the Indications, and Precautions for indications sections as described above, and the applicant accepted it.

(4) Dosage and administration

As a result of the review described in the "4.(iii).B.(5) Dosage and administration" of the Review report (1), PMDA has concluded that it is acceptable to select the dosage and administration as proposed, "The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition." provided that the following criteria and statements are included in the Precautions for dosage and administration section.

- Criteria for dose reduction, interruption, and discontinuation of lenvatinib at the occurrence of adverse events

- The efficacy and safety of concomitant use of lenvatinib with other antineoplastic drugs have not been established.

- It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. A dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse events.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to include the Dosage and administration and Precautions for dosage and administration sections as described above, and the applicant accepted it.

(5) Risk management plan (draft)

In order to investigate the safety of lenvatinib in routine clinical use, the applicant plans to conduct all-case post-marketing surveillance, which is to include all the patients with unresectable thyroid cancer who are to be treated with lenvatinib (100 patients, 2-year follow-up period). Based on the adverse events in Study 303, the priority investigation items of this surveillance are planned to be set as follows: hypertension, arterial thromboembolism, venous thromboembolism, proteinuria, renal disorder, and palmar-plantar erythrodysaesthesia syndrome.

As a result of the review described in the "4.(iii).B.(6) Post-marketing investigations" of the Review Report (1), PMDA has concluded that all-case post-marketing surveillance should be conducted to investigate the safety of lenvatinib in routine clinical use in Japan.

In addition, PMDA has concluded as follows:

- The primary investigation items of the surveillance need to include adverse events requiring attention during the treatment with lenvatinib, such as infections, haemorrhage-related events, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood TSH increased, in addition to those specified by the applicant.

- The follow-up period needs to be set based on the time of onset of each event included in the priority investigation items in clinical studies.

- The target sample size needs to be re-examined based on the estimated number of patients for whom lenvatinib is to be indicated during a certain period of time.

The PMDA's conclusion above was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- Clinical positioning of lenvatinib is unclear in relation to approved sorafenib tosilate (sorafenib) in patients with unresectable differentiated thyroid cancer. Thyroid cancer is a rare disease and it is

not easy to conduct a controlled clinical study. It is therefore necessary to collect patient history information, wherever possible, on presence or absence of the previous treatment with sorafenib via post-marketing surveillance so as to understand the effects of the previous treatment with sorafenib on the efficacy and safety of lenvatinib.

Based on the above discussion, PMDA instructed the applicant to re-examine the post-marketing surveillance plan.

The applicant responded as follows:

- The recruitment period of the post-marketing surveillance is set as 12 months. This surveillance is to include all the patients who receive lenvatinib during a certain period of time; and it is expected to include a total of 400 patients with unresectable thyroid cancer for whom lenvatinib is indicated.

- The primary investigation items of the surveillance are to be set as follows: hypertension, arterial thromboembolism, venous thromboembolism, proteinuria, renal disorder, palmar-plantar erythrodysaesthesia syndrome as well as infections, haemorrhage-related events, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood TSH increased.

- The follow-up period is set as 12 months based on the time of onset of the priority investigation items reported as adverse events in Study 303.

- The post-marketing surveillance is designed to adequately collect patient history information on the previous treatment with sorafenib so that the efficacy and safety of lenvatinib can be investigated in terms of presence or absence of the previous treatment with sorafenib.

PMDA considers as follows:
PMDA accepted the applicant's explanation. However, based on the analysis of the post-marketing surveillance, whether or not to make a change on the surveillance plan, such as extending the analysis set, should be reconsidered.

Based on the above, PMDA instructed the applicant to take appropriate measures accordingly, and the applicant accepted it.

Based on the above discussion, PMDA has concluded that the draft risk management plan should include safety and efficacy investigations as listed in the following table and additional pharmacovigilance activities and risk minimization actions should be conducted.

Safety and efficacy investigations in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Hypertension • Renal disorder • Haemorrhage • Arterial thromboembolism • Venous thromboembolism • Liver disorder • Gastrointestinal perforation and gastrointestinal fistulae • Posterior reversible encephalopathy syndrome • Cardiac disorder • Hand and foot syndrome • Hypocalcaemia • Haematotoxicity • Infections • Wound healing delayed	None	None
Efficacy specifications		
• Efficacy in routine clinical use		

Outline of additional pharmacovigilance activities and risk minimization actions in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization actions
• Early post-marketing phase vigilance • Post-marketing surveillance (all-case surveillance, for the outline of the plan, see the table below) • Post-marketing clinical studies (extension studies of Study 303 and Study E7080-J081-208)	• Provision of information obtained from early post-marketing surveillance • Preparation and provision of materials for healthcare professionals (guidance for proper use)

Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety of lenvatinib in routine clinical use
Survey method	All-case surveillance method
Patients population	Patients with unresectable thyroid cancer
Observation period	12 months
Planned sample size	400
Main investigation items	Primary investigation items: Hypertension, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood TSH increased Other main investigation items: Patient characteristics (histopathological type, presence or absence of RAI-resistance, presence or absence of previous treatment with sorafenib, comorbidity, etc.), treatment status of lenvatinib, concomitant medications and therapies, adverse events, efficacy, etc.

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 were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA has concluded that there should be no problem with conducting a regulatory review based on the submitted product 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, 5.3.5.1.2, 5.3.5.2.2). As a result, PMDA has concluded that the clinical studies as a whole were conducted in compliance with GCP and there should be no problem with conducting a regulatory review based on the submitted product application documents. Although the evaluation of the clinical studies as a whole was not affected, the following findings were noted in some study sites and the sponsor. PMDA therefore notified the heads of the concerned study sites and the applicant (sponsor) of the matter so that it could be resolved.

[Matters to be resolved]
Study sites

- Deviations from the study protocol (non-compliance with the procedure for start of the study treatment, with the provisions for treatment interruption of the study drug, and with the provisions for reporting of laboratory abnormal values to the sponsor, etc.)

Sponsor

- Deviations from the study protocol (non-compliance with the provisions for reporting of laboratory abnormal values to the sponsor) were overlooked by the sponsor, who had failed to appropriately monitor the laboratories.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the conditions for approval as shown below after modifying the indication and dosage and administration as shown below, provided that appropriate cautions will be included in the package insert and information concerning the proper use of lenvatinib will be provided appropriately after the market

launch; and the compliance with the proper use of lenvatinib will be ensured at medical institutions well equipped to cope with emergencies under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy. Since the product is an orphan drug, 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] Unresectable thyroid cancer

[Dosage and administration] The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition.

[Conditions for approval] The applicant is required to:

1. Develop a risk management plan and implement it appropriately.

2. Conduct a drug use-results survey involving all patients treated with the product after the market launch until data from a certain number of patients have been gathered in order to grasp the characteristics of treated patients, since the product has been studied only in a limited number of patients in clinical studies in Japan. At the same time, collect the safety and efficacy data of the product without delay and take necessary measures to ensure proper use of the product.

[Warnings]

Lenvatinib should be administered only to patients who are considered eligible for the treatment at medical institutions well equipped to cope with emergencies under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy. Consent should be obtained, before the initiation of treatment, from the patient or his/her family member who has been provided with a thorough explanation of the benefits and risks of the therapy.

[Contraindications]

1. Patients with a history of hypersensitivity to any ingredient in lenvatinib

2. Pregnant women or women who may be pregnant.

[Precautions for indications]

1. The efficacy and safety of lenvatinib in radioiodine-naïve patients with differentiated thyroid cancer have not been established.

2. Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib and the histopathological type etc., of the patients enrolled in the clinical studies described in the "Clinical Studies" section.

[Precautions for dosage and administration]

1. If any adverse drug reaction is observed, lenvatinib dose should be reduced, interrupted or discontinued, according to the symptom and severity, taking the following criteria into account. If treatment is continued at a reduced dose, the dose should be reduced to 20 mg, 14 mg, 10 mg, 8 mg, or 4 mg QD.

Criteria for dose reduction, interruption, and discontinuation

Adverse drug reaction	Severity	Measure
Hypertension	Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg	Continue lenvatinib, and initiate antihypertensive drug.
	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite antihypertensive treatment	Interrupt lenvatinib until the systolic blood pressure decreases to ≤150 mmHg and diastolic blood pressure to ≤95 mmHg and initiate antihypertensive drug. If lenvatinib treatment is resumed, reduce the dose one-level lower.
	Grade 4 adverse drug reaction	Discontinue lenvatinib.
The other adverse drug reactions	Intolerable Grade 2 or Grade 3 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline or ≤Grade 1. (For nausea, vomiting, and diarrhoea, perform appropriate treatments before interruption of lenvatinib. If control fails, interrupt lenvatinib.) If lenvatinib treatment is resumed, reduce the dose one-level lower.
	Grade 4 adverse drug reaction (For non-life-threatening laboratory abnormality, take measures as done for a Grade 3 adverse drug reaction.)	Discontinue lenvatinib.

Grade is rated in accordance with CTCAE version 4.0.

2. The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.

3. It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse event development.