26 March 2015
EMA/250082/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lenvima

International non-proprietary name: lenvatinib

Procedure No. EMEA/H/C/003727/0000

Note

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

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Administrative information

Name of the medicinal product:	Lenvima
Applicant:	Eisai Europe Ltd European Knowledge Centre Mosquito Way Hatfield Hertfordshire AL10 9SN UNITED KINGDOM
Active substance:	lenvatinib mesilate
International Nonproprietary Name	lenvatinib
Pharmaco-therapeutic group (ATC Code):	L01XE29
Therapeutic indication(s):	Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).
Pharmaceutical form:	Capsule, hard
Strengths:	4 mg and 10 mg
Route of administration:	Oral use
Packaging:	Polyamide/Aluminium/PVC/Aluminium blisters
Package size:	30 capsules

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List of abbreviations

ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anaplastic thyroid cancer
ATE	arterial thromboembolic event
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUCR	AUC ratio
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity
BCRP	breast cancer resistance protein
BID	*bis in die*, twice a day
BMI	body mass index
BP	blood pressure
BOR	best overall response
CAF	circulating angiogenic factor
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
CL/F	apparent total clearance following extravascular administration
CHMP	Committee for medicinal products for Human Use
Cmax	maximum observed concentration
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRF	case report form
CSE	Clinically significant adverse event
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
CV	coefficient of variance
CYP	cytochrome P450
CYP3A4	Cytochrome P450 3A4
DBP	diastolic blood pressure
DECISION	acronym for the Phase 3 sorafenib trial: “Stu**D**y of soraf**E**nib in lo**C**ally advanced or metastat**I**c patient**S** with radioactive **I**odine refractory thyr**O**id ca**N**cer”
DCR	disease control rate
DDI	drug-drug interaction
DFG	motif central to function of B-raf protein in both its inactive and active state
DLT	dose limiting toxicity
dSD	durable stable disease
DTC	differentiated thyroid cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG performance status
EMA	European Medicines Agency
ERK	extracellular signal-related kinase

FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FLT1	fms-like tyrosine kinase 1 (alternate name for VEGFR1)
FLT4	fms-like tyrosine kinase 4 (alternate name for VEGFR3)
GBq	gigabecquerel
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
Gr	grade
hERG	human *ether-à-go-go*
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQoL	Health Related Quality of Life
^{131}I	radiolabelled iodine
IC_{50}	half the maximal inhibitory concentration
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
IIR	independent imaging review
ITT	Intent to treat
Ki	inhibition constant
KIT	mast/stem cell growth factor receptor (tyrosine kinase)
LENV	lenvatinib
LVEF	left ventricular ejection fraction
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK (mitogen-activated protein kinase)/ERK kinase
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NA	not applicable
NC	not calculated
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	no observed adverse effects level
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
OOL	optional open label
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPE	palmar-plantar erythrodysaesthesia
PR	partial response
QD	*quaque die*, once a day
RAF	Rapidly Accelerated Fibrosarcoma
RECIST	Response Evaluation Criteria in Solid Tumors

RPLS	reversible posterior leukoencephalopathy syndrome
RPSFT	rank-preserving structural failure time
RR	radioiodine-refractory
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SCS	summary of the clinical safety
SD	stable disease
SELECT	acronym for the Phase 3 sorafenib trial: Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid
SGQ	sponsor-generated query
SMQ	standard MedDRA query
SY	subject-year
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
Tmax	time at which the highest drug concentration occurs
TSH	thyroid-stimulating hormone
VEGF	vascular endothelial growth factor
VEGFi	VEGF inhibitor
VEGFR	VEGF receptor
VTE	venous thromboembolic event
VzF	apparent volume of distribution
WBC	white blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eisai Europe Ltd submitted on 15 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lenvima, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 February 2013. The acceptability of an accelerated review was agreed upon by the EMA/CHMP on 24 July2014.

Lenvima, was designated as an orphan medicinal product on 26 April 2013 in the following indications: Treatment of follicular thyroid cancer (EU/3/13/1119) and Treatment of papillary thyroid cancer (EU/3/13/1121).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Lenvima as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The applicant applied for the following indication: Lenvima is indicated for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0040/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP/0040/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

New active Substance status

The applicant requested the active substance lenvatinib (mesilate) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 17 February 2011 and on 15 November 2012. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Eisai Manufacturing Ltd
European Knowledge Centre, Mosquito Way, Hatfield, Herfordshire, AL10 9SN, United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bart Van der Schueren

Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 15 August 2014.
- Accelerated Assessment procedure was agreed-upon by CHMP on 24 July 2014.
- The procedure started on 24 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2014 (Annex 2). In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- PRAC RMP Assessment Report endorsed by PRAC on 9 January 2015 (Annex 3)
- During the meeting on 22 January, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 January 2015 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 February 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of

Questions to all CHMP members on 4 March 2015 (Annex 5).

- PRAC RMP Advice, adopted by PRAC on 12 March 2015 (Annex 6)
- During the meeting on 26 March 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Lenvima.
- The CHMP adopted a report on similarity of Lenvima on similarity with Nexavar on 18 December 2014

2. Scientific discussion

2.1. Introduction

Problem Statement

Differentiated thyroid cancinoma (DTC)

Thyroid cancer is rare, representing less than 1% of all cancers (Hundahl, et al., 1998; Pacini, et al., 2012; Tuttle, et al., 2010). There are three main histologic types of thyroid carcinoma: differentiated, medullary, and anaplastic. Differentiated thyroid cancer (DTC) is the most common of all thyroid cancers accounting for approximately 90% to 95% of cases (Hundahl, et al., 1998). It arises from follicular epithelial cells. Based on histological appearance, DTCs are designated as either papillary (≈80%), follicular (≈10%), or Hürthle cell (≈5%). Hürthle cell thyroid carcinoma is currently considered as an oncocytic variant of follicular carcinoma.

The remaining 5% to 10% are either C cell-derived medullary (MTC) or anaplastic (ATC) thyroid carcinomas.

Prognosis and treatment

In general, prognosis for thyroid cancer at the time of diagnosis is good, with a 5 year relative survival rate of 98% (SEER Cancer Statistics Review, 2014) and a 10-year survival rate of 85% (Hundahl, et al., 1998). Up to 10-15% would either present with distant metastasis at diagnosis or develop them after initial treatment. Distant metastases are associated with 5-year survival rates of approximately 50% (Schlumberger et al., 1986; SEER Cancer Statistics Review, 2014), 10-year survival rates of 40% (Schlumberger et al., 1986), and 15 year survival rates of 30% (Schlumberger et al., 1986; Schlumberger et al., 1996). Differentiated thyroid cancer is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. First-line treatment for primary management of DTC is surgery (total thyroidectomy or unilateral lobectomy), often followed by radioiodine (131I) ablation and thyroxine therapy (European Society of Medical Oncology guidelines, Pacini, et al, 2012). The goals of this treatment strategy are to destroy any residual thyroid tissue and prevent locoregional recurrence. External beam radiotherapy may be indicated when complete surgical excision is not possible or when there is no significant uptake in the tumor (Pacini et al, 2012). Only 30% of patients with distant metastasis respond to radioiodine therapy with complete remission (Schlumberger, et al., 1999).

Tumor recurrence occurs in 3-25% of patients with DTC, depending on histology and tumor extension at diagnosis, with a median follow-up period of 16.6 years, 16% had local recurrence and 8% had distant metastases (which includes 2% with both local and distant metastases) (Mazzaferri and Kloos, 2001). Of the 5-20% who develop locoregional recurrences, approximately two-thirds involve cervical lymph nodes. Distant metastases in lung, bones and brain occur in up to 10% of patients and are associated with a

median survival of 5 years from the time of discovery of metastases (Schlumberger, et al., 1986; SEER Cancer Statistics Review, 2014). Approximately one-third of metastatic DTCs lose the functional ability to concentrate iodine and no longer respond to radioiodine (131I) treatment (Schlumberger, et al., 1996, Durante, et al., 2006).

Upon the absence or loss of 131I uptake, tumors assume a more aggressive behavior, resulting in a 10-year survival rate of approximately 10% (Schlumberger et al., 1996; Durante et al.,2006).

Single-agent or combination chemotherapy in radioiodine-refractory differentiated thyroid cancer (RR-DTC) offers patients little to no benefit, is associated with significant toxicity and is no longer indicated (Haugen and Sherman, 2013, Shimaoka, et al., 1985; Matuszczyk, et al., 2008; Pacini et al, 2012). Current clinical consensus guidelines recommend that patients with RR-DTC avoid traditional chemotherapy and move directly to treatment with antiangiogenic tyrosine kinase inhibitors (TKIs) in clinical trials (American Thyroid association guidelines, Cooper 2009; ESMO guidelines, Pacini et al., 2012; NCCN guidelines, Tuttle, et al., 2010).

To date, one TKI, sorafenib, has been approved in the European Union (EU) and United States (US) for the treatment of RR-DTC. This approval was based on the results of one Phase 3 study (the DECISION trial) of sorafenib in 417 subjects with progressive, locally advanced or metastatic RR-DTC (EPAR Nexavar). In this study, median PFS time was 10.8 months in the sorafenib group compared to 5.8 months in the placebo group (HR=0.587; 95% Confidence Interval (CI): 0.454, 0.758; one-sided p <0.0001) (see SmPC Nexavar).

About the product

Lenvima comprises the antineoplastic agent lenvatinib mesilate. Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET (see SmPC section 5.1).

The antitumor effects of lenvatinib in patients with thyroid cancer are based primarily on its activity against proangiogenic VEGFR2. Other potential mechanisms involve the inhibition of oncogenic FGFR1, FGFR2, and RET kinase (see non-clinical section).

Indication and dosage

Lenvima is formulated in 2 strengths of hypromellose hard capsules containing lenvatinib mesilate equivalent to either 4 mg or 10 mg of lenvatinib.

The applied indication was for the treatment of patients with progressive, radioiodine-refractory (RR) differentiated thyroid cancer (DTC).

The recommended indication is Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) (see SmPC section 4.1)

Lenvima treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies (see SmPC section 4.2).

The recommended daily dose of lenvatinib is 24 mg taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (see dose adjustment in SmPC section 4.2).

If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules in 2 strengths, containing lenvatinib mesilate equivalent to 4 mg and 10 mg lenvatinib as active substance.

Other ingredients are:

Capsule contents: calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose and talc;

Capsule shell: hypromellose, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172);

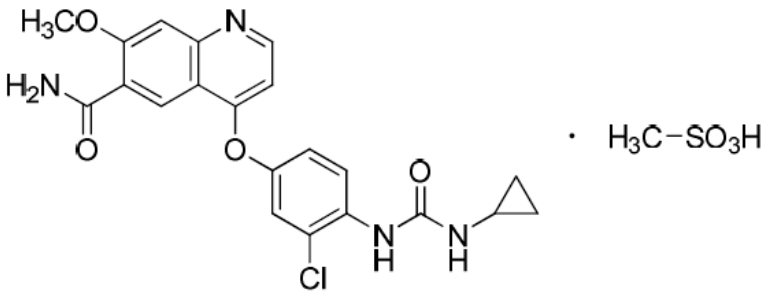
Printing ink containing: shellac, black iron oxide (E172), potassium hydroxide and propylene glycol

The product is available in blisters of polyamide/aluminium/PVC with a push through aluminium foil lidding.

2.2.2. Active Substance

General information

The chemical name of lenvatinib is 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate and it has the following structure:



The active substance is a white, non-hygroscopic, crystalline powder, slightly soluble in water and practically insoluble in ethanol. The structure of lenvatinib mesilatewas elucidated by using elemental analysis, ultraviolet-visible (UV-Vis) spectroscopy, infrared spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry. Lenvatinib is achiral.

Lenvatinib mesilate exhibits polymorphism. Polymorphism is controlled during the manufacturing process of the active substance..

Manufacture, characterisation and process controls

The manufacturing process of lenvatinib mesilate consists of two synthetic steps followed by salt formation. Five crystallisations ensure the control of the impurity profile of lenvatinib mesilate. Well defined starting materials with acceptable specifications are used.

A quality by design (QbD) approach was used in the process development of lenvatinib mesilate. A quality target product profile (QTPP) was defined for the finished product and the properties of the active substance shown to impact on this were defined as critical quality attributes (CQAs). Active substance CQAs are impurities, residual solvents, residual genotoxins, particle size, and polymorphic form.

Critical process parameters (CPPs) in the synthetic process were identified by risk assessment (including failure mode effects analysis, FMEA), process knowledge, and both uni- and multi-variate experiments. Each of the 3 steps contains CPPs and thus all are considered critical. Proven acceptable ranges (PARs) for all the CPPs have been defined. However, no design space is claimed by the applicant so for each step, only one CPP may be moved within its PAR with other CPPs help at their target set-point.

The quality of the active substance is assured by a control strategy composed of the above-mentioned PARs and a series of in process controls designed to limit impurities and residual solvents. Despite the QbD approach to development, the applicant employs traditional release testing to ensure the quality of the active substance. Data from the first process validation batch of lenvatinib mesilate is provided. The CPPs were all controlled within the PARs and the lenvatinib mesilate thus produced was of adequate quality and in line with the active substance specification.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. All potential impurities and the starting material (SM) itself have been evaluated according to CHMP guidelines on genotoxic impurities. This analysis is based on experimental and computational SAR analysis using DEREK and MCASE software systems and Ames-test. There have been no impurities detected above the reporting threshold (0.05%) in 10 batches. A HPLC method was developed to detect the 16 potential impurities. Specifications for only 2 from 16 potential impurities have been defined based on spiking studies. The spike study of genotoxic impurity demonstrates that during manufacturing process is able to purge to levels below the TTC of 60ppm, from 0.30% to 3ppm, in the intermediate. The genotoxic impurities show no detectable levels in 10 batches.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance, identification (IR, XRPD), assay (HPLC), related substances (HPLC), genotoxic impurities (HPLC), residual solvents (GC, HPLC), residual benzene (GC), water content (KF), heavy metals (USP), methanesulfonic acid content (ion chromatography), particle size (light diffraction measurement) and microbial limits (Ph Eur).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis data (6 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions at 5 ºC ± 3 ºC and for up to 6 months under accelerated conditions at 25 °C ± 2 ºC /60 ± 5 % RH according to the ICH guidelines were provided. The following parameters were tested: description, identification (XRPD), related substances, genotoxic impurities, water content and assay. No significant changes to any of the measured parameters was observed.

Stress testing on the active substance in the solid state was performed under conditions of heat (60 ºC), light exposure (ICH photostability conditions) and high humidity (30 ºC/75 % RH). Under the stress conditions of light exposure and high humidity, no degradation products were observed and therefore the active substance can be considered photostable and non-hygroscopic. Genotoxic impurities remain below LOQ or unchanged at 5°C and slightly increases at 25°C/60%RH.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Lenvatinib mesilate was found to be a novel tyrosine kinase inhibitor which works as an anticancer drug, and it was decided to develop it as an immediate release solid oral dosage form. The aim was to develop and oral immediate release form which allows patents to administer the drug themselves, easy to handle, and obtain desired bioability. The product is presented in multiple strengths easily distinguished by combination of shape, color, shape and prints to allow dose adjustments and minimizes risk of side effects and the mix-up of strengths and products.

The active substance stability, solubility, polymorphism and particle size characteristics were taken into account during the pharmaceutical development. Lenvatinib mesilate, potentially includes a genotoxic impurity and degradant, which is also a synthetic intermediate of lenvatinib. It was found to increase in the active substance by decomposition by heat stress. In addition, lenvatinib mesilate forms a gel when it is in contact with dissolution media. Therefore, the related substances and dissolution were designated as critical quality attributes for lenvatinib capsules.

Film-coated tablets were first developed and used in the early clinical trials. However, it was found that the excipients and process used to manufacture this pharmaceutical form had a negative impact on related substances and increased the level of the genotoxic impurity in the finished product. Because of these concerns, development of another formulation for commercial production was initiated. A capsule formulation was developed in order to address the manufacturability issues associated with the initial tablet manufacturing process. These were used for pivotal clinical studies and selected as the pharmaceutical form of the marketed product.

The excipients for lenvatinib capsules were selected to ensure both appropriate stability and dissolution of the finished product. Therefore, compatibility of the active substances with excipients, their functions, and their relative concentrations were studied.

Non-hygroscopic excipients were chosen to limit the level of water and reduce the risk of degradation of lenvatinib mesilate. Calcium carbonate was selected as a water insoluble inorganic diluent, which could effectively avoid gelation of the active substance without preventing dispersion of drug substance particles.

All excipients are well known pharmaceutical ingredients and for the majority, their quality is compliant with Ph Eur standards. The only non-pharmacopeial excipients are low-substituted hydroxypropyl cellulose and the hypromellose capsule shells. The specification for low-substituted hydroxypropyl cellulose complies with the National Formulary (NF) and is considered to be acceptable. The components of the capsules comply with the Ph Eur with the exception of butyl alcohol for which no Ph Eur monograph exists. This component complies with the NF monograph. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation used during clinical studies is the same as that proposed for commercialization.

A bioequivalence study was performed between capsules and tablets, which concluded that the same strength of capsules (10mg) could be used for pivotal clinical studies.

The manufacturing process is a standard process consisting of mixing, granulation, drying, milling, blending and encapsulation steps. An initial risk assessment for the manufacturing process at commercial production scale was performed so as to identify process parameters that were likely to have an impact on the CQAs of lenvatinib capsules.. Development and formal validation data are convincing that the physical state of the active substance is under control throughout manufacturing of the capsules. Nevertheless, the CHMP recommended testing the first 10 commercial batches intended for marketing in order to determine the physical state of lenvatinib mesilate in the finished product. The CHMP also recommended testing of the physical form (type C crystal level) of lenvatinib mesilate in formal stability studies up to the end (60 months) and in at least on the first 2 commercial batches of each strength to be included in the post approval stability studies.

Lenvatinib capsules are packaged in polyamide and polyvinyl chloride (PVC) laminated aluminium film with push-through aluminium foil blisters (Alu/Alu blisters). Specifications for the forming film and lidding foil have been provided. The specifications contain an IR identification test. The forming lid is stated to comply with Ph. Eur. 3.1.11, EC Directive 2002/72EC and EC Directive 78/142/EEC. The lidding foil is stated to comply with EC Directive 2002/72EC and EC Directive 78/142/EEC.

Manufacture of the product and process controls

The manufacturing process of Lenvima capsules consists in a conventional wet granulation of nine steps: mixing, granulation, drying, milling, blending, encapsulation, weight-sorting, bulk packaging, and blister packaging. The process is considered to be a standard manufacturing process.

Primary stability batches have been manufactured. Three batches of each strength (4 mg and 10 mg) were manufactured; two batches were manufactured at pilot scale and one batch was manufactured at full commercial scale. Formal validation of the process has been completed on 3 commercial batches ofeach strength. The full validation results have not been provided yet. The applicant made a declaration that the validation results are acceptable (process parameters within PARs and expected values; IPCs compliant, final results within specs and additional tests within expected range). As the manufacturing process is a standard process, this is considered acceptable. During formal validation, further investigation has been performed on the physical state of the active sunstance. The processes from drying through weight-sorting did not have any impact on the physical state of the active substance in the finished product.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (UV, HPLC, HPLC-PDA), related substances (HPLC), assay (HPLC), dissolution (Ph Eur), water content (Ph Eur), uniformity of dosage units (Ph Eur), and microbial limits (Ph Eur).

Batch analysis results are provided for 37 pilot scale batches used in clinical and stability studies confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. All batches were manufactured at the proposed manufacturing site.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data on 3 (1 commercial scale and 2 pilot scale batches per strength of finished product stored under long term conditions for up to 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. A commitment is provided that two additional full commercial scale batches of 4 mg and 10 mg capsules will be place on stability. A satisfactory stability protocol identical to the on-going stability studies at accelerated and long term conditions has been provided.

Samples were tested for description, dissolution, related substances, assay, water content and microbiological limits. The analytical procedures used are stability indicating.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Under long term and accelerated conditions after 24 months and 6 months respectively, no significant changes were observed and there was no difference between the 4 and 10 mg capsule strengths. During photostability studies no changes were observed in comparison to the initial time-point or to a control sample stored in an open dish in the dark.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of lenvatinib capsules. Therefore, there is no risk with respect to transmissible spongiform encephalopathy (TSE) agents, bovine spongiform encephalopathy (BSE), or other contamination with adventitious agents.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance. PARs are claimed for CPPs identified in both active substance and finished product manufacturing processes.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To test the first 10 commercial batches intended for marketing to determine the physical state of lenvatinib mesilate in the finished product.

- To test the physical state (type C crystal level) in the batches of the formal stability study up to the end (60 months) and in at least on the first 2 commercial batches of each strength to be included in the post approval stability studies.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal toxicology studies and the battery of safety pharmacology studies were conducted in accordance with Good Laboratory Practice (GLP) regulations. In addition, all GLP studies were conducted by laboratories in countries that adhere to the Organisation for Economic Co-operation and Development (OECD) system for mutual acceptance of chemical safety data.

Pharmacodynamic, pharmacokinetic, preliminary and dose-range finding (DRF) toxicology studies were generally non-GLP studies.

Nonclinical studies of lenvatinib were generally conducted using lenvatinib mesilate, and doses are expressed in terms of the mesilate salt.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamics effects of lenvatinib were evaluated in *in vitro* kinase inhibition (profiling) assays, kinetic interaction studies, X-ray analysis of the crystal structure of the VEGFR2-lenvatinib complex, *in vitro* cell-based assays, and *in vivo* studies in various human tumour xenograft models in athymic mice. *In vivo* studies in various human xenograft models included evaluation of the activity of lenvatinib as a single agent as well as in combination with other anticancer agents.

In vitro studies

Kinase Inhibition Profiling Studies 1 and 2 (Studies W-201208 and W-20120814)

Two kinase inhibition profiling studies against a total of 66 purified recombinant protein kinases (including tyrosine kinases and serine threonine kinases) showed that lenvatinib is a potent multiple kinase inhibitor. IC50 values were determined by measuring the cell-free kinase activities with lenvatinib

(0.3 - 10,000 nmol/L) by ELISA or mobility shift assay. The profile for sorafenib, another multikinase inhibitor in clinical use, was also studied under the same condition as a reference.

The most sensitive kinases for lenvatinib included VEGF receptors (VEGFR1 – 3), and RET with IC50 values below 10 nmol/L, specifically 4.7, 3.0, 2.3, and 6.4 nmol/L, respectively. The second highly sensitive group included FGF receptors (FGFR1 - 4), PDGFRα, and KIT with IC_{50} values between 10 and 100 nmol/L, specifically 61, 27, 52, 43, 29, and 85 nmol/L, respectively. All are typical pro-angiogenic and oncogenic pathway-related RTKs.

Against VEGFR1 – 3 and FGFR1 – 3, IC50 values for lenvatinib were several-fold lower than those of sorafenib. In particular, the IC50 of lenvatinib against FGFR4 was approximately 80-fold lower than that of sorafenib. In contrast, the IC50 values for lenvatinib against PDGFRα, PDGFRβ and RAF1 were higher than those of sorafenib. In these assays, lenvatinib was more selective to VEGF receptors and FGF receptors and less selective to PDGF receptors and RAF1 compared to sorafenib.

In regard to inhibition of PDGFR tyrosine kinases, PDGFRα and PDGFRβ, the inhibitory activity of lenvatinib towards PDGFRβ was lower than that for PDGFRα. A cell-free kinase inhibitory assay showed that IC50 values of lenvatinib for PDGFRα and PDGFRβ were 29 and 160 nmol/L, respectively. These values were about 10-fold and 53-fold higher, respectively, than that for VEGFR2 (3.0 nmol/L), indicating that the inhibition of PDGFRβ by lenvatinib is very weak.

With regards to the FGFRs, as compared to the IC50 values for FGFR-1 (61 nmol/L or 31.9 ng/ml), FGFR-3 (52 nmol/L or 27.2 ng/ml) and FGFR-4 (43 nmol/L or 22.5 ng/ml) the IC50 value for FGFR2 was 27 nmol/L (14.1 ng/ml). FGFR2 was more sensitive to inhibition by lenvatinib as compared to FGFR1, 3, 4.

IC50 values for the inhibition of the 66 protein kinases tested with lenvatinib or sorafenib were grouped into the following ranges: below 10 nmol/L, 10 – 100 nmol/L, 100 – 1000 nmol/L, 1000 – 10,000 nmol/L, and above 10,000 nmol/L. For lenvatinib, IC50 values in these ranges were observed against 5, 8, 16, 10, and 27 kinases, respectively. For sorafenib, IC50 values in the same ranges were observed against 3, 11, 14, 12, and 26 kinases, respectively, suggesting that the kinase selectivity of lenvatinib is comparable to that of sorafenib.

Kinase Inhibition Profiling Study 3 (Study No. W-20120815)

This study determined the inhibition constants (Ki) for selected kinases. The Ki values were calculated using a Dixon Plot of the inhibition by lenvatinib (0.3 – 260 nmol/L) under 6 different concentrations of ATP. Ki values of lenvatinib against VEGFR1, 2, and 3, and RET were approximately 1 nmol/L (1.3, 0.74, 0.71, and 1.5 nmol/L, respectively). Lenvatinib also inhibited other RTKs including FGFR1, 2, and 3, and KIT with Ki values of 22, 8.2, 15, and 11 nmol/L, respectively. The inhibition mode against these kinases was found to be competitive.

Kinetic Interaction Analysis against VEGFR2 (Study No. W-20140526)

This study determined the dissociation rate constant (koff = 1/ residence time), association rate constant (kon), and equilibrium dissociation constant (Kd = koff / kon) for VEGFR2. These values for the binding of lenvatinib and sorafenib against human recombinant protein of VEGFR2 including kinase domain (Leu834-Asn1162) were measured using a reporter displacement assay (Neumann, et al., 2011). The Kd value for lenvatinib against VEGFR2 was 2.1 nmol/L, which is about 16 fold lower than that of sorafenib. This difference is due to the balance for koff and kon values of lenvatinib, which are about 3.8-fold and 60-fold higher than for sorafenib, respectively. These results suggested that lenvatinib dissociated sooner from the target, but associated much more rapidly to the active site of VEGFR2, and the overall result was a superior binding affinity (based on a lower Kd value) to the target compared to sorafenib.

Crystal Structure of VEGFR2-Lenvatinib Complex (Study No. W-20140522)

X-ray analysis for the crystal structure of the VEGFR2-lenvatinib complex showed that lenvatinib binds to both the adenosine triphosphate (ATP)-binding site and the neighboring allosteric region in the kinase domain adopting an "aspartic acid-phenylalanine-glycine (DFG)-in" configuration, suggesting a different binding mode compared to sorafenib.

The amino acid residues located in the vicinity of lenvatinib or sorafenib with a maximum distance of 3.9 Å were identified as those belonging to an ATP-binding site including a gate-keeper residue (common site for protein kinases), or the neighboring region, a non-conserved allosteric region (Traxler and Furet, 1999). Among the total of 25 amino acid residues, 16 residues were common for lenvatinib and sorafenib. Lenvatinib and sorafenib binded to the ATP-binding site at their common core from the urea group to the quinoline ring (lenvatinib) and pyridine (sorafenib). They binded to the neighboring allosteric region via the cyclopropane ring (lenvatinib) or the 4-chloro-3-(trifluoromethyl) phenyl ring (sorafenib). This suggested a strong hydrophobic interaction between the cyclopropane ring of lenvatinib and the phenyl ring of Phe1047. Both compounds could exert their kinase inhibitory activity through binding to the ATP-binding site, while enhancing kinase selectivity through binding to the neighboring region (Liao, 2007; Zuccotto, et al., 2010; McTigue, et al., 2012).

Effects on VEGF-Driven VEGFR2 Phosphorylation, Proliferation, and Tube Formation in the HUVEC Model (Studies M03008, M03006, M03005, W-20100606)

Four studies were conducted to evaluate the effects of lenvatinib on VEGF-driven cellular functions of HUVECs, which could be considered as *in vitro* angiogenesis models, specifically VEGFR2 phosphorylation, proliferation, and three-dimensional organization for tube formation.

Lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation, proliferation, and tube formation in the HUVEC model in concentration-dependent manners (IC50HUVECphosphorylation=0.25 nM (0.11 ng/ml); IC50HUVECproliferation= 3.4 nM (1.28 ng/ml); IC50HUVECtube formation= 2.1 nM (0.90 ng/ml). In the fourth study (Study No. W-20100606) the effect of lenvatinib on HUVEC proliferation driven by both VEGF (20 ng/mL) and hepatocyte growth factor (HGF, a MET ligand [30 ng/mL]) was also studied. Lenvatinib (0.3 – 300 nmol/L) showed a concentration dependent, but partial inhibition (approximately 60% at 300 nmol/mL), as predicted by the kinase inhibitory profile in which lenvatinib strongly inhibited VEGFR2 but not MET.

Effects of Lenvatinib Metabolites on VEGF-Driven Proliferation of HUVECs (Study No. M06002)

Primary pharmacodynamic effects of lenvatinib metabolites M1, M2, and M3 produced by liver microsomes were evaluated by measuring the inhibitory effects on VEGF-driven proliferation of HUVECs M1, M2, and M3 showed concentration-dependent antiproliferative activity, with IC_{50} values of 57 nmol/L (95% confidence interval [CI]: 18 – 180), 250 nmol/L (95% CI: 240 – 270) and 230 nmol/L (95% CI: 120 – 440), respectively, against the VEGF-driven proliferation of HUVECs, suggesting that VEGFR2 inhibitory activities of M1, M2, and M3 were 6%, 1%, and 1%, respectively, of the activity of lenvatinib.

Additional literature data

Tohyama, et al. (2014) described the anti-proliferative activity of lenvatinib against 11 human thyroid cancer cell lines *in vitro*. Antiproliferative activity of lenvatinib was evaluated by using IC50 values and the ratios of the IC50 values of the thyroid cancer cell lines relative to that of Nthy-ori 3-1 cells. Lenvatinib did not show the potent in vitro antiproliferative activity for 9 out of the 11 cell lines with IC50 values being greater than 10 μM. Lenvatinib did, however, showed antiproliferative activity against the human DTC RO82-W-1 (= follicular TC cell line) and MTC TT cell lines (= medullary TC cell line), with IC50 values of 3.8 µM (1622 ng/ml) and 0.078 µM (33 ng/ml), respectively; moreover, it was selective against these two DTC cell lines compared with normal thyroid cells (T/N = 0.25 and 0.01, resp.). The results suggested that

RTK signaling pathways may have roles in oncogenic proliferation of these two human thyroid cancer cells lines.

Orally administered lenvatinib significantly inhibited tumour growth of 1 PTC (a major type of DTC), 4 FTC (another major type of DTC), 1 MTC, and 5 ATC xenografts in nude mice. Lenvatinib inhibited tumour angiogenesis in 5DTC and 5ATC xenograft models as evidenced by a decrease in MVD.

The results suggested the antitumor activity of lenvatinib against a broad panel of human thyroid cancer models can be primarily attributed to its anti-angiogenic effects. Okamoto, et al. (2013) evaluated the activity of lenvatinib in RET-gene fusion-driven *in vitro* assays. It was showed that lenvatinib suppressed the growth of papillary thyroid CCDC6-RET, KIF5B-RET and NcoA4-RET cancer cell lines (CCDC6-RET and NcoA4-RET account for more than 90% of the RET fusions in papillary thyroid carcinoma). Lenvatinib inhibited oncogenic RET signaling in vitro at concentrations in the 30-100 nM (15.69-52.30 ng/ml) range. The results suggest that lenvatinib can exert antitumor activity against RET gene fusion driven tumour models by inihibiting oncogenic RET fusion signaling and thus directly inhibit transformed cell growth. In addition, the results showed that lenvatinib can directly inhibit transformed cell growth at therapeutically relevant plasma exposures.

In vivo studies

Table 1: Summary of the anti-tumour effects of lenvatinib monotherapy

Tumour Cell Line	**Schedule**	**Lenvatinib dose (mg/kg)[a]**					**Study No.**
		1	**3**	**10**	**30**	**100**	
		T/C (%)					
K1 papillary thyroid carcinoma	QD×14	80%	71%	51%	28%	13%	A10004
		70%	61%	54%	30%	16%	M13012
RO82-W-1 follicular thyroid carcinoma	QD×21	63%	59%	42%	34%	20%	M13013
8305C anaplastic thyroid carcinoma	QD×14	68%	61%	42%	30%	21%	M13003
SW579 thyroid-derived squamous cell carcinoma	QD×14	NT	–1%	–18%	–20%	–23%	W-20120359
TT medullary thyroid carcinoma	QD×28	NT	NT	16%	5%	–6%	
PLC/PRF/5 hepatocellular carcinoma	QD×14	62%	44%	29%	16%	6%	K08004
		63%	54%	29%	14%	16%	W-20130793
H460 non-small cell lung cancer	QD×14	73%	72%	55%	29%	12%	M03012
Colo205 colorectal cancer	QD×11	50%	45%	26%	13%	4%	M03011

Anti-tumour effect is shown as T/C (%), where T and C are the change of tumour volume after Day 1 of dosing in the treatment and control groups, respectively.
NT = not tested, QD = once a day, T/C = treatment/control.
a: Dose expressed in terms of the mesilate salt.

K1 Human Papillary Thyroid Carcinoma Xenograft Model in Athymic Mice (A10004 and M13012)

Lenvatinib showed significant antitumor effects against K1 human papillary thyroid carcinoma xenograft model in athymic mice at doses of 30 and 100 mg/kg. The body weight loss (BWL) was within 10% (not severe) at all doses tested compared to the body weight at the initiation of dosing.

In a second model, lenvatinib showed significant and dose-dependent antitumor effects at doses from 3 to 100 mg/kg with a maximum effect giving a minimum mean T/C value of 16%, demonstrating

reproducible dose-dependent antitumor activity. In contrast, sorafenib showed significant antitumor effects at doses ≥ 30 mg/kg with higher minimum mean T/C values ranging from 47% to 35%, suggesting that the maximum antitumor effect of lenvatinib was greater than that of sorafenib in this model.

RO82-W-1 Human Follicular Xenograft Model in Athymic Mice (M13013)

Lenvatinib showed significant antitumor effects against RO82-W-1 human follicular thyroid carcinoma xenograft model in athymic mice (at doses from 1 to 100 mg/kg). The BWL was within 10% (not severe) at all doses tested compared to the body weight at the initiation of dosing (M13013).

In a second model, dose dependency was observed for lenvatinib between 1 and 100 mg/kg with a maximum effect giving a minimum mean T/C value of 20%. In contrast, sorafenib showed significant antitumor effects at doses ≥ 30 mg/kg in this model with higher minimum mean T/C values ranging from 55% to 38%, suggesting that the maximum antitumor effect of lenvatinib was greater than that of sorafenib in this model.

8305C Human Anaplastic Thyroid Carcinoma Xenograft Model in Athymic Mice (M13003)
Lenvatinib showed significant and dose-dependent antitumor effects against 8305C human anaplastic thyroid carcinoma xenograft model in athymic miceat doses from 1 to 100 mg/kg without severe BWL. MVDs (microvessel density – analysed using immunohistochemistry staining for the endothelial marker, CD31) in the tumors were decreased in a dose-dependent manner. Significant decreases in tumor MVD were observed at doses from 3 to 100 mg/kg. The good correlation of the antitumor effect with the decrease of tumor MVD suggested that lenvatinib exerted a significant antitumor effect through its antiangiogenesis activity.

SW579 and TT Human Thyroid Carcinoma Xenograft Models in Athymic Mice (W-20120359)

Lenvatinib showed a significant and dose-dependent antitumor effect against SW579 human thyroid-derived squamous cell carcinoma and TT human medullary thyroid xenograft models in athymic mice at doses of 3 to 100 mg/kg. Tumor regression, without severe BWL, was observed at 10 to 100 mg/kg.

Lenvatinib showed a significant and dose-dependent antitumor effect against the thyroid medullary carcinoma TT xenografts at doses of 10 to 100 mg/kg, with tumor regression observed at 100 mg/kg. Severe BWL was not observed at doses of 10 and 30 mg/kg; however, lenvatinib at a dose of 100 mg/kg caused some BWL, with a mean relative body weight (RBW) value of 0.87 compared to the body weight at the initiation of dosing.

Marked inhibition of RET autophosphorylation in the TT xenografts was observed at all doses at which lenvatinib exhibited antitumor activity. Since TT cells have a constitutively active mutant form of RET (C634W), which strongly drives the growth of the cells, this RET inhibition is postulated to contribute to the antitumor effect of lenvatinib against TT xenografts in this model.

PLC/PRF/5 Human hepatocellular carcinoma (HCC) Xenograft Model in Athymic Mice (K08004)

Lenvatinib showed significant antitumor effects against PLC/PRF/5 human HCC xenograft model in athymic mice at doses from 3 to 100 mg/kg. BWL was continuously observed in 5 of 6 mice in the vehicle control group resulting in a mean RBW value of 0.91 at Day 15 compared to the body weight at the initiation of dosing. This suggests that the BWL was likely a result of tumor burden (cachexia-like). This BWL was weakly enhanced at the high dose of lenvatinib (100 mg/kg), with a mean RBW value of 0.81.

Another experiment was performed to compare the antitumor effect of lenvatinib with that of sorafenib in the PLC/PRF/5 human HCC xenograft model in athymic mice. The results suggested that the maximum antitumor effect of lenvatinib was greater than that of sorafenib in this model.

H460 Human non-small cell lung cancer (NSCLC) Xenograft Model and Colo205 Human Colorectal Cancer Xenograft Model in Athymic Mice (M0312 & M030011)

Also in the H460 Human NSCLC Xenograft Model and the Colo205 Human Colorectal Cancer Xenograft Model in Athymic Mice, lenvatinib showed antitumor effects at all doses without severe BWL.

Effects of lenvatinib on plasma fibroblast growth factor 23 in mice (Study W-20140842)

The effects of oral lenvatinib mesilate at 3 and 10 mg/kg and oral sorafenib tosylate at 9 and 30 mg/kg were examined against plasma fibroblast growth factor 23 (FGF23) levels 24 hours after the administration in mice.

Lenvatinib mesilate significantly increased plasma FGF23 level at a dose of 10 mg/kg in mice. At a dose of 3 mg/kg, no significant elevation was seen as compared to controls. Taking into account the 96.28% protein binding in mice, the free Cmax in mice at 3 mg/kg = 3.72% of 1965.1 ng/ml = 73 ng/ml. This value corresponds to about 9 times the free Cmax in humans at therapeutic doses (7.9 ng/ml).

Sorafenib tosylate at 9 and 30 mg/kg did not show significant elevation of plasma FGF23 levels.

Secondary pharmacodynamic studies

The binding of lenvatinib to a panel of 50 non-kinase receptors known to play significant biological roles (ExpresSProfile) was evaluated in vitro at concentrations of 1 and 10 µmol/L. No significant binding (>50% inhibition) to any receptor of the ExpresSProfile was observed at the tested concentrations, except for the 5-hydroxytryptamine receptor 1B (58%) and human norepinephrine transporter (50%) at 10 µmol/L.

It should be noted that at therapeutic dose levels of 24 mg/day, total Cmax amounted to 573 ng/ml. Taking into account 98.62% protein binding, free Cmax attained 7.9 ng/ml. As such no secondary pharmacodynamic effects are expected.

Safety pharmacology programme

The safety pharmacology of lenvatinib was evaluated in *in vitro* and *in vivo* studies.

Table 2: Overview of safety pharmacology studies

Type of Study and Test System	GLP Compliance	Study Number
Effect on hERG Tail Current Recorded from Stably Transfected HEK293 Cells	Yes	DJNR1029
Effects on Action Potential Parameters in Isolated Papillary Muscles of Guinea-Pig	Yes	B030403
Effects on Cardiovascular System and Body Temperature by Oral Administration in Conscious Dogs	Yes	B030402
Effects on Respiratory Function by Oral Administration in Rats	Yes	S03019
Effects on General Physical Condition and Behavior by Oral Administration in Rats	Yes	B030401

GLP = Good Laboratory Practice, hERG = human ether-à-go-go-related gene.

Central Nervous system

Lenvatinib (E7080) at 10, 30, and 100 mg/kg, was administered orally, by gavage, as a single dose to conscious male Sprague-Dawley IGS rats to evaluate the effects of the drug on the central nervous system using Irwin's method. E7080, up to 100 mg/kg, showed no effects on general physical condition and behaviour in rats.

Cardiovascular system

Two *in vitro* electrophysiology studies were conducted to assess the effect of lenvatinib on the human ether-à-go-go-related gene (hERG) tail current recorded from stably transfected HEK293 cells (whole-cell patch-clamp method) or action potential parameters in isolated guinea-pig papillary muscle (glass microelectrode method).

In the first study, lenvatinib inhibited hERG tail current in a concentration-dependent manner with a statistically significant inhibition of tail current observed at concentrations of 10 and 30 µM. Lenvatinib inhibited hERG tail current in a concentration-dependent manner, with 25%, 50%, and 75% inhibitory concentration values of 5.13, 11.89 (= 6.2 µg/ml), and 25.70 µmol/L, respectively.

In the second *in vitro* study, lenvatinib, at 1 and 10 µmol/L (100 µM could not be dissolved), showed no significant effect on the action potential parameters (Resting membrane potential (RMP), action potential amplitude (APA), maximal upstroke velocity of depolarization (V max), and action potential duration at 50% (APD50) and 90% (APD90) repolarization) in isolated papillary muscles of guinea-pigs.

Lenvatinib was administered orally, by gavage, as a single dose to conscious male and female beagle dogs at doses of 6 and 30 mg/kg to evaluate the effects on the cardiovascular system, and on body temperature. E7080 at 6 and 30 mg/kg (~ 30x20/37x70kg=1135 mg ⇔ HRD = 24 mg/d) had no significant effects on heart rate, mean blood pressure, ECGs (including QT), or body temperature except for a minimal increase in mean blood pressure within the normal biologic range.

The lack of effect on ECG parameters in the in vivo study and the weak inhibitory effects of lenvatinib in the hERG assay (IC50 = 11.89 µmol/L or 6,2 µg/ml) at a concentration approximately 10-fold higher than the total maximum observed concentration (Cmax) at the clinical dose of 25 mg (0.544718 µg/mL from Day 1 of Cycle 2 in Study E7080-E044-101) and 785-fold higher than the free Cmax at the human therapeutic dose, suggest that lenvatinib has a low potential to cause QT prolongation.

Respiratory System

The effects of a single oral dose of lenvatinib mesilate (10, 30, and 100 mg/kg) on respiratory function (respiratory rate, tidal volume, and minute volume) in conscious SD rats were evaluated using unrestrained whole body plethysmography. Lenvatinib at doses up to 100 mg/kg (~100x6/37x70kg=1135 mg) showed no effects on respiratory rate, tidal volume, or minute volume in rats.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted which was considered acceptable by CHMP.

2.3.3. Pharmacokinetics

The pharmacokinetic profile of lenvatinib was evaluated by *in vivo* studies with athymic mice (BALB/c AnNCrj-nu/nu), Sprague Dawley (SD) rats, beagle dogs, and cynomolgus monkeys. The strains and species evaluated were those used in pharmacology and toxicity studies. For assessments of metabolic characteristics, *in vitro* studies using hepatocytes, recombinant metabolic enzymes, liver microsomes or other subcellular fractions of the liver were also conducted.

Method

A method using HPLC with UV detection was validated for quantification of lenvatinib in plasma samples of mice, rats, dogs, and cynomolgus monkeys. In these validation studies, plasma concentration of lenvatinib was expressed in terms of the mesilate salt. Radiolabeled lenvatinib mesilate ([^{14}C] lenvatinib mesilate and [^{14}C]CB-lenvatinib mesilate) were synthesized to conduct mass balance and metabolite identification studies. The concentration of radioactivity derived from carbon 14 in the blood, plasma, tissues, urine, bile, and faeces was determined by LSC with external standard method. The concentration of radioactivity was expressed as the equivalent of lenvatinib mesilate (µg eq./mL or g).

Absorption

The pharmacokinetic profiles of lenvatinib in mice, rats, dogs, and cynomolgus monkeys were characterized by a low total plasma clearance (100.2 – 368.3 mL/h/kg) and a small to moderate volume of distribution (391.5 – 1610.0 mL/kg). The terminal elimination phase half-life after intravenous administration was 2.05 to 5.27 hours. After oral administration of lenvatinib mesilate at 3 mg/kg as a solution, lenvatinib was absorbed rapidly and had absolute bioavailability in mice (64.4%), rats (68.7%), dogs (70.4%), and monkeys (78.4%).

Table 3: Pharmacokinetic Parameters for Lenvatinib in animals

Species / Strain / Gender	Dosing Route	Doses[a] (mg/kg)	$AUC_{(0\text{-inf})}$ (µg·h/mL)	CL_p (mL/h/kg)	V_{ss} (mL/kg)	$t_{½}$ (h)	C_{max} (µg/mL)	t_{max} (h)	F (%)
Mouse / BALB/c AnNCrj-nu/nu / Female	IV	3	8.686	345.4	714.3	2.05	7.0542[b]	NA	NA
	PO	3	5.596	NA	NA	2.09	1.9651	0.5	64.4
	PO	10	27.720	NA	NA	1.74	10.5100	0.5	NC
	PO	30	118.198	NA	NA	1.85	31.2565	1	NC
Rat/SD/Male	IV	3	30.107	100.2	391.5	3.65	14.0567[b]	NA	NA
	PO	3	20.697	NA	NA	3.61	6.1671	0.5	68.7
	PO	10	78.321	NA	NA	5.27	16.6450	0.5	NC
	PO	30	145.580	NA	NA	4.95	23.2015	1	NC
Dog/Beagle/ Male	IV	3	8.417	368.3	1610.0	5.27	2.2889[b]	NA	NA
	PO	3	5.481	NA	NA	4.76	1.2717	2	70.4
Monkey/ Cynomolgus/ Male	IV	3	12.900	237.7	793.7	4.28	4.6427[b]	NA	NA
	PO	3	10.272	NA	NA	4.07	2.5013	2	78.4

Doses and plasma concentrations for lenvatinib were expressed as those of the mesilate salt, and related parameters were calculated. In mice, each parameter except t_{max} was calculated with the average concentration of 3 animals, and in other species, each value except t_{max} represents the mean of 4 animals. The t_{max} represents the mode value, except for mice. F was calculated using the formula: $AUC_{(0\text{-inf})}$ in oral dosing / $AUC_{(0\text{-inf})}$ in intravenous dosing × 100.

$AUC_{(0\text{-inf})}$ = area under the concentration-time curve from zero time extrapolated to infinite time, CL_p = total plasma clearance, C_{max} = maximum observed concentration, F = absolute bioavailability, IV = intravenous, NA = not applicable, NC = not calculated, PO = oral, SD = Sprague Dawley, $t_{1/2}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs, V_{ss} = volume of distribution at steady state.

a: Lenvatinib mesilate was administered as solution in all administration groups.

b: Concentration at 5 minutes for intravenous dosing.

Source: Study Nos. B03014 (mouse), B03015 (rat), B03016 (dog), and B04003 (monkey).

Overall, repeated-dose toxicokinetic studies of lenvatinib in male and female rats, dogs, and cynomolgus monkeys conducted with once daily oral doses for up to 26, 4, and 39 weeks, respectively, indicated no systemic accumulation of lenvatinib in the toxicology studies. Systemic exposures in males and females were generally comparable in each species. With the exception of rats, systemic exposure of lenvatinib was not affected by repeated administration in these species. In dogs at doses < 30 mg/kg, the systemic exposure generally increased in a dose-proportional manner. The systemic exposure increased in a less than dose-proportional manner at higher dose levels in rats (>10 mg/kg). In contrast, in monkeys, systemic exposure increased in a more than a dose-proportional manner at low dose levels (0.1 – 3 mg/kg). Unlike the rat or the monkey, the systemic exposure in humans increased in a dose-proportional manner (see clinical pharmacokinetics section).

Distribution

Tissue distribution of radioactivity was investigated after a single oral administration of 14C-lenvatinib mesilate (3 mg/kg) to male SD rats and male cynomolgus monkeys and after a single oral administration of 14C-CB-lenvatinib mesilate (3 mg/kg) to male cynomolgus monkeys.

In rats, the highest concentrations of radioactivity were found at 0.5 hours postdose (Tmax) in most tissues (the small intestine, liver, adrenal gland, and stomach showed concentrations 1.19 to 2.59 times higher than that in plasma), and decreased almost in parallel with that in blood. Elimination half-life was 1.9 days.

In monkeys, the highest concentrations of 14C-lenvatinib-radioactivity were found at 4 hours postdose (Tmax) in the bile in gall bladder, being 556.73 times that in the plasma. The mean concentrations of radioactivity in the urine in bladder, gall bladder, liver, choroid, ciliary body, and renal cortex were next highest, being 57.85-10.11 times that in the plasma. At 24 hr postdose, the choroid, iris, large intestine, sclera, cornea, and lens reached their maxima.

The mean concentrations of radioactivity in many tissues decreased almost in parallel with that in the plasma. Elimination half-life was 3.43 days.

In monkeys, the highest concentrations of 14C-CB-lenvatinib-radioactivity were found at 2 hours postdose (Tmax). The radioactive concentrations in the bile in gall bladder and urine in bladder were the highest, being 33.59 and 24.55 times those in the plasma, respectively. The radioactive concentrations in the choroid and liver were the next highest, being 7.14 and 7.02 times those in the plasma, respectively. The radioactive concentrations in the gall bladder, iris, renal cortex, kidney, ciliary body, renal medulla, and lung were 3.28 to 1.49 times those in the plasma. The radioactive concentration in the central nervous system was 0.07 times or lower than that in the plasma. Elimination half-life was 3.70 days.

Protein Binding and Distribution in Blood Cells

The plasma protein binding of lenvatinib mesilate (0.3 to 30 µg/mL) in athymic mice, SD rats, beagle dogs, cynomolgus monkeys, and humans was determined by equilibrium dialysis in vitro (Study No. B09009). Incubation was conducted for 72 hours at 37 °C. Among the species tested, lenvatinib exhibited the highest plasma protein binding in human, independent of concentrations (97.87% to 98.62%), followed by rat (97.70% to 98.20%), athymic mouse (96.28% to 96.92%), monkey (95.90% to 96.17%), and dog (89.71% to 91.75%).

To assess the specific proteins that bind lenvatinib in human plasma, protein binding of lenvatinib mesilate (0.3 to 30 µg/mL) to albumin, α1-acid glycoprotein, and γ-globulin was determined by equilibrium dialysis *in vitro* (Study No. B09011). Lenvatinib mainly bound to albumin, and the contribution of α1-acid glycoprotein and γ-globulin to lenvatinib protein binding was minor in human plasma. Based on the results at the lowest lenvatinib mesilate concentration tested (0.3 µg/mL), the contributions of albumin, α1-acid glycoprotein, and γ-globulin to the human plasma protein binding of lenvatinib were estimated to be 93.2%, 6.1%, and 0.7%, respectively.

Blood to plasma concentration ratios (Rb) of ^{14}C-lenvatinib mesilate (0.1 to 10 µg/mL) in athymic mice, SD rats, beagle dogs, cynomolgus monkeys, and humans were determined in vitro after a 30-minute incubation at 37 °C. A species difference in the Rb of ^{14}C-lenvatinib was observed, and ranked from highest to lowest as follows: dog > monkey = mouse ≥ rat > human. The Rb values in animals declined with increasing concentration; however, in human, the Rb was constant between 0.1 and 10 µg/mL.

The *in vitro* transfer ratios of ^{14}C-lenvatinib mesilate to blood cell were 23.1%, 22.1%, and 18.8% in the mouse; 8.86%, 7.59%, and 4.36% in the rat; 51.4%, 44.3%, and 42.1% in the dog; 29.7%, 21.9%, and 18.3% in the monkey; and 17.2%, 14.5%, and 14.8% in the human at the spiked 14C- lenvatinib mesilate blood concentration of 0.1, 1, and 10 µg/mL, respectively.

As for the stability of ^{14}C-lenvatinib mesilate in the blood, the radiochemical purity declined in the dog blood. The decreased rate was low as approximately 10%, but taking account of dog showing higher Rb than other species, it could not be fully excluded that decomposed ^{14}C-lenvatinib mesilate in dog blood may be distributed to blood cells more than unchanged ^{14}C-E7080.

Placental transfer studies
Placental transfer was investigated after a single oral administration of 14C-lenvatinib mesilate (3 mg/kg) to pregnant rats (Study No. AE-6750-G). On Days 13 and 18 of pregnancy, the concentrations of radioactivity in fetuses were low, and were 2% or less of the concentration in maternal plasma at 0.5 hours post-dose, the first sampling time point. The distribution of radioactivity for each foetus was 0.02% or less of the dosed radioactivity.

Placental transfer of lenvatinib mesilate in rats (on day 13 and 18 of pregnancy) was low (2% or less of the concentration in maternal plasma).

Metabolism

In vitro and *in vivo* studies using lenvatinib, [^{14}C] lenvatinib, or [^{14}C]CB-lenvatinib were conducted to determine the metabolic profile of lenvatinib.

Lenvatinib mesilate (final concentration: 10 µg/mL) was incubated at 37°C for 60 minutes in mouse, rat, dog, monkey, and human liver microsomes (protein concentration: 1 mg/mL) with or without the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), and the reaction mixtures were analyzed by liquid chromatography coupled with mass spectrometry (LC/MS) to investigate the in vitro metabolism of lenvatinib (Study No. B03025).

8 metabolites (M1, M2, M3, M4, M5, M6, M7, and M8) were detected in at least one animal species as well as in human liver microsomes. M1, M2, and M3 were identified as decyclopropylated, demethylated, and N-oxidated forms of lenvatinib, respectively. M1 could be a chemical (or non-enzymatic) degradation product, as M1 was detected in lenvatinib solution and in the incubation mixtures without microsomes or NADPH. M4 was proposed as a hydroxylated form at the cyclopropyl group of lenvatinib, M5 was proposed as the quinoline form, formed by O-dearylation, M6 was proposed as a form hydroxylated at the cyclopropyl group of M2, M7 was proposed as a form doubly hydroxylated at cyclopropyl group, and M8 was proposed as the N-oxidated form of M2.

Six metabolites (M1, M2, M3, M4, M5, and M7) were common among the species tested. M6 and M8 were detected in monkey and human liver microsomes but not in mouse, rat, and dog liver microsomes. In the human liver microsomes, M2 appeared to be a major metabolite. All metabolites in human liver microsomes were also qualitatively represented in monkey liver microsomes. Six metabolites out of eight (M1, M2, M3, M4, M5, and M7) were also detected in rat liver microsomes.

To determine the CYP-mediated metabolism of lenvatinib in humans *in vitro*, lenvatinib was incubated with recombinant human CYPs. CYP3A4 was the predominant (≥80%) isoform contributing to the CYP-dependent metabolism of lenvatinib in humans in vitro over the concentration range of 0.005 to 10 µg/mL, followed by CYP1A2 (2.4% to 7.6%) and CYP2B6 (3.0% to 6.7%). To further evaluate CYP isoforms responsible for the CYP-dependent metabolism of lenvatinib, the effects of CYP isoform-specific inhibitors on lenvatinib metabolism were also assessed in HLMs. The results obtained further showed that CYP3A4 was a major CYP isoform involved in the CYP-dependent metabolism of lenvatinib in HLM.

In addition, aldehyde oxidase (AO) contributes to the formation of M2´ and M3', the major metabolites in human feces.

To clarify the metabolic profiles of lenvatinib *in vivo*, the metabolites after oral administration of [^{14}C]lenvatinib mesilate to rats and a single monkey at 30 mg/kg were investigated (Study No. B10006). In this study, 36 radioactive components in total were found in rat and monkey samples, and were assigned serial numbers with the prefix “Met” (Met 1 to Met 36). Based on comparisons of retention times and mass spectral data with the corresponding references, Met 14 (me37), Met 28 (me88), Met 32-1 (me107), Met 33 (me114), and Met 35 (me116) were identified as M5, M1, M3, M2, and lenvatinib, respectively.

In addition to oxidative metabolism, one of the major metabolic pathways for lenvatinib in the rat and monkey appeared to be glutathione conjugation at the quinoline moiety, and 15 glutathione conjugation-related metabolites including Met 12 (me36) and Met 15 (me40) were detected in this study.

Three metabolites were isolated from monkey urine samples, and their chemical structures were determined by NMR to be Met 13 (me33) further oxidized from Met 12 (me36), Met 16 (me45) dimerized of Met 21 (me47), and Met 20 (me49) conjugated from Met 21 (me47) and Met 19-2 (me44) forming disulfide, respectively (Study No. C10320).

The metabolic profiles of lenvatinib were further investigated following single oral administrations of [^{14}C]lenvatinib mesilate to male rats and monkeys at 3 mg/kg (Study No. AE-6748-G). Plasma, liver, kidney, urine, feces, and bile were collected and subjected to metabolite analyses using LC/MS(MSn). In this study, 41 radioactive peaks on HPLC radiochromatograms were found in rat and monkey samples, and the metabolites were assigned serial numbers with the prefix “m” (m1 to m41).

In these *in vivo* studies, the presence of the oxidized human metabolites, M1 (me88), M2 (me114), M3 (me107), M5 (me37), M2´(me118), and M3´(me115) were confirmed by LC/MS analysis of rat or monkey samples after single oral administrations of lenvatinib. An additional study was conducted to clarify the metabolic profile of lenvatinib in monkeys using ^{14}C-labeled lenvatinib radio-labeled on the chlorobenzene moiety. After a single oral dose of ^{14}C-CB-lenvatinib at 3 mg/kg to cynomolgus monkeys, radioactive components in biological samples were analyzed. More than 90% of plasma radioactivity was extracted with methanol, and major component in plasma was lenvatinib. Unchanged lenvatinib was found in bile and feces but not in urine. The main primary metabolic pathway of lenvatinib was indicated to be the cleavage of *O*-aryl bond to form mCB31 (ER-236273), and further biotransformations of mCB31 (conjugate with glucuronic acid, sulfuric acid, glutathione, and *N*-acetyl glucosamine with or without hydroxylation) were confirmed, resulted in forming many kinds of metabolites.

Excretion

After oral administration of [^{14}C] lenvatinib mesilate to rats and cynomolgus monkeys or [^{14}C]CB-lenvatinib mesilate to monkeys, greater than or equal to 90% of the radioactive dose was recovered in the excreta by 168 hours post-dose. In rats, fecal excretion via bile was the main route of excretion, while in monkeys fecal and urinary excretion was a major excretion route of radioactivity after dosing of [14C]lenvatinib mesilate and [14C]CB-lenvatinib mesilate, respectively. These results indicated that metabolites derived from the quinoline moiety were excreted mainly in the feces, and those from the chlorobenzyl moiety were excreted primarily in the urine.

Table 4: Excretion of radioactivity after a single oral administration of lenvatinib to male rats and monkeys

Data Source	Species/Strain Test Article/Dose (mg/kg)	Cumulative Excretion of Radioactivity up to 168 Hours[a]		
		Urine	Feces	Total
Study No. AE-4150-G	Rat/SD [^{14}C]Lenvatinib mesilate/3	12.2	87.2	99.4
Study No. AE-4151-G	Monkey/Cynomolgus [^{14}C]Lenvatinib mesilate/3	17.2	72.8	90.0
Study No. AE-6917-G	Monkey/Cynomolgus [^{14}C]CB-lenvatinib mesilate/3	79.9	13.6	93.5

Dose is expressed as the mesilate salt. Values represent the mean values of 3 animals.

CB = chlorobenzene, SD = Sprague Dawley.

a: Value was expressed as percentage of dose.

The excretion of radioactivity into milk was investigated after a single oral administration of 3 mg/kg [^{14}C]lenvatinib mesilate to lactating SD rats (Study No. AE-6750-G). The concentration of radioactivity in milk was higher than that in plasma, indicating a relatively high transfer of lenvatinib into milk. However, the concentration of radioactivity in milk decreased rapidly with a similar time profile as that in plasma, suggesting no tendency for lenvatinib to remain in milk for a long period.

Pharmacokinetics drug interactions

The induction of CYPs, UGTs, and P-gp by lenvatinib was evaluated in vitro (Study Nos. XT063020 and XT103078). Treatment of cultured human hepatocytes with up to 3 µmol/L lenvatinib had a tendency to slightly increase CYP3A but had no effect on CYP1A1, CYP1A2, CYP2C9, and P-gp did not induce CYP2B6, UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 enzyme activities or mRNA expressions.

Additionally, the inhibition of CYPs and UGTs by lenvatinib was studied in vitro (Study Nos. B03023, PK-Test-0072, PK-Test-0040, PK-Test-0079, and XT105084). Lenvatinib mesilate (100 µmol/L) weakly inhibited the activities of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6. Lenvatinib showed virtually no inhibitory effects on CYP2A6 and CYP2E1. Lenvatinib exhibited a potent inhibitory effect on CYP2C8 (IC50 = 10.1 µmol/L) and a weak inhibitory effect on CYP3A (IC50: approximately 100 µmol/L) in human liver microsomes.

The potential inhibitory activity of lenvatinib mesilate (0.03 to 30 µmol/L) on UGTs (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was assessed in HLM using UGT isoform specific substrates. Lenvatinib inhibited UGT1A1 and UGT1A4 with IC_{50} values of 10.6 and 14.0 µmol/L, respectively. Lenvatinib weakly inhibited UGT1A9, with 31.9% inhibition observed at 30 µmol/L; however, the IC_{50} value for this enzyme was greater than 30.0 µmol/L. There was little or no evidence of inhibition of UGT1A6 and UGT2B7 by lenvatinib.

A series of in vitro studies was conducted to assess the substrate recognition and inhibitory activity of lenvatinib on the known human transporters, including P-gp, BCRP, OATPs, OATs, OCTs, and BSEP.

The roles of P-gp in mediating the membrane permeability of [14C]lenvatinib and the potential inhibition of P-gp-mediated [3H]digoxin transport by lenvatinib were assessed using human P-gp expressing and control LLC-PK1 cell monolayers (Study No. GE-0556-G). These results demonstrated that lenvatinib was a substrate for P-gp. Lenvatinib weakly inhibited P-gp-mediated transport, and the IC_{50} for the inhibition of [3H]digoxin transport mediated by P-gp was estimated to be more than 30 µmol/L.

The potential of [14C]lenvatinib to serve as a substrate for BCRP and the potential inhibition of BCRP-mediated [3H]prazosin transport by lenvatinib were assessed using human BCRP expressing and control LLC-PK1 cell monolayers (Study No. GE-0791-G). In this study, it was shown that lenvatinib was a BCRP substrate and it weakly inhibited BCRP-mediated transport (IC_{50} > 30 µmol/L).

To assess whether lenvatinib is a substrate or inhibitor for OAT1, OAT3, OCT2, OATP1B1, and OATP1B3, the transport of lenvatinib and inhibition of the various transporters by lenvatinib were examined using specific transporter expressing cells (Study No. GE-0791-G). These results indicated that lenvatinib was not a substrate of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3. The inhibition of these transporters by lenvatinib was evaluated by assessing the inhibition of cellular uptake of radiolabeled typical substrates for each transporter. Lenvatinib showed concentration-dependent inhibitory effects on OAT1, OAT3, OCT2, and OATP1B1 with the IC_{50} values of 7.36, 4.11, 10.8, and 7.29 µmol/L, respectively, and minimal or no inhibitory effect on OATP1B3 (IC_{50} >30 µmol/L).

The potential for [14C]lenvatinib to be a substrate for OCT1 and BSEP, and the potential of lenvatinib to inhibit these transporters were assessed using OCT1 expressing HEK293 cells and BSEP expressing closed inside-out vesicles (Study No. GE-0942-G), respectively. Lenvatinib was not a substrate for OCT1 and BSEP. Lenvatinib showed concentration-dependent inhibitory effects on OCT1- and BSEP-mediated uptake of each respective radiolabeled typical substrate with IC_{50} values of 14.9 and 14.2 µmol/L.
In Study No DMPKT2012-004, the potential inhibition of human AO activity by lenvatinib and its metabolites (M1, M2, M3, M2´, M3´, and M5) was evaluated using human liver cytosol. AO specific activity was assessed using phthalazine, known to be a substrate of AO, by measuring the concentration of its metabolite, phthalazone, with liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS). Lenvatinib did not inhibit AO activity (IC50 >100 µmol/L).

2.3.4. Toxicology

All pivotal toxicity studies were performed in compliance with Good Laboratory Practice (GLP) regulations, and designed in accordance with the relevant guidelines.

Single dose toxicity

The single dose toxicity of lenvatinib was evaluated in oral single-dose toxicity studies in rats, followed by a 4-day or 4-week observation period, and in dose escalation studies in dogs and monkeys.

Table 5: Overview of single dose toxicity studies with lenvatinib mesilate

Study Number	Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)	GLP
TKB02006	Rat/Sprague Dawley	Oral gavage	Single	100, 300, 1000	No
S04094	Rat/Sprague Dawley	Oral gavage	Single	0, 500, 1000, 2000	Yes
TKB02022	Dog/Beagle	Oral capsule	Single (Dose escalation method)	100, 300, 1000	No
S03060	Monkey/Cynomolgus	Oral gavage	Single (Dose escalation method)	0, 30, 100, 300, 1000	No

Rats

In both the oral dose range-finding (DRF) toxicity study (Study No. TKB02006) and the GLP-compliant single-dose oral toxicity study (Study No. S04094) lenvatinib mesilate was suspended with 75% polyethylene glycol (PEG) 400 aqueous solution and administered as a single oral dose, by gavage, to male and female SD rats (3 animals/sex/group in the DRF, 5 animals/sex/group in the GLP compliant study) (vehicle control, 75% PEG 400 aqueous solution). In the DRF study, at 1000 mg/kg, decreased food consumption was observed in males, and red spots in the stomach were observed macroscopically in both males and females. Watery contents in the small intestine were observed in 1 female rat at 1000 mg/kg. No abnormalities were observed in any rats administered 100 or 300 mg/kg.

In the GLP-compliant study, a 4-week observation period was included. Delayed deaths (observed from Day 14 onward) were observed in 3 animals administered 1000 or 2000 mg/kg. In these animals, decreased activity, hypothermia, staining of the nose region, chromaturia (reddish urine), or discoloration of the eyeball were observed before death. At necropsy, dilatation, mucosal thickening, and red focus were observed in the stomach and duodenum. In addition, agglomeration of food and test article was found in the stomach or occluded the duodenum. Similar GI changes were observed in surviving animals at 1000 or 2000 mg/kg. White discoloration of incisors, decreased food consumption, and subsequent suppression of body weight gain were observed in these groups. No test article related changes were observed at the dose of 500 mg/kg.

Dogs

Lenvatinib mesilate was administered orally in gelatin capsules, as a single dose, to 1 male and 1 female beagle dog in a dose escalation study (Study No. TKB02022). Each dog received single doses of 100, 300, or 1000 mg/kg as a 3-fold trituration with lactose with an interval of 1 week between doses in a dose escalation manner.

There were no deaths. No toxicologically significant changes in clinical signs, body weight, or food consumption were observed in the dogs orally administered doses up to 300 mg/kg. At 1000 mg/kg, the female dog showed vomiting immediately after administration.

Maximum observed concentration (Cmax) and area under the concentration-time curve from zero time to 24 hours (AUC(0-24)) values increased with dose escalation from 100 to 300 mg/kg. Cmax and AUC(0-24) values at 1000 mg/kg were lower than those at 300 mg/kg.

Monkeys

Lenvatinib mesilate was administered orally by gavage, as a single dose, to 2 male cynomolgus monkeys at doses of 0 (vehicle control, 75% PEG 400 aqueous solution, 30, 100, 300, or 1000 mg/kg with an interval of 1 day between each dose in a dose escalation study (Study No. S03060). Both animals were necropsied after completion of the observation period following the final administration.

There were no deaths. No abnormal clinical signs were induced by lenvatinib treatment except for watery stool, which was also present following dosing with the vehicle. One male showed decreased food consumption after administration of 300 mg/kg and higher. Macroscopically, abnormal materials in the stomach and watery contents in the small and large intestine were observed in both animals treated with lenvatinib, while red spots in the stomach were only observed in 1 animal.

Cmax and AUC(0-24) values at 30 mg/kg were 13.31 µg/mL and 95.19 µg·h/mL, respectively. The plasma concentration of lenvatinib 2 hours after administration did not increase proportionally with administered dose between 100 and 1000 mg/kg.

Repeat dose toxicity

Table 6: Overview of repeat dose toxicity studies in rats with main findings

Species Number/Group Study ID	**Duration**	**Route Dose (mg/kg)**	**Major findings**
SD Rat 3M/3F TKB02007 Not GLP	1 week	Oral gavage 0, 100, 300, 1000 (75% PEG 400/ suspension)	≥ 100 mg/kg: ↓ platelet, ↑ AST and ALT, mineralization in kidney, stomach, heart and aorta, ↑ thickness of epiphysial growth plate, myocardial degeneration, and hypoplasia in bone marrow 1000 mg/kg: Lethality (2F), ↓ activity, soft stool, watery stool, ↓ food consumption and body weight
SD Rat 3M/3F TKB02008 Not GLP	1 week	Oral gavage 0, 10, 30, 100 (water for injection/ solution)	≥ 10 mg/kg: ↑ thickness of epiphysial growth plate 100 mg/kg: ↓ platelets (F), mineralization in stomach (M)
SD Rat 10M/10F S03016 GLP	4 weeks	Oral gavage 0, 10, 30, 100 (75% PEG 400/ suspension)	100 mg/kg: Lethality from Day 22 (4M, 2F), ↓ activity, soft stool, ↓ food consumption and body weight ↓ RBC, Hb, Ht, platelet, reticulocyte, albumin, globulin, ↑AST and ALT, cholesterol, BUN, creatinine, proteinuria All doses: Histologic lesions in bone (↑ thickness of epiphysial growth plate and cartilage), kidney (glomerulopathy), ovary (follicular atresia), incisor (dysplasia), testes (hypocellularity of seminiferous epithelium) At MD and HD only: liver (sinusoidal dilatation), adrenal gland (sinusoidal dilatation and cortical necrosis), stomach (increased mucous cells), small intestine (duodenal gland inflammation and foamy cell/neutrophil accumulation), and tongue (epithelial atrophy)

SD Rat 10M/10F (LD) 16M/16F (control &HD) S04001 GLP	4 weeks +4 weeks recovery (control &HD)	Oral gavage 0, 1, 15 (75% PEG 400/ suspension)	1 mg/kg: incisor dysplasia (1M, 1F) 15 mg/kg: severe anorexia, ↓ platelets, reticulocyte count ↑ ALT, cholesterol, ALP, proteinuria ↓ testes weight Histologic lesions in bone (↑ thickness of epiphysial growth plate and cartilage), kidney (glomerulopathy), ovary (follicular atresia), incisor (dysplasia), testes (hypocellularity of seminiferous epithelium) Evidence of partial recovery
SD Rat 10M/10F S05039 GLP	13 weeks	Oral gavage 0, **0.4**, 2, 10 (water for injection/ solution)	2 & 10 mg/kg: ↓ RBC, eosinophil, platelet, albumin, globulin ↑ MCV, MCH, neutrophil, monocyte, AST and ALT, cholesterol, glucose, BUN 10 mg/kg: ↓ body weight, proteinuria Histologic lesions in bone (↑ thickness of epiphysial growth plate and cartilage), kidney (glomerulopathy), ovary (follicular atresia), liver (sinusoidal dilatation), brain (changes in blood vessels of choroid plexus), incisor (dysplasia), testes (hypocellularity of seminiferous epithelium), adrenal gland (sinusoidal dilatation and cortical necrosis), stomach (mucosal hyperplasia), small intestine (duodenal gland inflammation) 2 mg/kg: less severe changes in incisors, ovaries and submaxillary glands

SD Rat 15M/15F S08037 GLP	26 weeks	Oral gavage 0, **<u>0.4</u>**, 2, 10 (water for injection/ solution)	10mg/kg: Lethality from Day 84 (8M, 3F), soft stool, ↓ food consumption and body weight Histologic lesions in bone (↑ thickness of epiphysial growth plate and cartilage), kidney (glomerulopathy and glomerulonephropathy), ovary (follicular atresia), brain (perivascular exudate in choroid plexus), incisor (dysplasia), testes (hypocellularity of seminiferous epithelium, ↓ weight:-19%), adrenal gland (sinusoidal dilatation and cortical necrosis), small intestine (distension in 13M/11F, duodenal inflammation, cystic dilatation of duodenal glands). Other changes found in bone marrow (hypocellularity), vagina (mucification), epididymides (desquamated seminiferous epithelial cells), pituitary (basophilic cell vacuolation), stomach (mucosal hyperplasia and inflammatory cell infiltration in glandular stomach, medial necrosis of arterioles and erosion), intestine (accumulation of foamy cells and neutrophils, crypt hyperplasia, submucosal edema and decreased goblet cells), submaxillary glands (acinar hypertrophy), thymus (atrophy), heart (adventitial thickening of arterioles), liver (Kupffer cell hypertrophy or hyperplasia and pigmentation of periportal hepatocytes), common bile duct (cholangitis), pancreas (pancreatitis, fatty necrosis and decreased zymogen granules), and spleen (trabecular mineralization and lymphoid depletion) were considered to be secondary effects of the pharmacology-related changes or deteriorated condition. 2 mg/kg: less severe changes in incisors, kidneys, spleen, and adrenal glands 2 & 10 mg/kg: ↓ RBC (-10%), ↑ MCV, MCH (+14%), neutrophil (x2-4), monocyte (x4-5), lymphocyte (x2), ALT (+11%), cholesterol (+122%M, +26%F), BUN ↓ albumin (up to -25%), A/G ratio (up to -18%) proteinuria

Note: NOAEL values are indicated in bold and are underlined.

Table 7: Overview of repeat dose toxicity studies in dogs with main findings

Species Number/Group Study ID	**Duration**	**Route Dose (mg/kg)**	**Major findings**
Beagle dog 1M/1F TKB02027 Not GLP	7 days	Oral capsules 0, 30, 100, 300 (3-fold trituration with lactose)	300 mg/kg: watery stool, ↓ food consumption and body weight, ↓ lymphocytes, ↑ AST and ALT All doses: Histologic lesions in liver (mononuclear cell infiltration, single cell necrosis of hepatocytes), GI tract (↓ goblet cells, focal acute inflammation in lamina propria, lymphoid depletion/necrosis)

Beagle dog 3M/3F B-5108 GLP	4 weeks (shortens to 15 days at LD & MD and to 8 days at HD) HD 20-day recovery	Oral capsules 0, 2, 6, 30 (10-fold trituration with lactose)	30 mg/kg: Severe GI toxicity, vomiting, watery stool, ↓ body weight (up to -14.5%) and food consumption, anorexia ↓ reticulocytes ↑ fibrinogen, AST and ALP, cholesterol, BUN 2 & 6 mg/kg: similar clinical signs, helatology and serum chemistry changes, but less severe All doses: Histologic lesions in kidney (glomerulopathy), ovary (follicular atresia), testes (hypocellularity of seminiferous epithelium), adrenal gland (sinusoidal dilatation and cortical necrosis), vascular lesions (arterial fibrinoid necrosis & parenchymal changes in various tissues, a.o. GI tract) Recovery of clinical signs and vascular effects, except for 1M (moribund/sacrificed on day 13 of recovery)
Beagle dog 3M/3F (LD) 5M/5F (control &HD) S03077 GLP	4 weeks + 4 week recovery (control &HD)	Oral capsules 0, 0.1, 0.5 (10-fold trituration with lactose)	0.5 mg/kg: watery stool Histologic lesions in kidney (glomerulopathy), arterial fibrinoid necrosis in the gallbladder, lymphoid depletion in jejunum & ileum ≥0.1 mg/kg: testes (hypocellularity of seminiferous epithelium), epididymides (desquamated seminiferous epithelial cells) Full recovery of all effects

Table 8: Overview of repeat dose toxicity studies in monkeys with main findings

Species Number/Group Study ID	**Duration**	**Route Dose (mg/kg)**	**Major findings**
Cynomolgus monkey 1M/1F SBL47-83 GLP	2 weeks	Oral capsules 0, **1**, 10, 100 (2-fold trituration with lactose)	100 mg/kg: soft/watery stool, ↓ food consumption and body weight, ↑ AST and ALT, bilirubin, BUN, creatinine Arterial fibrinoid necrosis in gallbladder (M); mucosal atrophy in colon, duodenum, cecum, rectum; inflammation of duodenal glands 10 mg/kg: ↓ food consumption and body weight Arterial fibrinoid necrosis in colon (F), mucosal atrophy in colon (F)

Cynomolgus monkey 3M/3F (LD) 5M/5F (control, MD&HD) SBL47-86 GLP	4 weeks + 4 week recovery	Oral capsules 0, **<u>0.3</u>**, 3, 30 (3-fold trituration with lactose)	30 mg/kg: Lethality (1F, Day 21), ↓ food consumption and body weight, anorexia, watery stool, proteinuria ↑ AST, ALT, bilirubin, BUN, creatinine Histologic lesions in kidney (glomerulopathy), testes (hypocellularity of seminiferous epithelium), duodenum (decreased mucus and inflammation of the duodenal glands), vascular lesions (arterial fibrinoid necrosis/degeneration in gallbladder, stomach, cecum, uterus & focal hemorrhages in the intestine, gallbladder and choroid plexus) 3 mg/kg: vascular changes in gallbladder and focal hemorrhage in the choroid plexus (1M) Recovery of all lesions (histologic lesions in testes only partially recovered)
Cynomolgus monkey 3M/3F SBL47-94 GLP	13 weeks	Oral gavage 0, **<u>0.1</u>**, 0.5, 3 (water for injection/ solution)	3 mg/kg: Lethality (1F, Day 75), anorexia, ↓ body weight, watery stool Histologic lesions in kidney (glomerulopathy), duodenum (atrophy of duodenal gland), ovaries (follicular atresia) 0.5 mg/kg: follicular atresia in the ovaries
Cynomolgus monkey 4M/4F SBL038-031 GLP	39 weeks	Oral gavage 0, **<u>0.1</u>**, 0.5, 3 (water for injection)	3 mg/kg: Lethality (1M, Day 51), anorexia, ↓ body weight, watery stool Histologic lesions in kidney (glomerulopathy), gallbladder (focal arterial degeneration/fibrinoid necrosis, submucosal inflammatory cell infiltration, choroid plexus in the brain (eosinophilic exudate, arterial fibrinoid necrosis), femur (increased thickness of epiphysial growth plate), duodenum (atrophy of duodenal gland, duodenal crypt hyperplasia), ovaries (follicular atresia) Other changes observed in the vagina (epithelial atrophy), pituitary (vacuolation of basophilic cells), and pancreas (decreased zymogen granules) occurred secondary to pharmacology-related changes. ↓ incidence of menstruation 0.5 mg/kg: Histologic lesions in kidneys (glomerulopathy), femur (increased thickness of epiphysial growth plate), and ovaries (follicular atresia) ↓ incidence of menstruation

Note: NOAEL values are indicated in bold and are underlined.

Genotoxicity

The genotoxicity of lenvatinib was evaluated in a standard battery of in vitro and in vivo studies. The battery consisted of the in vitro reverse mutation assay in bacteria (Ames test), in vitro mouse lymphoma tk assay, and in vivo micronucleus assay in rats.

Table 9: Overview of genotoxicity studies with lenvatinib mesilate

Type of test/study	**Test system**	**Concentrations/ Metabolising system**	**Results**

ID/GLP			
Gene mutations in bacteria S03007 GLP	*S. typhimurium* (TA98, TA100, TA1535, TA1537) + E.coli strain WP2 *uvrA*	Up to 5000 µg/plate +/- S9	Negative
Gene mutations and chromosome aberrations in mammalian cells S03008 GLP	L5178Y TK+/- Mouse Lymphoma	1) 3h treatment +/- S9 100-200 µg/ml 2) 24h treatment -S9 Up to 22.5 µg/ml	Negative
Chromosomal aberrations *in vivo* S05032 GLP	SD Rat, micronuclei in bone marrow	Tested up to the limit dose 2000 mg/kg	Negative

Carcinogenicity

In accordance with the ICH S9 guideline which states that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, no study evaluating the carcinogenic potential of lenvatinib was submitted.

Reproduction Toxicity

In accordance with the ICH S9 guideline, the reproduction and developmental toxicity assessment for lenvatinib is comprised of only EFD studies in both rats and rabbit. Because lenvatinib was teratogenic in the rat and rabbit EFD studies, fertility and early embryonic development studies, and pre- and postnatal development toxicity studies were not conducted.

Table 10: Rat embryo-fetal development studies with lenvatinib mesilate

Species Number/Group Study ID	Duration	Route Dose (mg/kg)	Major findings
SD rat 7F S05104 Not GLP	Day 6 to Day 17 of pregnancy	Oral gavage 0, 0.2, 2, 15, 100 (water/ solution up to 15 mg/kg or 75% PEG 400/ suspension for 100 mg/kg)	≥ 2 mg/kg: Decreased body weight (–18% to –29% on Day 20 of pregnancy) and food consumption 100% post-implantation loss due to early embryo-fetal resorption 0.2 mg/kg: No toxicity in dams and foetuses

SD rat 20F S05152 GLP	Day 6 to Day 17 of pregnancy	Oral gavage 0, 0.1, 0.3, 1.0 (water/ solution)	1 mg/kg: ↓ food consumption and body weight (–14% on Day 20 of pregnancy) ≥0.3 mg/kg: ↓ fetal body weights ≥0.1 mg/kg: fetal external abnormalities (mandibular macrognathia, cryptophtalmia, abnormal tails, parietal edema) and skeletal abnormalities (discontinued rib cartilage, hemicentric thoracic centrum, split cartilage of thoracic centrum, retardation of fetal ossicifation split of vertebral centrum)

Table 11: Rabbit embryo-fetal development studies with lenvatinib mesilate

Species Number/Group Study ID	**Duration**	**Route Dose (mg/kg)**	**Major findings**
NZW rabbit 3F S05062 Not GLP	4 days	Oral gavage 0, 25, 100, 400 (75% PEG 400/ Aqueous solution)	All doses: ↓ body weights, food consumption (minimal to no on Day 4 at ≥100 mg/kg), reddish gastric mucosa 400 mg/kg: few feces
NZW rabbit 5F S05063 Not GLP	Day 6 to Day 18 of pregnancy	Oral gavage 0, 0.8, 4, 20 (water for injection/ solution)	20 mg/kg: Moribund condition (1F), few feces, ↓ activity, ↓ food consumption and body weight 4 mg/kg: ↓ food consumption and body weight, abortion (2F) 0.8 mg/kg: abortion (2F) All doses: complete fetal resorption, vaginal hemorrhage
NZW rabbit 5F S05119 Not GLP	Day 6 to Day 18 of pregnancy	Oral gavage 0, 0.03, 0.1, 0.3 (water for injection/ solution)	0.3 mg/kg: 1 abortion on Day 21 ≥0.1 mg/kg: slight ↑ post-implantation loss, ↓ live fetuses
NZW rabbit 20F S06009 GLP	Day 6 to Day 18 of pregnancy	Oral gavage 0, 0.03, 0.1, 0.5 (water for injection/ solution)	0.5 mg/kg: ↓ food consumption (up to -47%) and body weight (up to -5.8%) abortion (7F), complete resorption (10F) 1 live fetus with multiple anomalies (retroesophageal subclavian artery, fused rib, thoracic hemivertebra and misshapen arch of lumbar vertebra) 0.1 mg/kg: fused rib (each fetus)

A 2-week dose range finding study in juvenile rats

In order to determine the dosing regimen and the dose levels for the pivotal study in juvenile rats, a 2-week dose range-finding study was conducted with 2 phases. Lenvatinib mesilate was administered

orally, by gavage, once daily for 2 weeks to male and female SD rats (5 animals/group/sex) at doses of 0 (vehicle control, water for injection), 0.2, 0.4, 1, or 5 mg/kg from postnatal day (PND) 7 (Phase 1) or at doses of 0, 0.4, 1, 5, 25 mg/kg from PND21 (Phase 2).

Cmax and $AUC_{(0-24)}$ increased dose-proportionally, and there were no biologically significant differences in systemic exposure between males and females. Following repeated administration, the systemic exposure on Day 14 was relatively lower than on Day 1; however, these differences were not considered biologically significant by the applicant.

An overview of the findings including toxicokinetics (as mean values of male and female data) is presented below.

Table 12: 2-week dose range-finding study in juvenile rats

Doses (mg/kg)	**Toxicities**	**Cmax (ng/mL)**	**AUC (ng.h/mL)**
Phase I (dosing initiated on PND 7)			
0.2	Slight changes in BW, BUN and bone measurement	D1: 128.09 D14: 77.47	1289.96 737.25
0.4	Less severe changes in BW and bone measurement, and increases in BUN and total cholesterol Histology: changes limited to the incisor, kidneys, heart, and adrenals All changes were reversible after 14-day recovery	D1: 203.71 D14: 143.1	2810.07 1122.83
1	**Mortality : 7 out of 8/sex (day 4-13), attributed to severe intestinal toxicity sometimes accompanied by peritonitis.** Decreased BW, changes in bone measurement (shorter/narrower bone) and delayed eyelid opening Histology: incisor (dysplasia), kidneys (glomerulopathy), adrenals (sinusoidal dilatation and cortical necrosis), bone (↑epiphysial growth plate), heart (thrombosis), and intestines (mucosal inflammatory cell infiltration).	D1: **481.61** D14: ND	**5666.93** ND
5	**Mortality : 8 out of 8/sex (day 8-12)** See 1 mg/kg	D1: 4051.32 D14: ND	46197.93 ND
Phase II (dosing initiated on PND 21)			
0.4	No toxicologically significant changes	D1 : 172.88 D14 : 125.82	1404.15 972.58
1	No toxicologically significant changes	D1 : 456.42 D14 : 321.62	3298.06 1928.87
5	Less severe changes in BW and FC in males and bone measurement in both sexes Histology: changes limited to the incisors, adrenals, and bone	D1 : 2893.37 D14 :2270.39	22007.37 12441.32
25	**Moribond condition in 1 out of 8/sex on last day, related to fasting** Decreased BW and FC, delayed vaginal opening and shorter/narrower bone	D1 :15712.41 D14 :5678.36	128762.71 60448.51

	↑ ALT, AST, BUN, total bilirubin, and total cholesterol, ↓ glucose and Ca Histology: incisor (dysplasia), kidneys (glomerulopathy), adrenals (sinusoidal dilatation and cortical necrosis), bone (↑epiphysial growth plate), intestines (inflammation/ cystic dilatation in duodenal glands), testes (hypocellularity), and brain (eosinophilic exudate and arterial fibrinoid necrosis in choroid plexus).		

In phase I, the lowest dose of 0.2 mg/kg can be considered as the NOAEL, while in phase II, the dose of 1 mg/kg was considered to be NOEL.
In summary, toxicity of lenvatinib was more prominent in PND7 juvenile rats than PND21 rats. Lenvatinib mesilate at doses of 1 mg/kg and higher were lethal in PND7 animals while no death was observed up to 25 mg/kg in PND21 animals.

An 8-week toxicity study in juvenile rats

Because of the severe toxicities observed in the DRF when dosing the animals from PND7, the pivotal study was conducted with animals of the age of PND 21. Lenvatinib mesilate was administered orally by gavage once a day for 8 weeks to male and female SD rats (10 animals/group/sex) from PND 21 at doses of 0 (vehicle control, water for injection), 0.4, 2, or 10 mg/kg.

The Cmax and $AUC_{(0-24)}$ were increased proportionally. No gender difference and no effect of repeated dosing on Cmax and $AUC_{(0-24)}$ was observed. Differences in systemic exposure observed following repeated administration were not considered biologically significant by the applicant.

An overview of the findings including toxicokinetics (as mean values of male and female data) is presented below.

Table 13: 8-week toxicity study in juvenile rats with a 4-week recovery period

Doses (mg/kg)	Toxicities	Cmax (ng/mL)	AUC (ng.h/mL)
0.4	No significant changes	D1: 266 D56: 235	1882 1507
2.0	• Broken teeth (incisors) from Day 31, ↓ BW gain and FC • In the open field test, the number of rearing was decreased in males. • Clinical pathology: ↑ WBC, NEU, and ALT. • Changes in the bone measurement (short, narrow). • Histopathology changes: limited to the incisors, femur, and kidneys.	D1: 1428 D56: 1896	10857 8575
10	**Mortality :** 6M, 7F between Day 26 and Day 51, accompanied by diarrhea, ↓ BW and FC Death/moribundity attributed to primary duodenal lesions with complications including occasional bacterial infection. • Diarrhea and broken teeth (incisors) from Day 18 or 22, blackish stool • ↓ BW and FC resulted in the secondary delay in physical development (prepuce separation/vaginal opening). • Open field test: delay in latency, decreased number of square ambulation, and decreased rearing. • Clinical pathology: o ↓RBC, HGB, HCT, WBC, Glu, TP, Alb, Glo, and Ca o ↑NEU, ALT, AST, ALP, BUN, and T-Chol • Histopathology: incisors (dysplasia), bones (increased epiphysial growth plate/cartilage/articular cartilage), kidneys (glomerulopathy and glomerulonephropathy associated with proteinuria), adrenals (sinusoidal dilatation and cortical necrosis), duodenum (cystic dilatation and inflammation of duodenal glands), and brain (perivascular eosinophilic exudate and arterial fibrinoid necrosis in choroid plexus). • Changes in the bone measurement (short/narrow bone) were considered related to growth retardation and/or histologic changes in the bone. After **recovery:** sporadic diarrhea at 10 mg/kg and broken teeth at 2 mg/kg Tendency to recover butBW, FC of 2 and 10 mg/kg groups still lower than control, proteinuria still present and bone still short/narrow. Minimal residual histologic changes in the incisors, femur, kidneys, adrenals, and duodenum.	D1: **7939** D56: **6356**	**56492** **38510**

Toxicokinetic data

Rats

The median time at which the highest drug concentration occurred (tmax) was between 0.25 and 1.5 hours after administration. No apparent gender difference was observed in the pharmacokinetic parameters. The Cmax and $AUC_{(0-24)}$ of lenvatinib increased approximately dose-proportionally from 0.4 to 10 mg/kg on Days 1 and 181 (149) in males and females, respectively. The pharmacokinetic parameters of lenvatinib were not significantly affected by repeated administration, except at doses of 30 mg/kg and above, the mean systemic exposure decreased after a 4-week administration.

Dogs

The median tmax was 2 hours after dosing. The mean Cmax and AUC(0-24) of lenvatinib increased dose proportionally from 0.1 to 0.5 mg/kg. No difference in the pharmacokinetic parameters was observed between males and females in any dosing group. No apparent changes in pharmacokinetic parameters as a result of repeated administration for 4 weeks were observed in males.

Monkeys

The median tmax values were between 1 and 4 hours after administration. No apparent gender difference in Cmax or AUC(0-24) was observed. The mean Cmax and AUC(0-24) generally increased in a more than dose-proportional manner from 0.1 to 3.0 mg/kg in males and females on Day 1. There were no significant changes in Cmax or AUC(0-24) after repeated administration for up to 39 weeks.

Table 14: Comparative overview of AUC values at steady state in rats, dogs, monkeys and humans

	Steady State AUC (µg·h/mL)						
Species	**Rat[a]**		**Dog[b, c]**		**Monkey[d]**		**Human[e]**
Method of Administration	**PO**		**PO**		**PO**		**PO**
Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male and Female**
Dose (mg/kg)							
0.1	—	—	0.1413	0.1329	0.2051	0.2649	
0.4	3.2102	3.5546	—	—	—	—	
0.5	—	—	0.5576	0.5683	1.5418	1.2944	
2	18.2235	17.0003	2.6325	2.7832	—	—	4.224095
3	—	—	—	—	11.1901	8.3662	
6	—	—	7.1801	7.0213	—	—	
10	55.6223	71.1701	—	—	—	—	
30	—	—	15.3712	39.3136	—	—	

AUC = area under the concentration–time curve.
a: 26-week toxicity study (Study No. S08037).
b: 4-week toxicity study (1) (Study No. B-5108).
c: 4-week toxicity study (2) (Study No. S03077).
d: 39-week toxicity study (Study No. SBL038-031).
e: Dose administered was 25 mg, Cycle 2 Day 1, Study E7080-E044-101.

Table 15: Comparative overview of Cmax values at steady state in rats, dogs, monkeys and humans

	Steady State C_{max} (µg/mL)						
Species	**Rat[a]**		**Dog[b, c]**		**Monkey[d]**		**Human[e]**
Method of Administration	**PO**		**PO**		**PO**		**PO**
Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male and Female**
Dose (mg/kg)							
0.1	—	—	0.0191	0.0208	0.0332	0.0388	
0.4	0.5053	0.9497	—	—	—	—	
0.5	—	—	0.1045	0.1016	0.2904	0.2310	
2	4.0121	3.9652	0.3668	0.3771	—	—	0.544718
3	—	—	—	—	1.8855	1.7407	
6	—	—	0.5244	0.9468	—	—	
10	10.1696	19.2626	—	—	—	—	
30	—	—	1.2482	2.4443	—	—	

C_{max} = maximum observed concentration.
a: 26-week toxicity study (Study No. S08037).
b: 4-week toxicity study (1) (Study No. B-5108).
c: 4-week toxicity study (2) (Study No. S03077).
d: 39-week toxicity study (Study No. SBL038-031).
e: Dose administered was 25 mg, Cycle 2 Day 1, Study E7080-E044-101.

Local Tolerance

Specific local tolerance studies for lenvatinib have not been conducted. Local tolerance of lenvatinib was assessed by examination of the GI tissues from oral administration studies.

Other toxicity studies

An in vitro 33 NRU phototoxicity study was conducted (Study No. SBL038-070) to assess the phototoxic potential of lenvatinib because lenvatinib absorbs light within the range of 290 to 700 nm, and has an affinity to melanin based on the slow elimination of radioactivity in the tissues containing melanin. These results showed that lenvatinib had no phototoxic potential under the conditions employed in the in vitro 3T3 NRU phototoxicity test.

2.3.5. Ecotoxicity / environmental risk assessment

Table 16: Summary of main study results

Substance (INN / Invented Name): Lenvatinib / Lenvima			
CAS-number: 857890-39-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake-flask	3.30	No Potential PBT
PBT-statement :	The compound is not considered as PBT nor vPvB		

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00012	µg/L	< 0.01 threshold

Lenvatinib $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log K_{ow} does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

Lenvatinib was evaluated for its inhibitory activity against a variety of kinases. The most sensitive kinases for lenvatinib included VEGFR (1, 2, and 3), RET, FGFR (1, 2, 3, and 4), PDGFRα, and KIT. The precise mechanism of action of lenvatinib is not elucidated, but it has shown mainly antiangiogenic properties *in vitro* and *in vivo*, and direct inhibition of tumour growth was also observed in *in vitro* models. (see SmPC section 5.1).

It should be noted that at therapeutic dose levels of 24 mg/day, total C_{max} amounted to 573 ng/ml. Taking into account 98.62% protein binding, free C_{max} attained 7.9 ng/ml. As such IC_{50} levels for antiproliferative effects on medullary and follicular thyroid cancer cell lines are 4.2- to 205-fold higher than the free plasma concentrations at human therapeutic dose levels. The antitumor activity *in vitro* of RET-gene fusion driven tumour models occurs at plasma exposures 2- to 7-fold above free plasma concentrations at therapeutic dose levels. As such the anti-tumour effect of lenvatinib is considered to be primarily due to its anti-angiogenic action and where relevant to its inhibition of oncogenic RET fusion signaling and thus direct inhibiton of tumour growth. Limited effects on FGFR1-4 are expected.

Regarding the potential secondary pharmacodynamic effects of lenvatinib, no significant binding (greater than 50% inhibition) of lenvatinib to any of the 50 receptors was observed at the tested concentrations with the exception of binding to the 5-hydroxytryptamine (serotonin) receptor 1B (58%) and human norepinephrine (noradrenalin) transporter (50%) at 10 µmol/L (5.2 µg/ml). These are not considered relevant at human therapeutic dose levels.

Results of the non-clinical safety pharmacology studies suggest that lenvatinib has a low potential for exerting adverse effects on the CNS, cardiovascular system, or the respiratory system. The lack of effect on ECG parameters in the *in vivo* study and the weak inhibitory effects of lenvatinib in the hERG assay at a concentration approximately 10-fold higher than the total maximum observed concentration (C_{max}) at the clinical dose of 25 mg (0.544718 µg/mL from Day 1 of Cycle 2 in Study E7080-E044-101) and 785-fold higher than the free C_{max} at the human therapeutic dose, suggest that lenvatinib has a low potential to cause QT prolongation. No significant effects on heart rate and mean blood pressure were noted in the *in vivo* study in dogs. However, hypertension is an identified risk associated with clinical use of lenvatinib and other inhibitors of the VEGF/VEGFR pathway (see RMP). Furthermore, in the lenvatinib clinical studies, there was a numerically higher incidence of QTc-prolongation events with lenvatinib in patients with advanced malignancy and associated complications (see clinical safety section).

In human liver microsomes, M2 (me114, demethylated form of lenvatinib) was identified as the major metabolite and CYP3A4 was the predominant enzyme ($\geq$ 80%) involved in the CYP-dependent metabolism of lenvatinib. Major metabolic pathways in rats and monkeys are suggested to be oxidation by CYP and aldehyde oxidase (AO), and conjugation by glutathione. These pathways are qualitatively the same in humans. Quantitative comparisons between species have not been discussed. However as can be concluded from the mass balance study of [^{14}]C-Lenvatinib in Humans (E7080-E044-104), the identified

human metabolites are limited to small percentages, with the so-called major metabolite M2 accounting for 4.76% in feces and 0.133% in urine (and around the limit of quantification in plasma (<1 ng/mL)).

The contribution of lenvatinib metabolites to the overall pharmacological activity is considered negligible.

Lenvatinib and its metabolites are excreted in rat milk with concentrations being higher than those in plasma. It is not known whether lenvatinib is excreted in human milk (see SmPC section 5.3). Excretion of lenvatinib in milk is addressed in the RMP. A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding (see SmPC sections 4.6 and 4.3).

Regarding drug-drug interaction potential, lenvatinib showed minimal (CYP3A) or no induction potency on CYPs, UGTs and P-gp up to 3 µmol/L in human hepatocytes.

For intestinal enzymes induction, the studied exposure range of lenvatinib (0.3 µmol/L, 1µmol/L and 3µmol/L) proposed in study n°XT063020 do not to cover the maximum concentration according to the guideline on the investigation of drug interactions. Additional physiologically based PK (PBPK) simulations to investigate the DDI risk for lenvatinib and the CYP3A4 probe substrate, midazolam, where all inhibition effects were disabled, and only the effect of induction was kept, was conducted. However, the *in vitro* data on the potential induction, in particular induction of CYP 3A4 in the intestine, are not considered sufficient. In this context, an *in vivo* study with midazolam as a probe substrate for CYP3A4 should be provided post-marketing (see clinical pharmacokinetics and RMP) to investigate adequately the potential of lenvatinib for CYP3A4 induction. *In vitro* data that could generate a better estimate of the induction activity of lenvatinib could be provided concomitantly.

All IC_{50} values for CYPs, UGTs, AO, and transporters were more than 1 µmol/L, and thus, the potential for clinical DDI of lenvatinib by inhibition of these drug metabolizing enzymes and drug transporters in liver and kidney is considered to be low.

In addition, two clinical drug-drug interactions studies were conducted (Study E7080-A001-004 and study E7080-A001-007) in which it was shown that the impact of ketoconazole (CYP3A4/P-gp inhibitor) on lenvatinib human PK was small and that repeated administration of rifampicin (CYP3A4/P-gp induction) did not lead to clinically relevant interaction (see clinical pharmacokinetics); thus indicating that the potential for drug-drug interactions of lenvatinib via CYP3A and P-gp as a victim was low.

Toxicology

Repeated oral administration of lenvatinib to SD rats (up to 26 weeks), beagle dogs (up to 4 weeks), and cynomolgus monkeys (up to 39 weeks) resulted, at clinically relevant exposures, in toxicological changes in various organs and tissues related to the expected pharmacologic effects of lenvatinib including glomerulopathy, testicular hypocellularity, ovarian follicular atresia, gastrointestinal changes, bone changes, changes to the adrenals (rats and dogs), and arterial (arterial fibrinoid necrosis, medial degeneration, or haemorrhage) lesions in rats, dogs, and cynomolgus monkeys. Elevated transaminase levels asociated with signs of hepatotoxicity, were also observed in rats, dogs and monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated (see SmPC section 5.3).

Soft stool and watery stool were observed as GI effects in rats, dogs, and monkeys and were accompanied with histopathologic changes including hemorrhage, inflammation, ulcer, mucosal atrophy, submucosal edema and crypt hyperplasia. In particular, bloody and blackish stool were observed in dogs at lethal doses. All species showed anorexia at higher doses and experienced lethality/severe morbidity. The corresponding plasma exposures in rats, dogs and monkeys to these lethal doses were about 10–fold higher, 2-fold lower, or 1.7-fold higher, respectively, than the ones obtained in humans at the therapeutic recommended dose. Reversibility appeared after a 4-week off-dose period. GI perforation, fistula

formation and significant body weight loss have been observed in clinical trials with lenvatinib. Some of the gastrointestinal toxicities may be related to the expression of VEGFR1 in the gastrointestinal tract (Hagedorn et al., 2005). Human data on VEGFR1 expression in the duodenum are not available. The relevance for humans of the duodenal lesions observed in rats and monkeys can therefore not be excluded. Gastro-intestinal toxicities have been included in the RMP as important potential risk (see RMP).

Lenvatinib caused bone changes characterized by increased thickness of epiphysial growth plate in rats and monkeys and dysplasia in incisors in rats as evidenced by white discoloration and fracture. Partial reversibility was apparent in rats. Bone lesions were more pronounced and occurred earlier in rats (after 4 weeks, at 10 mg/kg) compared to monkeys (after 39 weeks, at 0.5 mg/kg) and incisor changes were observed in rats only. Because of the differences in growth characteristics between rodent and human bone, these lesions are not considered relevant to adult humans that lack an active growth plate. Similar effects have also not been reported during clinical trials with lenvatinib. However, the effects on bone were observed in monkeys at plasma exposures about 4–fold lower, than the ones obtained in humans at the therapeutic recommended dose of 24 mg QD. Moreover, growth plate abnormalities in children have been observed after administration of other VEGF/VEGFR blocking agents (Voss et al., Pediatr Blood Cancer, 2014) (see also juvenile studies below). Therefore, the effects on growth plate are considered to be potentially clinically relevant, in particular for children. Bone and teeth abnormalities in the pediatric population are covered in the RMP as important potential risk (see RMP).

Testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) were observed in repeated-dose toxicity studies in animals at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum tolerated human dose. These findings were reversible at the end of a 4-week recovery period (see SmPC section 5.3). In the absence of clinical data, these effects on the ovaries and testes in rats, dogs, and monkeys have been reflected in the SmPC (see SmPC sections 4.6 and 5.3). Male and female fertility is included in the RMP as important potential risk.

Pancreatic toxicity of lenvatinib was observed in rats and monkeys during nonclinical development. In addition, clinical data suggest that lenvatinib (as the other members of this class of compounds) may exert pancreatic toxicity and therefore pancreatitis was considered as an important potential risk (see RMP).

Repeated-dose toxicokinetic studies of lenvatinib in male and female rats, dogs, and monkeys conducted with once daily oral doses for up to 26, 4, and 39 weeks, respectively, indicated no systemic accumulation of lenvatinib in the toxicology studies.

Embryo-fetal toxicity was observed in the EFD studies of lenvatinib both in rats and rabbits in the absence of maternal toxicity. The NOAEL for maternal toxicity was 0.3 mg/kg in rats and 0.1 mg/kg in rabbits. A fetal NOAEL in rats could not be established because external and skeletal abnormalities were observed at the lowest dose tested (0.1 mg/kg). The fetal NOAEL in rabbits was 0.03 mg/kg. At 0.1 mg/kg an above, external, visceral, or skeletal anomalies were noted. No toxicokinetic data were provided for the rat or rabbit EFD studies. Nevertheless, the developmental toxicity was shown to occur at levels well below the human exposure (25 mg QD) by using exposures estimated from a separate study (rats) or the dose normalized to body surface area (rabbits). These findings indicate that lenvatinib has a teratogenic potential, likely related to the pharmacologic activity of lenvatinib as an antiangiogenic agent (see SmPC Section 5.3).

Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment (see sections 4.4 and 4.6).

Lenvatinib, in the presence or absence of S9 activation, showed no mutagenic effects on bacterial strains and was not mutagenic or clastogenic in the mouse lymphoma tk assay. In addition, it did not induce in vivo clastogenic effects in rat bone marrow micronucleus assay when administered orally at doses up to 2000 mg/kg. Thus, lenvatinib was not genotoxic.

In view of the observed teratogenicity and/or in accordance with the ICH S9 guideline, fertility and early embryonic development studies, pre- and postnatal development toxicity studies and carcinogenicity studies were not conducted which is considered acceptable.

Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21 and was observed at exposures that were respectively 125- or 12-fold lower compared with the exposure at which mortality was observed in adult rats, suggesting an increasing sensitivity to toxicity with decreasing age (see SmPC section 5.3). Though mortality was attributed to complications related to primary duodenal lesions, additional toxicities to immature target organs may also have contributed.

The toxicity of lenvatinib was more prominent in younger rats (dosing initiated on PND7) compared with those with dosing initiated on PND21 and mortality and some toxicities were observed earlier in the juvenile rats compared with adult rats administered the same dose level. Growth retardation, secondary delay of physical development, and lesions attributable to pharmacologic effects (incisors, femur [epiphyseal growth plate], kidneys, adrenals, and duodenum) were also observed in juvenile rats (see SmPC section 5.3).

In conclusion, there are remaining uncertainties with respect to the exact aetiology and hence the extrapolation to children of the increased toxicity risk. It is therefore unknown until what corresponding age in children this increased sensitivity may persist and caution is needed in the absence of clinical data (see SmPC sections 4.2 and 5.3).

Lenvatinib was negative in the in vitro 3T3 neutral red uptake (NRU) phototoxicity test.

Specific local tolerance studies have not been conducted since the product is administered orally, which is considered acceptable.

Regarding the environmental risk, LogKow was determined to be 3.3 using the shake-flask method. Therefore, an assessment for PBT is not necessary. The applicant provided published data to calculate the prevalence of the disease population targeted by Lenvima and this was used to refine Fpen. Using the refined Fpen, a PECsw was calculated that was far below the action limit. Therefore, lenvatinib is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Apart from the toxicities that were included in the RMP as described above, there are no specific non-clinical issues that require further action post-marketing.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 17: Tabular overview of clinical studies

- Biopharmaceutics and clinical pharmacology studies in the lenvatinib development program

Study No. and Type	Population	Number of Subjects[a]	Treatment (Monotherapy or Combination)
Phase 1/1b Studies			
E7080-A001-001 Comparative bioavailability	Healthy subjects	20	NA
E7080-A001-002 Thorough QT study	Healthy subjects	52 (51 received lenvatinib)	NA
E7080-A001-003 Food effect study	Healthy subjects	16	NA
E7080-A001-004 DDI study with ketoconazole	Healthy subjects	18	NA
E7080-A001-005 Renal impairment	Healthy subjects and subjects with renal impairment	8 healthy subjects; 18 subjects with renal impairment	NA
E7080-A001-006 Hepatic Impairment	Healthy subjects and subjects with hepatic impairment	8 healthy subjects; 18 subjects with hepatic impairment	NA
E7080-A001-007 DDI study with rifampin	Healthy subjects	15	NA
E7080-A001-008 Comparative bioequivalence	Healthy subjects	60	NA
E7080-E044-104 Mass balance study	Subjects with solid tumors or lymphomas	6	Monotherapy

- Main clinical efficacy and safety studies in the lenvatinib development program

Protocol Number / Study Status	Indication	Study Design and Lenvatinib Dosage	Number of Subjects Treated
Thyroid Cancer: Controlled Pivotal Phase 3 Study			
E7080-G000-303 D-B Randomization Phase: **Completed** Extension Phase, including OOL: **Ongoing** Efficacy cut-off: 15 Nov 2013 Safety cut-off: 15 Mar 2014	RR-DTC	Multicentre, randomized 2:1, double-blind, placebo-controlled, parallel group, 2-arm Randomization Phase: LENV 24 mg or placebo QD continually OOL LENV Extension Phase: (placebo-treated subjects only) Starting dosage of LENV 24 mg QD continually. After Protocol Amendment 04: starting dosage of LENV 20 mg QD continually	Total, 392 Randomized Phase: LENV, 261 Placebo, 131 OOL Lenvatinib: Total, 111 LENV 24, 84 LENV 20, 27
Thyroid Cancer: Phase 2 Studies			
E7080-G000-201 Treatment Phase: **Completed** Extension Phase: **Ongoing**	Advanced thyroid cancer: RR-DTC, MTC	Multicentre, open-label, single-arm LENV 24 mg QD continually (2 subjects received LENV 10 mg BID)	Total, 117 DTC, 58 MTC, 59
E7080-J081-208 **Ongoing**	Advanced thyroid cancer: RR-DTC, MTC, ATC	Multicentre, open-label, single-arm LENV 24 mg QD continually	Total, 35[a] DTC, 22 MTC, 4 ATC, 9
Phase 1 and Phase 2 Studies in Other Indications			
E7080-E044-101 Completed	Advanced solid tumours or lymphoma	Phase 1, open-label, dose-escalation S-A LENV 0.2 mg to 32 mg continual QD dosing	Total, 82
E7080-A001-102 Completed	Advanced solid tumours, lymphoma or melanoma	Phase 1, open-label, dose-escalation S-A LENV intermittent (0.1 to 3.2 mg) or continual (3.2 to 12 mg) BID dosing, or in combination with temozolomide	Total, 109 MTC, 5 DTC, 1 Schedule 1: 18 (intermittent) [b] Schedule 2: 59 (continual) [c] Schedule 3: 32 (combination)[b]
E7080-E044-104 Completed	Advanced solid tumours or lymphoma	Phase 1, open-label, nonrandomized S-A LENV 24 mg, single radiolabelled dose (Study Phase) and continual QD nonradiolabelled dosing (Ext. Phase)	Total, 6

Protocol Number/ Study Status	Indication	Study Design and Lenvatinib Dosage	Number of Subjects Treated
E7080-J081-105 Completed	Advanced solid tumours	Phase 1, open-label, single-centre, dose escalation S-A LENV 20 mg or 24 mg continual QD dosing	Total, 9
E7080-G000-203 Completed	Recurrent malignant glioma	Phase 2, open-label, multicentre, 3-cohort, S-A LENV 24 mg continual QD dosing (all cohorts) vs. bevacizumab (Cohort 1 only)	Cohort 1: 80 (LENV, 42) Cohort 2: 39 Cohort 3: 32
E7080-G000-204 Completed	Advanced endometrial cancer who progressed after platinum-based, first-line chemotherapy	Phase 2, open-label, single-arm, 2-stage, multicentre S-A LENV 24 mg continual QD dosing	Total, 133
E7080-G000-206 Completed	Unresectable Stage III or IV melanoma (with [Cohort 2] and without [Cohort 1] *BRAF* V600E mutation)	Phase 2, open-label, 2-cohort, multicentre S-A LENV 24 mg continual QD dosing (both cohorts)	Total, 182 Cohort 1, 93 Cohort 2, 89
E7080-J081-103 Completed	Solid tumors	Phase 1, nonrandomized, singlecenter, multidose, openlabel, dose escalation study E7080 administered orally at doses ranging from 0.5 mg BID to 20 mg BID (1 to 40 mg/day) for 2 weeks followed by a 1-week withdrawal period	40/ 28 enrolled but 27 treated

"Complete" study is defined as one in which the protocol-defined primary analysis has been conducted and a Clinical Study Report has been prepared.

ATC = anaplastic thyroid cancer, BID = twice daily, D-B =double-blind, DTC =differentiated thyroid cancer, Ext = extension, LENV =lenvatinib, MTC =medullary thyroid cancer, OOL = optional open-label (LENV treatment extension phase only for subjects who received placebo in the double-blind Randomization Phase), QD = once daily, S-A = single-agent, RR = radioiodine-refractory.

a: One additional subject was enrolled in Study 208 but was not treated.

b: Subjects who received lenvatinib intermittently (Schedule 1) or combination therapy (Schedule 3) were not included in the pooled analysis for safety.

c: Only subjects enrolled in the continual dosing, monotherapy portion of the study (Schedule 2) were included in the pooled analysis for safety. This also includes subjects from the expanded melanoma cohort.

This application is for the capsule formulation of lenvatinib. Film-coated tablets containing the drug substance lenvatinib mesilate were first developed and used in the early stages of Phase 1 and Phase 2 clinical studies including Study 201. Lenvatinib hard capsules were developed and used in all subsequent Phase 1 to 3 studies.

2.4.2. Pharmacokinetics

A number of *in vitro* studies were performed to determine the plasma protein binding, the metabolism, and the potential of Lenvatinib to be a substrate of a number of drug transporters. Lenvatinib was also tested as an inhibitor and inducer of drug metabolising enzymes and drug transporters.

The clinical pharmacology studies included 6 studies in healthy subjects (E7080-A001-001, -002, -003, -004, -007, -008), one study in healthy subjects and subjects with renal impairment (E7080-A001-005), one study in healthy subjects and subjects with hepatic impairment (E7080-A001-006), and one mass balance study in subjects with advanced solid tumours (E7080-E044-104). The clinical pharmacology studies also included studies on bioavailability of different formulations, food effect, drug-drug interaction (DDI) and potential effects on the QT interval.

The doses ranged from either 0.1 mg to 24 mg twice daily (BID) or 0.2 mg to 32 mg once daily (QD). Studies were conducted in male and female healthy subjects, individuals of different racial origin (few data on non-Caucasian and non-Asian population) and in subjects with solid tumours or lymphomas.

A population PK (PopPK) analysis (Report CPMS-E7080-007R-v1) for lenvatinib was based on pooled data collected from:

- Phase 1 trials in healthy subjects (Studies E7080-A001-001, E7080-A001-002, E7080-A001-003, E7080-A001-004, E7080-A001-007, E7080-A001-008), plus E7080-A001-005, and E7080-A001-006 which included otherwise healthy renally and hepatically impaired subjects,
- 3 Phase 1 clinical trials in subjects with solid tumours including lymphoma refractory to existing therapies or for which no treatment is available (Studies E7080-E044-101, E7080-A001-102, and E7080-J081-103), an additional Phase 1 trial in subjects with solid tumours (Study E7080-J081-105),
- a Phase 2 trial in subjects with advanced or recurrent thyroid cancer (Study E7080-J081-208),
- a Phase 2 trial in subjects with medullary and ^{131}I refractory, unresectable differentiated thyroid cancers (Study E7080-G000-201), and
- a Phase 3 trial in subjects with ^{131}I-refractory differentiated thyroid cancer (Study E7080-G000-303) was conducted.

This analysis was conducted to describe the PK of lenvatinib and identify covariates explaining intersubject variability in lenvatinib PK. The covariates included demographics, clinical laboratory data, and tumour type (DTC, MTC, and other).

Absorption

Lenvatinib, from both tablet and capsule formulations, was rapidly absorbed after oral administration with a time to reach maximum concentration of drug in plasma (t_{max}) typically observed 1 to 4 hours post-dose. The observed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ after a single dose of 24 mg (SD) in healthy volunteers were 325 (105) ng/mL, 2990 (974) ng.h/mL and 3010 (974) ng.h/mL, respectively (Study A001-005). In patients, Cmax and exposure after administration of a single 24 mg dose appear to be higher than in healthy volunteers: values of 655 (97) ng/mL and 4905 (2145) ng.h/mL have been observed for Cmax and AUC(0-24), respectively (Study A001-102). There were no data after multiple dosing in healthy volunteers.

In the POPPK analysis healthy volunteers had a 15% higher CL/F compared with subjects with malignant solid tumours.

The absolute bioavailability of lenvatinib was not determined.

Influence of food

Study E7080-A001-003

The primary objective of this trial was to determine the effect of food on the bioavailability of lenvatinib following single oral administration of a capsule containing 10 mg E7080 with and without a meal. The study was a Phase I, open-label, randomized, single-dose, 2-treatment (dosing condition), 2-period, 2-sequence, cross-over study in healthy volunteers. Sixteen subjects (12 males and 4 females) received 10 mg of E7080 as a single dose under the two different conditions (fed versus fasting) in a randomised order. Two single dose administrations (one in each of the two consecutive treatment periods) were separated by a washout period of 14 days between the two dosing. “Fasting” was defined as deprivation of food for ≥ 10 hours (tap water was allowed), whereas “fed” was defined as administration of the drug 30 minutes after the start of a standard high-fat breakfast (approximately 150 calories of protein, 250 calories of carbohydrate, and 500 to 600 calories of fat).

The administration of a single oral dose of 10 mg lenvatinib with a standard high-fat breakfast was associated with non-significant increases in lenvatinib $AUC_{(0\text{-}inf)}$ (ratio%, 90% CI: 106.3, 95.66 to 118.09) and $AUC_{(0\text{-}t)}$ fold (ratio%, 90% CI: 103.7, 92.25 to 116.50). However, Cmax point estimate was reduced by approximately 5% compared to that in the fasted state. As the 90% CIs of the ratio of this pharmacokinetic parameter were without the standard bioequivalence range, these results indicated that food delays the rate of absorption in a significant way. In addition, median t_{max} for lenvatinib was approximately 2-fold increased after administration with food (4.02 h) compared to administration in the fasted state (2.02 h).

Study E7080-E044-101

Study E7080-E044-101 was an open-label, non-randomized, dose escalation study in eighty-two male and female subjects with solid tumors or lymphomas resistant or refractory to existing therapies or for whom no treatment was available. This Phase 1 study was designed to determine the maximum tolerated dose (MTD) for lenvatinib. A pilot evaluation of the influence of food on lenvatinib pharmacokinetic at the MTD (25 mg) was also conducted in this study.

Eleven subjects entered and completed the food effect pilot study at a once daily lenvatinib dose of 25 mg (2 x 10 mg tablets and 5 x 1.0 mg tablets). These subjects were randomly assigned to receive a single oral dose of 25 mg lenvatinib administered after a high-fat breakfast (approximately 150 calories of protein, 250 calories of carbohydrate, and 600 calories of fat) or following at least a 10 hour fast on the morning or either Cycle 1 Day 15 or Cycle 1 Day 22. The effect of food on lenvatinib pharmacokinetics was evaluated by comparing $AUC_{0\text{-}24}$ and Cmax.

Administration of a single oral dose of 25 mg lenvatinib after a standardized high fat breakfast had no impact on the mean plasma exposure ($AUC_{0\text{-}24}$) for lenvatinib. Compared to overnight fasting, the mean maximum plasma concentration (C_{max}) of lenvatinib was slightly reduced in the presence of food (2 %). The 90% CIs of the ratio of this pharmacokinetic parameter being without the standard bioequivalence range, it indicated that food significantly decreases the rate of absorption of lenvatinib. Moreover, t_{max} was prolonged in the fed conditions (5 hours, median value) compared with the fasted conditions (2 hours, median value) and the difference was statistically significant ($p = 0.0146$), indicating that dosing with food delays the time to maximum plasma concentrations (t_{max}).

Bioequivalence (BE)

The relative bioavailability of the 10 mg capsule and 10 mg tablet was determined in healthy volunteers (E7080-A001-001 (Relative Bioavailability)). This was a single-centre, single-dose, open-label, randomized, 2-period cross-over study conducted in 20 healthy men under fasting conditions. The objective was to determine the relative bioavailability of a capsule formulation to a tablet formulation. The subjects received either one 10-mg capsule or one 10 mg tablet on the first day of the first period. The subjects received the study drug following an overnight fast of at least 10 h. They received the alternate formulation on the first day of the second period. There was a 1-week (7-day) washout between the 2 treatment periods. Nineteen subjects completed the study.

Mean total exposure ($AUC_{(0\text{-}inf)}$) of the 10-mg lenvatinib capsule was approximately 10% less than that of the 10-mg lenvatinib tablet. Mean C_{max} for the capsule was approximately 14% lower than that of the tablet. Median t_{max} was 2.0 hours for both the capsule and tablet. Mean $t_{1/2}$ values for the capsule and tablet were comparable (27.6 h and 29.1 h, respectively). The variability in exposures was low, with the highest coefficients of variation, C_{max}, less than 26% for both formulations. Even though the study was not powered for BE, the 90% confidence intervals for $AUC_{(0\text{-}inf)}$ and $AUC_{(0\text{-}t)}$ were within the 80% to 125% confidence interval typically used to demonstrate BE. However, the lower bound of the confidence interval for Cmax (79.84%) was outside the 80% bound.

In vitro dissolution studies and the bioequivalence study E7080-A001-008 showed the bioavailability equivalence among lenvatinib 10-mg capsules with the different Type-C crystal levels. Absorption and disposition profiles of lenvatinib were consistent with linear PK over a 0.8-mg to 32-mg range for single and repeat dose (Study E7080-E044-101).

A bioavailability study comparing the 4-mg to the 10-mg capsule was not done. The 4-mg capsule was shown to have a similar dissolution profile as 10-mg capsule. Additionally, proportionate increases in lenvatinib exposure (based on dose normalized $AUC_{(0\text{-}24)}$ and C_{max}) following single doses and at steady-state, were seen over the 0.2-mg to 32-mg QD dose range (E7080-E044-101) and the 0.1- to 12-mg BID dose range (E7080-A001-102). Also, the 4-mg strength capsule is proportionally similar in its active and inactive ingredients to the 10-mg strength.

The 4- and 10-mg capsules (and occasionally the 1-mg) were used in most of the Phase 1 and 2 trials. The 4- and 10-mg capsules were used in the Phase 3 trial and are the intended commercial formulation.

Distribution

As there is no study with intravenous administration of lenvatinib, the volume of distribution has not been determined. Apparent volume (V/F) was generally not reported in the studies with healthy volunteers. Only in the renal and hepatic impairment studies (Studies A001-005 and A001-006), values were reported. The total values were 428 (153) L and 408 (216) L, respectively, and the unbound values were 6700 (4460) L and 6760 (6370) L, respectively. In the patient studies, the reported Vz/F values ranged from 50.5-92 L (Study E044-101) and 136-312 L (Study J081-103). At steady state, the values ranged from 43.2-121 L (Study E044-101) and 155-261 L (Study J081-103).

The estimated V/F values from the POPPK analysis showed values of 49.3, 30.7 and 37.1 L for the central and 2 peripheral compartments, respectively.

In humans, the *in vitro* plasma protein binding of lenvatinib (concentration range: 0.3 to 30 µg/mL, mesilate) was 97.87% to 98.62%, with binding mainly to albumin and to a lesser extent to α1-acid-glycoprotein and γ-globulin. Protein binding was linear across concentrations. This observation was confirmed *in vivo*, with serum protein binding values ranging from 96.6% to 98.2% (Study E7080-J081-103).

The *in vitro* blood-to-plasma concentration ratio of lenvatinib remained constant (0.589 to 0.608) in humans over the concentration range tested (0.1 to 10 µg/mL [^{14}C]lenvatinib mesilate). The predominance of lenvatinib in plasma over blood was also confirmed in the mass balance study, where blood concentrations were 29% and 36% lower than plasma concentrations for total radioactivity and lenvatinib, respectively.

Elimination

Excretion

Following Cmax, the plasma concentrations of lenvatinib declined bi-exponentially. The mean terminal elimination half-life (t1/2) of total lenvatinib ranged from 20.6 hours to 34.3 hours in the studies in healthy volunteers. The mean terminal exponential half-life of lenvatinib was approximately 28 hours. The PK of lenvatinib was characterised by an oral clearance of 6.7 L/hour (Study E7080-E044-104). In the population PK analysis, CL/F was 6.56 L/h and its %CV was 25.5%.

After administration of an oral solution of lenvatinib in the mass balance study, 85.5% of the administered dose has been found in urine or as metabolites in faeces. Degradation of lenvatinib in faeces is judged unlikely and urinary excretion of unchanged drug is negligible. Metabolism appeared to be the major elimination pathway for lenvatinib and the excretion of lenvatinib and its metabolites occurred mainly via the faecal route.

Metabolism

In vitro results with recombinant CYPs indicated that CYP3A4 was the predominant (>80%) isoform contributing to the CYP-dependent metabolism of lenvatinib in humans, followed by CYP1A2 (5.2% to 6.5%) and CYP2B6 (5.2% to 5.7%). Aldehyde oxidase (AO) is responsible for the metabolisation to M3' and M3' glucuronide.

The *in vivo* metabolism has been studied in a human radiolabelled study E7080-E044-104. In this absorption, distribution, metabolism, excretion (ADME) study, in which 24 mg of ^{14}C-lenvatinib (approximately 100 µCi (~3.7 MBq)) was administered to 3 men and 3 women with advanced solid tumours or lymphomas, who were unsuitable for, or had failed, existing therapies, most of the recovered radioactivity was found in faeces, 64% of mean total recovery, and 25% of mean total recovery recovered in urine (i.e. 89% of the dose was recovered in the excreta) (see SmPC section 5.2).

In the mass balance study, the mean recovery of ^{14}C-radioactivity was 89%, with approximately 64% excreted in the feces and 25% in the urine. In urine and faeces, 0.38% and 2.5%, respectively of the radioactive dose was found as lenvatinib. Fractions of the dose eliminated in the urine as unchanged lenvatinib were not dependent on the dose administered. The M3' metabolite was the predominant analyte in excreta (~17% of the dose), followed by M2' (~11% of the dose) and M2 (~4.4% of the dose) (see SmPC section 5.2).

In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radiochromatograms while the M2 metabolite accounted for an additional 2.5%. Based on $AUC_{(0-inf)}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively (see SmPC section 5.2).

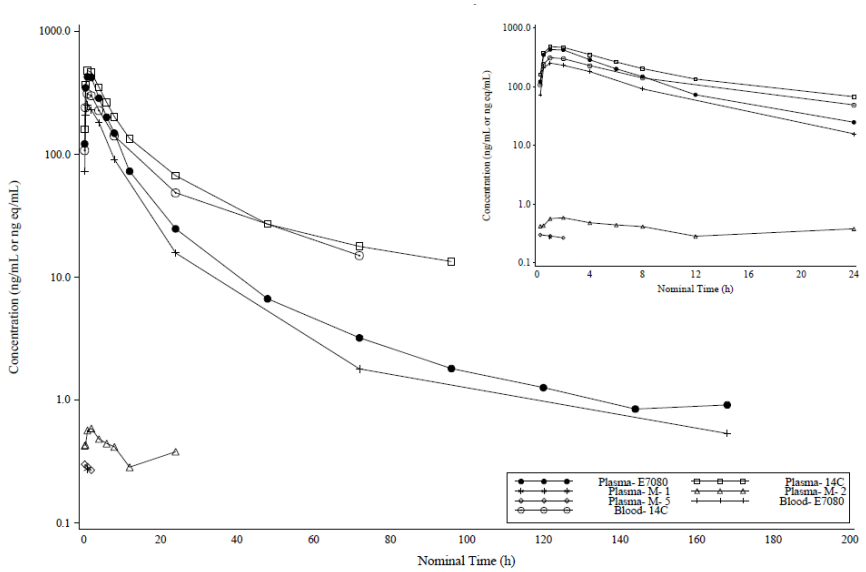
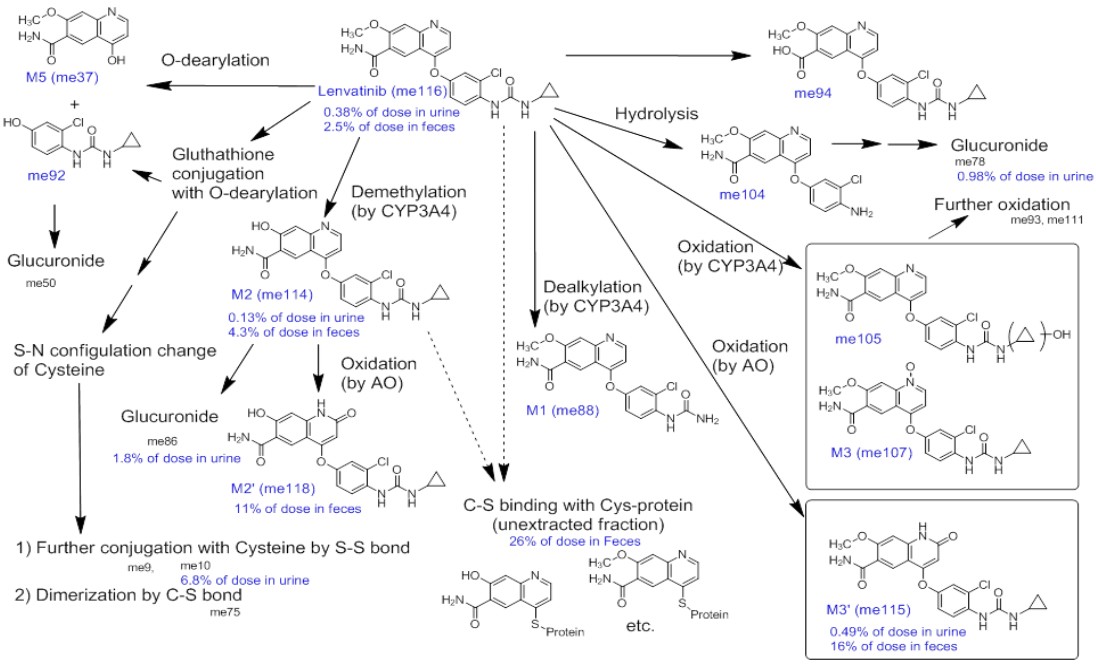


Figure 1: Semi-Log plot of mean total radioactivity, E7080 and key metabolites in plasma and blood, study phase, pharmacokinetic analysis set

Extraction recovery of radioactivity in plasma samples appeared to decrease in time (with a minimum of 10% 72h after administration) and was, for the later time-points, also highly variable (%CV up to 46%).80% of the recovered radioactivity in excreta (urine and faeces) was identified.

Based on the *in vivo* data, the following overview of metabolic pathways for lenvatinib in humans has been proposed.



In total, the contribution to lenvatinib clearance in human is summarized in the table below. The ratio of aldehyde oxidase (AO): CYP3A: non-enzymatic process is approximately 3:4:3 in humans.

Table 18: Contribution to Lenvatinib Clearance in Humans

Responsible enzyme	Contribution %	
AO	17.4%	
CYP3A	20%	27.8%
CYP3A (methanol unextractable fraction)	7.8%[a]	
Non-enzymatic (GSH derivative)	6.8%	22.8%
Non-enzymatic (methanol unextractable fraction)	16%[a]	
Sub total	68%	
Unknown (Not recovered)	11%	
AO = aldehyde oxidase, CYP = cytochrome P450, GSH = glutathione. a: maximally estimated value.		

Inter- and intra-individual variability

In normal healthy subjects, variability (as coefficient of variation [%CV] of AUC, fasted subjects) ranged from about 8% to 20%. In Study E7080-A001-102 (Combination Therapy), PK parameters exhibited moderate to high variability, with %CV estimates ranging from 19.44% to 78%. Compared to normal subjects, subjects with renal or hepatic impairment had greater variability (39% to 45%). In a formal population PK analysis, the %CV of basal apparent total clearance following extravascular administration (CL/F) was 25.5%.

In order to explain inter-individual variability in lenvatinib exposure (AUC), in the POPPK analysis for lenvatinib, the effect of various covariates was tested on CL/F, and formulation, H2-blockers, proton pump inhibitors, antacids, and combined category of pH elevating agents was tested on relative bioavailability. None of these influenced in an important way the pharmacokinetics of lenvatinib.

Dose proportionality and time dependencies

Dose-proportionality

In patients with solid tumours administered single and multiple doses of lenvatinib once daily, exposure to lenvatinib (Cmax and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32 mg once-daily (QD) (see SmPC section 5.2).

In study E7080-E044-101, the observed $t_{1/2}$ values decreased with increasing dose. However from a dose of 6.4 mg on, this appeared to be relatively stable.

When data from E7080-E044-101 and E7080-J081-103 were combined, the dose-normalized Cmax was very consistent across doses of 4 mg and higher, although variability was high across the lower doses (less than 4 mg). Cmax showed a linear profile at clinical doses, i.e., 4 mg or higher. In vitro study data indicate that lenvatinib is a substrate of permeability glycoprotein (P-gp). Thus, a likely explanation of the nonlinearity of Cmax at lower doses is that P-gp expressed in the gut has an efflux functional effect on lenvatinib, which leads to slower absorption of lenvatinib at these doses.

From the POPPK analysis, the CL/F was reported to be 6.56 L/h and this value appeared to be constant upon repeated dosing and through different dosing levels.

For the linearity in CL/F, the PK model was run without the effect of dose on CL/F. There was an increase of 128.176 points in the objective function value, from 64389.472 to 64517.648. In addition, the PK model was run without the effect of dose on F1 and again there was an increase of 62.288 points in the objective function value, from 64389.472 to 64451.76. To further investigate the relationship between dose and CL/F, the final PK model was run using only capsule formulation PK data and without estimating F1. This is of value as the term “F1” is a relative bioavailability term in the model linking the tablet and

to-be-marketed capsule formulations. Adding dose effect on CL/F decreased the objective function value by 5.067 points (from 37346.978 to 37341.901, which is not statistically significant).

Time-dependency

Upon multiple dosing, steady-state plasma concentrations were achieved within 5 days. Lenvatinib displayed minimimal accumulation at steady state. Over the dose range 3.2 to 32 mg, the median accumulation index (Rac) ranged from 0.96 (20 mg) to 1.54 (6.4 mg).

This was consistent with the approximately 28 hour half-life of lenvatinib and once daily administration. Apparent clearance and volume of distribution were generally similar between first dose and steady-state and between doses.

Special populations

In the population PK analysis, apparent total clearance following oral administration (CL/F) was 15% higher in healthy subjects compared to patients and hence the extent of exposure (AUC) was slightly lower for healthy subjects. The PK parameters of lenvatinib were similar in subjects with DTC, medullary thyroid cancer (MTC) and other tumour types.

- **Elderly**

Table 19: Pharmacokinetics in Special Populations: Elderly – Healthy Volunteers

	Age 65-74 (older subjects number)	**Age 75-84 (older subjects number)**	**Age 85+ (older subjects number)**	**Total (total number of subjects)**
Pharmacokinetic Trials – healthy volunteers				
E7080-A001-001	0	0	0	20
E7080-A001-002	1	0	0	52
E7080-A001-003	0	0	0	16
E7080-A001-004	0	0	0	18
E7080-A001-005	13	2	0	26
E7080-A001-006	0	0	0	26
E7080-A001-007	0	0	0	15
E7080-A001-008	0	0	0	60
Total:	14	2	0	233

Source: individual clinical study reports.

In the population PK analysis that included data from 196 healthy subjects and 583 patients, age was not a significant covariate that could account for the inter-subject variability in the PK of lenvatinib (CPMS-E7080-007R-v1). Median dose and weight adjusted lenvatinib exposure in cancer patients receiving lenvatinib capsules was 3480 ng•h/mL for subjects with age ≤65 years and 3710 ng•h/mL for subjects with age >65 years.

- **Impaired renal function** (study E7080-A001-005)

A Phase 1, multicentre, open-Label, non-randomized, single-dose, pharmacokinetic and safety study of E7080 (24 mg) administered to subjects with mild, moderate, and severe renal impairment and to healthy subjects was submitted to describe and compare the PK of lenvatinib from a single 24-mg oral dose of lenvatinib administered to subjects with mild, moderate, or severe renal impairment (N=6 in each

group) and to healthy subjects (N=8) distributionally matched in age, sex, and body mass index (BMI) and to describe the safety of a single 24-mg oral dose of lenvatinib. Both total (bound + unbound) and unbound drug concentrations of lenvatinib were determined. A method using a centrifugal ultrafiltration followed with LC-MS/MS was used to determine unbound lenvatinib in plasma.

C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ exhibited moderate to high variability. For subjects with mild, moderate, and severe renal impairment, overall exposure ($AUC_{(0-inf)}$) to lenvatinib was estimated to be 1.01, 0.90, and 1.22 times that of normal subjects. The half-life for lenvatinib was similar between the normal and the renally impaired subjects. Using a regression method, no statistically significant correlation between lenvatinib exposure and creatinine clearance (CL_{cr}) was observed.

Lenvatinib exposure, based on AUC0-inf data, was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively (see SmPC section 5.2)..

- **Impaired hepatic function** (study E7080-A001-006)

A Phase 1, multicentre, open-label, single-dose pharmacokinetic and safety study of lenvatinib in subjects with mild (10 mg) (Child-Pugh A), moderate (10 mg) (Child-Pugh B), and severe hepatic impairment (5 mg) (Child-Pugh C) and normal hepatic function (10 mg) evaluated the PK of lenvatinib from a single oral dose of 10 mg in subjects (N=6) with mild and moderate hepatic impairment and from a single oral dose of 5 mg in subjects (N=6) with severe hepatic impairment compared to a single oral dose of 10 mg in healthy subjects with (N=8) normal hepatic function and to assess the safety of lenvatinib in subjects with hepatic impairment compared to subjects with normal hepatic function.

The median half-life was comparable in subjects with mild, moderate, and severe hepatic impairment as well as those with normal hepatic function and ranged from 26 hours to 31 hours. The percentage of the dose of lenvatinib excreted in urine was low in all cohorts (<2.16% across treatment cohorts).

Lenvatinib exposure, based on dose-adjusted AUC0-t and AUC0-inf data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively.

- **Gender**

The effect of gender on the pharmacokinetics of lenvatinib was evaluated in the population PK analysis. No significant differences between sexes were found in lenvatinib exposure.

- **Race**

The effect of race on the pharmacokinetics of lenvatinib was evaluated in the population PK analysis. According to this POP PK analysis, the PK of lenvatinib was unaffected by race.

- **Weight**

The effect of weight on the pharmacokinetics of lenvatinib was evaluated in the population PK analysis. In this POP PK analysis, weight (37.8 – 178 kg) added as an allometric constant on CL/F and volume parameters showed a statistically significant effect, but only explained 1.2 % of the inter-individual variability on CL/F. PK simulations showed a major overlap in the steady-state exposure in the presence and absence of this covariate.

Subjects with body weight <60 kg had 36% higher exposure compared with subjects >60 kg.

Pharmacokinetic interaction studies

Based on *in vitro* metabolism and transporter data (see non-clinical aspects), drug-drug interactions of lenvatinib were designed to assess effects of P-gp inhibition, CYP3A induction and inhibition on lenvatinib as a substrate, and to assess potential for lenvatinib to inhibit CYP2C8 and CYP3A.

Effects of other drugs on the pharmacokinetics of lenvatinib (as victim)

- Study E7080-A001-004 with ketoconazole (CYP3A4 and PgP inhibitor)

The objective of the study E7080-A001-004 was to assess the influence of simultaneous CYP3A4 and P-gp inhibition using ketoconazole on lenvatinib PK following single-dose oral administration of 5 mg lenvatinib (formulated as a capsule) to healthy volunteers and to evaluate the safety, in healthy subjects, of a single dose of 5 mg lenvatinib administered with and without simultaneous CYP3A4/P-gp inhibition (ketoconazole). Ketoconazole inhibits CYP3A, P-gp and BCRP. Ketoconazole (400 mg once daily for 18 days) increased lenvatinib AUC about 15% and Cmax increased about 19% following administration of 5 mg lenvatinib on Day 5. The half-life of lenvatinib was not affected suggesting that inhibition of enterocyte P-gp was responsible for the changes observed rather than inhibition of CYP3A. In the population PK analysis, CYP3A inhibitors decreased CL/F by 7.8% (CPMS-E7080-007R-v1).

- Study E7080-A001-007 with rifampin (CYP3A4 and PgP inducer)

The objective of the study E7080-A001-004 was to assess the influence of P-gp inhibition and simultaneous P-gp and CYP3A4 induction on lenvatinib PK following single-dose oral administration of 24 mg lenvatinib to healthy volunteers and to evaluate the safety and tolerability of a single dose of 24 mg lenvatinib administered alone, following P-gp inhibition and following simultaneous induction of P-gp and CYP3A4 in healthy subjects.

Coadministration of a single dose of rifampin (600 mg) with 24 mg of lenvatinib increased lenvatinib AUC and Cmax by 31% and 33%, respectively, without prolonging half-life. Following multiple doses of rifampin (600 mg once daily for 21 days) and a single 24 mg dose of lenvatinib on Day 15, lenvatinib AUC and half-life were reduced by 18% and 27%, respectively, while Cmax was unchanged. This result reflected the net effect of enzyme induction and P-gp inhibition. The effect of strong CYP3A induction in the absence of P-gp inhibition was estimated. As expected, the effect of induction in the absence of P-gp inhibition was slightly greater than the net effect of the combination of the 2 effects of rifampin. This finding represents a worst case scenario for the effect of a strong inducer on lenvatinib exposure since it is assumed that the P-gp inhibition effect on the PK of lenvatinib is similar under induced and non-induced conditions even though it is known that P-gp is also subject to PXR mediated induction. The effect of induction was relatively small, and consistent with *in vitro* and *in vivo* metabolism data.

- Temozolomide (TMZ)

As part of a study primarily assessing the benefit of co-administration of lenvatinib with TMZ in subjects with melanoma, lenvatinib's PK parameters were assessed. This study was not designed as a formal DDI study. Coadministration of TMZ with lenvatinib (24 mg QD) did not alter lenvatinib's PK parameters.

- Carboplatin – paclitaxel

As part of a study primarily assessing the benefit of coadministration of lenvatinib with carboplatin and paclitaxel in subjects with non-small-cell lung cancer, the PK parameters of all 3 drugs were assessed (Study E7080-J081-110). This study was not designed as a formal DDI study. Lenvatinib PK parameters following coadministered with carboplatin and paclitaxel were similar to those observed with lenvatinib monotherapy. The PK parameters of carboplatin and paclitaxel with coadministration of lenvatinib were generally consistent with historical values observed without lenvatinib coadministration.

- H2-blockers, proton pump inhibitors

In the population PK analysis of lenvatinib (CPMS-E7080-007R-v1), for DDI, co-administration of CYP3A4 inhibitors and inducers, proton pump inhibitors, H2-blockers, antacids and combined category of pH

elevating agents were tested. Agents that elevate gastric pH (H2-blockers, proton pump inhibitors, and antacids) did not have a significant effect on the absorption and bioavailability of lenvatinib.

Effects of lenvatinib on the pharmacokinetics of other drugs (as perpetrator)

- Midazolam as CYP3A4 substrate

A human physiologically based pharmacokinetic (PBPK) model was developed for lenvatinib (Study DMPKA2013-156), to simulate the human AUC profiles of midazolam with or without coadministration of lenvatinib, and to assess the potential risk of drug-drug interaction (DDI) between lenvatinib and the CYP3A4 substrate midazolam.

In the original physiologically based pharmacokinetic (PBPK) model DDI simulation analysis, the fumic was calculated by Simcyp (Prediction Toolbox) based on logPo:w (partition-coefficient, the ratio of concentrations of a compound in the 1-octanol and water at equilibrium) , compound type, pKa, assay pH, and microsomal protein concentration. The fumic for CYP3A4 was calculated to be 0.503 based on 1 mg/mL microsomal protein concentration in the *in vitro* assay condition for CYP3A4 time-dependent inhibition. Fumic was also measured in an *in vitro* assay at 1 mg/mL microsomal protein concentration and determined to be 0.74. With the new fumic value, DDI simulation for lenvatinib and CYP3A4 substrate midazolam was reevaluated and the geometric mean AUC ratio (AUCR) for midazolam was determined to be 1.18 with 95% CI of 1.16 - 1.20 and 1.22 with 95% CI of 1.20 – 1.24, respectively, for co-administration with 24-mg and 32-mg doses of lenvatinib, indicating low DDI risk.

- Repaglinide

In vitro, lenvatinib exhibited a weak to moderate, reversible inhibition of CYP2C8 (see non-clinical aspects). A human physiologically based pharmacokinetic (PBPK) model was developed for lenvatinib (Study DMPKA2013-156), to simulate the human AUC profiles of repaglinide with or without coadministration of lenvatinib, and to assess the potential risk of drug-drug interaction (DDI) between lenvatinib and the CYP2C8 substrate repaglinide.

For the DDI simulation, repaglinide was given as a 0.25-mg oral dose either alone or concomitantly on Day 1 with lenvatinib 24 mg p.o. dose QDx8 (Day 1-Day 9). In an additional simulation, repaglinide 0.25-mg p.o. was dosed with a supratherapeutic 32-mg p.o. dose of lenvatinib. This was done as a “worst case” scenario to confirm the effect at excessively high lenvatinib concentrations.

The geometric mean AUCR for repaglinide 0.25-mg p.o. with or without lenvatinib 24-mg and 32-mg were 1.005 and 1.007, respectively, suggesting a less than 1% increase in exposure to repaglinide when concomitantly given with lenvatinib. The results of these simulations suggested no DDI risk between lenvatinib and repaglinide, even at supratherapeutic doses.

- Warfarin

Regarding R-Warfarin and CYP3A4: Lenvatinib is a reversible inhibitor of CYP3A4 with inhibition constants (Ki and Ki´) of 106.4 µmol/L and 57.0 µmol/L, respectively. These constants were derived using a complex type inhibition model (Study No. B03023). For enterocytes and according to the EMA Guideline on the Investigation of Drug Interactions, the [I]/Ki was calculated to be 3.9 (24-mg QD dose) using the lower Ki of 57 µmol/L. As the [I]/Ki was less than 10, DDI is not considered a concern for the CYP3A4 reversible inhibition in enterocytes.

Regarding the systemic circulation relevant CYP3A4 reversible inhibition DDI concern, the [I]/Ki was calculated to be 0.0004 using Cmax,ss of 518 ng/mL (Study E7080-J081-105) at the maximum clinical dose (24 mg QD) and fu of 0.02 and the lower Ki of 57 µmol/L. As this calculated [I]/Ki value was much less than 0.02, there is no DDI concern for the CYP3A4 reversible inhibition in the systemic circulation.

Lenvatinib also exhibited weak time-dependent inhibition of CYP3A with kinact of 0.0835 minutes-1, and Ki of 72.266 µmol/L (Study PK-TEST-0040). Based on the physiologically based modeling of the CYP3A4 probe substrate midazolam (Study DMPKA2013-156), lenvatinib did not significantly inhibit CYP3A4. Effects on warfarin pharmacologic effect via this mechanism would be trivial (lower potency enantiomer marginally affected).

Lenvatinib only slightly increased CYP3A4 mRNA expression (Study XT063020) and thus is not an inducer of CYP3A4 (He et al., 1997).

Regarding R-Warfarin and CYP1A2: The *in vitro* data indicated lenvatinib neither inhibits nor induces CYP1A2 (Study XT063020, Study B03023, and Study PK-Test-0079).

Regarding S-Warfarin, and CYP2C9: Lenvatinib neither inhibits nor induces CYP2C9 (Study XT063020, Study B03023, and Study PK-Test-0079).

- Levothyroxine

Thyroxine is generally administered to subjects with DTC or medullary thyroid cancer (MTC) as standard of care. In contrast, thyroxine is not generally administered to subjects with other solid tumor types. The PK parameters of lenvatinib were similar in subjects with DTC and MTC compared to subjects with other solid tumor types (CPMS-E7080-007R-v1). This indicated thyroxine did not affect lenvatinib PK.

2.4.3. Pharmacodynamics

Mechanism of action

Lenvatinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in angiogenesis, tumour growth and metastatic progression. Lenvatinib was evaluated for its inhibitory activity against a variety of kinases. The most sensitive kinases for lenvatinib included VEGFR (VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4)), RET, fibroblast growth factor (FGF) receptors (FGFR1, 2, 3, and 4), the platelet derived growth factor (PDGF) receptor PDGFRα, and KIT. The precise mechanism of action of lenvatinib is not elucidated, but its anti-angiogenic activity appears to be its primary effect, while anti-proliferative activity is rather limited at least in *in vitro* assays (see non-clinical section).

Primary pharmacology

Inhibition of several kinases is thought to contribute to anti-tumor activity of lenvatinib and to its toxicity. Pharmacodynamic properties relative to efficacy and safety of lenvatinib that are expected based on its mechanism of action (inhibition of VEGFRs, FGFRs and PDGFRs) were discussed. The safety profile of lenvatinib in patients is largely similar to other VEGFR-targeting TKIs with hypertension and proteinuria being the most prominent adverse reactions. Inhibition of several types of tyrosine kinases (VEGFRs, FGFRs, PDGFRs) may potentially contribute towards the embryotoxicity observed after administration of lenvatinib to pregnant animals during organogenesis and towards impaired wound healing. FGFR inhibition causes antiangiogenic effects and therefore embryotoxic/teratogenic effects are possible safety concerns in treatment with FGFR inhibitors (see non-clinical aspects and SmPC section 5.3). Increased inorganic phosphorus can occur as a result of FGFR inhibition and hyperphosphatemia is a known FGFR-inhibition associated safety signal given that FGFR1c signaling in the kidney regulates phosphate reabsorption and calcium homeostasis upon binding to a ligand, FGF-23 (Tacer, et al, 2010; Javier, et al, 2012; Kharitonenkov, et al., 2009; Lanske, et al, 2013).

Lenvatinib has also activity against PDGFR tyrosine kinases although the IC50s were lower for PDGFRβ. PDGFRα is expressed on vascular smooth muscle cells and pericytes surrounding vascular endothelial cells, and has roles for stabilizing newly formed vasculature. Inhibition of PDGFRα may contribute towards

the antiangiogenic activity of lenvatinib. Publicly available and relavely limited non-clinical data (Roberts et al, 2005) and clinical data (Lewis et al, 2009; Smith et al, 2014; Wang et al, 2014 in regards to more specific PDGFR inhibitors do not currently inform on particular additional toxicities.

Genetic differences in PD response

An overview of known molecular alterations in differentiated thyroid cancer that form a basis for increased targeted therapeutic possibilities for patients with thyroid cancer was provided (Xing et al., 2013; Alonso-Gordoa et al., 2015; Elisei et al., 2012; Volante et al., 2009).

The RAS/RAF/mitogen-activated protein kinase (MAPK) pathway seems to be one of the main pathways involved in the tumorigenesis of thyroid cancer. RAS, BRAF mutations or RET/PTC rearrangements have been observed in almost 70% of PTC whereas FTC predominantly includes alterations in RAS and PAX8/PPARγ. Although RAS mutations have been associated with worse prognosis in both PTC and FTC, larger studies are required for definitive conclusions regarding their prognostic value (Alonso-Gordoa et al., 2015). Molecular profiling of Hurthle cell tumors suggests that they represent a unique class of thyroid malignancies at a genetic level (Ganly et al, 2013; Wells and Santoro, 2014).

In Study E7080-G00-201, genotype analyses performed in a subset of patients (n=23 of 58 DTC subjects on study) suggested a benefit in patients harboring RAS mutations (Sherman et al., 2011).

In retrospective placebo-controlled analysis in the pivotal Study 303, lenvatinib PFS benefit compared with placebo was maintained regardless of BRAF or RAS mutation status, and neither mutational status appeared to be predictive for lenvatinib benefit (Schlumberger et al., 2015). In the Study 303, genotype analyses performed in about 47% of randomized subjects showed that 27.9% of patients in the lenvatinib arm and 11.7% of patients in the placebo arm had tumours with a RAS mutation; 21.1% of patients receiving lenvatinib and 32.2% receiving placebo had tumours with a BRAF mutation (Tahara et al., 2014, Schlumberger et al., 2015).

Biomarkers analysis

Serum biomarkers: circulating angiogenic factors (CAFs)

In the Study E7080-G000-303, focused analysis of 3 serum biomarkers VEGF, Ang2, and soluble Tie2 (sTie2) (pre- and post-treatment levels) was performed in both the treatment and placebo arms (Tahara et al., 2014). Blood samples were collected during the randomisation phase for biomarker discovery and validation from all subjects prior to the first dose of the study drug, on Day 15 of the first cycle and on Day 1 of all subsequent cycles.

The analysis of these specific serum markers was based on biomarker data obtained from various clinical studies of lenvatinib across several different indications. Notably, biomarkers have been investigated in multiple indications across various Phase 2 studies including thyroid cancer (DTC, MTC, and anaplastic thyroid cancer), HCC, glioblastoma, endometrial cancer, renal cell carcinoma and melanoma (with or without BRAF V600E). Exploratory biomarkers including a broad panel of 45 circulating circulating angiogenic factors (CAFs) as well as tumour genetic markers were investigated across these various Phase 2 studies to gain insight into the PD markers as well as predictive markers for response to treatment (Vergote et al., 2014; Cabanillas et al., 2014, Schlumberger et al. 2012, Funahashi et al., 2013, Sachdev et al. 2013). Increases in circulating levels of VEGF and PlGF have been observed following treatment with various VEGFR-targeted TKIs and are suggested as potential PD markers for these agents (Murukesh et al., 2010). The panel of selected CAFs (combination of ELISA and multiplex assays) was based on published literature as well as preclinical translational research with lenvatinib.

A graphical anlysis was performed to describe the link between exposure and different serum biomarkers including thyroglobulin for DTC, calcitonin and CEA for MTC, free T4 and TSH, apoptosis marker (caspase 3/7, cytochrome C, and M-30 neo-antigen) and circulating cytokine and angiogenic factors (CAFs). CAFs included: angiogenic growth factor (EGF, FGF2, IL-6, TGF-α,VEGF/VEGF(100), VEGF-D, PGF), chemokine (GM-CSF, MIP-1α, MIP-1β, Rantes, SDF-1α, G-CSF), endothelium function (Ang2/Ang2(90), Tie-2, sVEGFR-1, sVEGFR-2, sVEGFR-3, PDGF-AA, PDGF-AB, PDGF-BB), interleukin/immune response (IL-1α, IL-1rα, IL-10, IL-12 (p40), IL-13), others (FLT3LG). Subsequently, baseline CAFs values were tested as predictors of lenvatinib efficacy (inhibition of tumor growth) using a model based analysis. Percentage changes of CAFs from baseline at Cycle 1 Day 8 and Cycle 2 Day 8 were also tested in tumor growth inhibition model and PFS analysis as described below. Consistently with findings in other Phase 2 studies of lenvatinib, an increase in VEGF levels and a decrease in Ang-2 and sTie-2 levels from baseline were observed in Study 303 at various post-treatment time points. Ang2 levels correlated with ORR and PFS (OS data was too immature for correlative analysis). Similarly, significant association was observed between PFS and low baseline VEGF alpha and angiopoietin-2 levels (p=0.02 and HR=0.386) (Ball et al, 2012).It was noted that all patients treated with lenvatinib showed superior clinical benefit compared with placebo regardless of baseline Ang-2 levels (Tahara et al., 2014). Baseline VEGF levels did not show significant correlation with clinical outcome measures such as PFS. In contrast, baseline levels of VEGF in a study with motesanib in DTC or MTC did correlate with response on treatment (Bass et al., 2010).

In addition to 3 above-mentioned serum biomarkers (Ang2, sTie2, and VEGF), serum levels of FGF23, a peptide hormone regulating mineral metabolism, were measured in study 303. Analysis of serum levels of FGF-23 in pretreatment (baseline) and post-treatment (at Cycle 1 Day 15 [C1D15] and Cycle 2 Day 1 [C2D1]) blood samples collected in the Study 303, showed that FGF-23 levels were higher in the lenvatinib arm compared with the placebo arm (Study W-20140951). Increase in plasma levels of FGF-23 has been considered as a compensatory mechanism of FGFR1 inhibition (Kim et al., 2011).

In the study 201, most subjects were taking thyroid hormone (levothyroxine) during the study (66% of subjects in the DTC cohort and 86% in the MTC cohort). Thyroglobulin levels decreased after lenvatinib treatment in most subjects. Higher drop in thyroglobulin levels post lenvatinib treatment was associated with higher response rate. Also lower baseline tumor size was associated with higher response rate.

Biomarkers of apoptosis, circulating endothelial cells and imaging biomarkers using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) were evaluated in a limited number of patients in phase 1 and 2 studies.

Secondary pharmacology

QT assessment

In the clinical program, a thorough QT study was performed (E7080-A001-002). This study was conducted in 52 healthy volunteers. This was a single center, single-dose, randomized, double-blind, placebo controlled, three treatment, three–way crossover study (each a 14-day period) conducted to evaluate the potential for QT/QTc prolongation by 32 mg lenvatinib using a placebo control and moxifloxacin (Avelox 400 mg) as the positive control.

The QTcF change from baseline (ΔΔQTcF) was evaluated from serial electrocardiograms. The relationship between lenvatinib plasma concentration and QTcF was analysed with linear mixed-effects modeling.

50 subjects completed the study. Two subjects withdrew consent prior to completion. The mean age of subjects was 34 (SD = 13.8) years.

Lenvatinib plasma concentrations were measured; the peak plasma level (arithmetic mean ± SD) of 417 ± 201.8 ng/ml was observed at a median of 3.0 h. At this plasma level, the change in QTcF is projected

to – 4.83 msec (90% CI -6.12 to – 3.53). The median half-life was 21.3 h. Mean peak plasma levels of moxifloxacin reached 3.2 µg/ml and were observed at a median of 2.0 h after dosing.

Following administration of a single 32 mg dose, lenvatinib did not exert a clinically relevant effect on ΔΔQTcF. A small QTc shortening effect was observed and QTc prolongation exceeding 10 ms could be confidently excluded. The mean ΔΔQTcF was negative at all time points postdosing with the exception of 23.5 hours and the upper bound of the CI did not exceed 2 ms at any time point. Concentration effect modeling suggested lenvatinib does not cause QTc prolongation at clinically relevant, high plasma levels.

Relationship between plasma concentration and effect

Exposure - Efficacy after a starting dose of 24-mg (in Phase 3 Study 303)

Graphical PK/PD analysis of OS, ORR, DCR, CBR, dSD, maximum change in tumour size, and time to response with lenvatinib AUC based on starting dose of 24 mg or dose intensity did not reveal any direct relationship.

A time-to-event analysis for efficacy using data only from the Study E7080-G000-303 was conducted to explore the relationship between lenvatinib exposure (AUC_{0-24}) and the primary efficacy endpoint (PFS), as well as several secondary and exploratory endpoints (e.g., OS and ORR) using S-plus 8.1. It also identified other predictors of PFS in patients with DTC. The analysis described the relationship between lenvatinib exposure and longitudinal tumour size measurements in subjects with DTC and identified covariates that affect this relationship.

All the exposure-response analyses except tumour size included 260 subjects with DTC who received lenvatinib from Study 303. For PFS, 107 subjects had observed events and 153 subjects had censored events.

Kaplan–Meier and Cox regression analysis showed that lenvatinib treated subjects showed similar PFS across the full range of exposures (AUC_{0-24} between 1410 and 10700 ng.h/mL).

A similar analysis for PFS and $AUC_{Dose\ Intensity}$ showed that subjects in the 4th quartile of lenvatinib exposure had an apparent poorer PFS relative to the other lenvatinib quartiles (Kaplan-Meier plots not shown). This finding however was driven by a disproportionate randomization of early dropout subjects to this quartile. Eighteen of the 36 early dropout subjects were randomized to the 4th quartile. The early drop-out subjects had a higher proportion of poor prognostic confounding baseline factors (like higher baseline tumour size and larger ECOG scores) which influence PFS. Once all subjects with PFS ≤2 months were removed from the data set, comparable PFS was seen for all quartiles.

Baseline factors which were found to be significant predictors of PFS were body weight, ECOG performance status, baseline tumour size, and M-Stage. Treatment-emergent hypertension was associated with a longer PFS. Other subject characteristics (age, sex, race) or previous anti-VEGF therapy were not significantly associated with PFS in subjects with DTC. An early assessment of change in tumour size (Week 8) was also a significant predictor of PFS and higher reduction in tumour size at Week 8 was associated with longer PFS.

The final population PK model was used to derive individual PK parameters and lenvatinib exposures, which were then incorporated into the PK/PD datasets to be used in the subsequent population PK/PD analyses.

A PK/PD model was developed to describe tumor growth inhibition by lenvatinib. NONMEM 7.2 was used for this purpose. The dataset used for this purpose included data from 374 subjects for which baseline and at least one postdose tumour assessment was available. Out of 374 subjects, 248 subjects received active treatment of lenvatinib and 126 subjects received placebo. A total of 2373 tumour size

observations were included. Of the 374 total subjects, 183 were female, 295 were white, and 243 had papillary DTC. The population age and weight ranged from 21 to 89 years (median = 63 years) and 31 to 165 kg (median = 74 kg), respectively. Two hundred eighty five subjects received previous anti- VEGF therapy. Most subjects were classified with an ECOG PS = 0 (N = 210) or ECOG PS = 1 (N = 152), with 12 subjects ECOG PS >1. Median baseline tumour size was 59.2 mm, ranging from 15.1 to 331 mm. Hypertension Grade 2 or higher was experienced by 68.5% of subjects in the lenvatinib arm compared with 14.3% in the placebo arm.

Eta shrinkage for the 3 parameters of the tumour growth inhibition model, KG, KL and λ, was 34.0%, 30.5% and 40.0% respectively. The effects of covariates were tested only on both KG and KL as they have borderline shrinkage. Previous VEGF therapy, histology effect, and |ECOG > 1 on KG and gender, ECOG > 0, baseline tumour size and histology on KL was tested. The number of subjects with M-stage IVB was 4 (1.05%) and race Black/African American was 8 (2.14%). Thus, the effects of these covariates were not tested.

The multivariate analysis with backward deletion resulted in a final longitudinal tumour size model with significant effects of sex, ECOG, and baseline tumour size on KL. Compared to the base model, the addition of the 3 significant covariates reduces IIV on KL by 7%. Longitudinal tumour size data was described by a linear growth rate constant and linear kill rate dependent of lenvatinib AUC based on dose intensity between two tumour assessment and an exponential resistance factor. The final model had significant effects of sex, ECOG, and baseline tumour size on KL. The KL was 15.7% lower for subjects with ECOG PS >0, was 22.1% lower in females and decreased with the increase in baseline tumour size (power function = -0.45).

Regarding gender, although statistically significant, the effect size was small. The kill rate was 22% lower for female compared to males. The subgroup analysis in E7080-G000-303 CSR reported the hazard ratio compared to placebo group of 0.21 (95% CI 0.14 – 0.32) for males and 0.26 (0.16 – 0.41) for females. Cox univariate regression analysis results for PFS for the lenvatinib arm showed that gender was not a significant predictor of PFS.

PK/PD analysis for tumour size showed that reduction in tumour size (the sum of the longest diameter for target lesions) was correlated to lenvatinib exposure (see Figure 2).

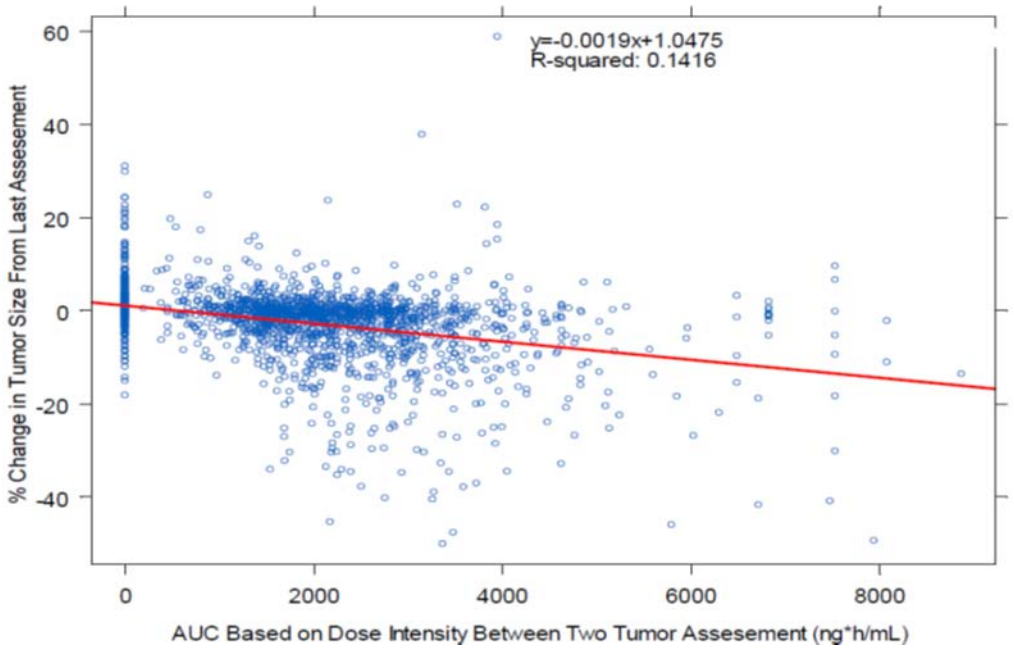


Figure 2: Change in tumour size correlated to lenvatinib exposure using a tumour growth inhibition model

Exposure-Response Analyses for Safety

The objectives of the exposure response analyses for safety of lenvatinib in subjects with DTC (Study E7080-G000-201, Study E7080-J081-208, and Study E7080-G000-303) were to explore the relationship between lenvatinib exposure and the occurrence of the AEs of hypertension, proteinuria, weight loss, fatigue, and thromboembolic event and time to first dose reduction.

Exposure-response analyses were graphically conducted for hypertension, proteinuria, diarrhea, nausea, and vomiting using AUC based on starting dose and AUC based on dose intensity, which was defined as total dose (mg) during the study divided by the duration of study (in days) on a per-subject basis.

Two of the most frequently reported clinically significant events observed with lenvatinib were hypertension and proteinuria, and both are mechanism-related events. The occurrences of hypertension (as the Medical Dictionary for Regulatory Activities [MedDRA] preferred term) and proteinuria were highest during the first 6 months of exposure, and then declined over subsequent time periods.

Additional exposure-response analyses for two of these AEs (hypertension and proteinuria) were conducted using binary logistic regression analysis with NONMEM version 7.2.0 (ICON Development Solutions, Ellicott City, MD) interfaced with PDxPop 5.0 (ICON Development Solutions, Ellicott City, MD).

For the hypertension model, systolic and diastolic blood pressure data obtained during the first cycle in subjects with DTC from Studies E7080-G000-201, E7080-J081-208, and E7080-G000-303 were used to derive CTC grades. The PK/PD dataset for hypertension included 1216 hypertension records from 458 (placebo = 131, lenvatinib treated = 327) subjects. Proteinuria AE grades were derived from dipstick test/24 h urine measurements for Studies E7080-J081-208 and E7080-G000-303. The PK/PD dataset for proteinuria model development consisted of 6290 proteinuria AE records from 412 (placebo = 131, lenvatinib treated = 281) subjects. For weight loss and fatigue, thromboembolic events CRF recorded AE data were used. The PK/PD dataset these AE analyses included 5331 AE records from 458 (placebo = 131, lenvatinib treated = 327) subjects from Studies E7080-G000-201, E7080-J081-208, and E7080-G000-303. Probabilities of having AEs of Grade 0, 1, 2, and higher were estimated as a function of lenvatinib exposure and other predictors such as demographics (age, sex, race, body weight), ECOG performance status, previous anti-VEGF therapy and prior antihypertensive therapy. Exposure-response

relationships for response time to first dose reduction and thromboembolic events were evaluated graphically.

Hypertension

The probability of hypertension Grade 2 and 3 increased gradually with increased in lenvatinib C_{min}. Prior use of antihypertensive drugs (indicating a prior condition of hypertension) increased the probability of experiencing hypertension post-lenvatinib treatment.

For non-Japanese subjects with no prior condition of hypertension, at the median C_{min} of 51.5 ng/mL, the probability of hypertension with CTC Grade 2 and 3 was estimated to be 22.9% and 5.11%, respectively.

For Japanese patients, the probability increased by 5.2% for CTC Grade 2 and 1.82% for CTC Grade 3. Data from Studies E7080-G000-201, E7080-J081-208, and E7080-G000-303 showed that prior hypertension condition increased the probability of CTC Grade 2 and 3 hypertension in Japanese subjects by 16.3% and 8.09%, respectively.

Proteinuria

The PK/PD analysis for proteinuria indicated that the time course of proteinuria events was described by a proportional odds model with the effect proportional to log-transformed lenvatinib cumulative AUC. The slope of the effect on the logit scale was estimated at -0.172 ug·h/mL. Based on data from Studies E7080-G000-201, E7080-J081-208, and E7080-G000-303, the probability of proteinuria Grade 1 and 2 increased rapidly up to cumulative AUC values of approximately 200 ug·h/mL followed by a slow rise thereafter.

For Japanese patients, slope (logit scale) for the effect of lenvatinib exposure was estimated to be 2.72 times higher than for non-Japanese. At the median cumulative AUC of 444 µg*h/mL the probability of experiencing proteinuria of CTC Grade 1, 2 and 3 for non-Japanese subjects was 10.1%, 1.21%, and 0.03%, respectively. In Japanese patients, the probability increased to 36.7%, 6.92%, and 0.2% for CTC Grade 1, 2, and 3, respectively.

Overall, the results showed that lenvatinib exposure based on starting dose was a significant predictor for the occurrence of any grade proteinuria, nausea, and vomiting, and for Grade 3 or higher hypertension. Increased lenvatinib exposure based on dose intensity was a statistically significant predictor for any grade hypertension, proteinuria, nausea, and vomiting, and for Grade 3 or higher proteinuria.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Intravenous data were not provided therefore it is not possible to judge whether absorption is high based on absolute bioavailability. However, it has been estimated from the mass balance study in humans to be in the order of 85.5% (see SmPC section 5.2). *In vitro* data indicated that lenvatinib permeability was comparable to the highly permeable compound prazosin, and 10-fold greater than the poorly permeable compound, mannitol. Solubility data showed that the highest clinical dose (24 mg) is not soluble in 250 mL of water in the pH range of 3 to 7. Therefore, lenvatinib is considered to be poorly soluble but as absorption cannot be definitively stated as >90% it is unknown if it is BCS class II or IV.

Lenvatinib, from both tablet and capsule formulations, is rapidly absorbed after oral administration with a time to reach maximum concentration of drug in plasma (t_{max}) typically observed 1 to 4 hours post-dose (see SmPC section 5.2). The exposure in patients after multiple dosing appeared to be higher than in

healthy volunteers, which has been confirmed in the POPPK analyses, where it is estimated that the CL/F in healthy volunteers is 15% higher compared with subjects with malignant solid tumours.

Although the degree of intestinal/first-pass metabolism via CYP3A4 cannot be determined, data from a mass-balance study indicated that it is at most low to moderate.

Two clinical studies investigated the effect of food on the pharmacokinetics of lenvatinib, one in healthy volunteers and one in patients. Food did not affect the extent of absorption, but slowed the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations were delayed by 2 hours (see SmPC section 5.2). These studies showed only a minimal effect of food. Lenvatinib capsules should be taken at about the same time each day with or without food (see sections 4.2 and 5.2). The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

A tablet formulation was used in the early clinical development of lenvatinib. A capsule formulation, which will be the commercial formulation, was used for the subsequent development of lenvatinib including Phase 3 trial. Bioequivalence between the 10 mg lenvatinib capsule (New formulation) and the 10 mg lenvima tablet (Old formulation) was shown through the bioequivalence Study 001. The observed small differences in exposure with the two formulations are not considered clinically relevant. Bioequivalence for batches containing various levels of polymorph in the range seen for batches manufactured according to the current manufacturing process and used in the pivotal clinical study was shown. The 4-mg capsule meets the criteria for waiver of *in vivo* BE studies for lower strengths.

The level of lenvatinib protein binding is yet not considered to be known. The *in vivo* percentage of unbound lenvatinib in plasma in the renal impairment study (Study A001-005) (7.70% ± 3.31%) was much higher than what has been observed *in vitro* (1.4-2.1%) and the reported protein binding in serum (96.6-98.2%) (Study E7080-J081-103). This is probably due to the high variability associated with the bioanalytical method used for the former study (reflected also in the failure of the incurred sample reanalysis: 59 out of 68 samples differed often >70% with the original values).

Results from the mass balance study indicate that 40% of lenvatinib-related material in plasma (under the form of parent and M2) appears to be covalently bound to macromolecules. Considering that covalent binding to macromolecules is only one of the different mechanisms of DILI and in view of the recommended daily dose the DILI induction potential of lenvatinib is considered low. However, from the clinical studies and the treatment emergent liver events noted within these studies the presence of DILI associated with lenvatinib administration cannot be ruled out. DILI should be further followed in the framework of genetic characterisation of potential predicitive biomarkers for treatment-related safety issues (see clinical pharmacodynamic).

As there is no study with intravenous administration of lenvatinib, the volume of distribution has not been determined. In patients, the median apparent volume of distribution (Vz/F) of the first dose ranged from 50.5 L to 92 L and was generally consistent across the dose groups from 3.2 mg to 32 mg. The analogous median apparent volume of distribution at steady-state (Vz/Fss) was also generally consistent and ranged from 43.2 L to 121 L (see SmPC section 5.2).

Lenvatinib is a substrate for MDR1 (P-gp) and BCRP. However these transporters did not appear to impact on the absorption of lenvatinib. In animal studies (rats and monkeys) some distribution to the brain has been observed, potentially showing that lenvatinib is only a moderate to weak substrate of P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, and BSEP (see non-clinical aspects and SmPC section 5.2).

In vitro, cytochrome P450 3A4 was shown as the predominant (>80%) isoform involved in the P450 mediated metabolism of lenvatinib. However, *in vivo* data indicated that non-P450-mediated pathways contributed to a significant portion of the overall metabolism of lenvatinib. Consequently, *in vivo*, inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure (see SmPC sections 5.2 and 4.5).

In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite (see also non-clinical aspects). M2' and M3', the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase .

Data from a human mass balance/excretion study indicated lenvatinib is extensively metabolised in humans. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (e.g., glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerisation). These *in vivo* metabolic routes align with the data provided in the *in vitro* studies using human biomaterials (see SmPC section 5.2).

The totality of data gathered from the different clinical studies for which phenotype data were available (476 subjects in total), showed that there was no effect of phenotypes for CYP2C19 on lenvatinib exposure (data not shown). Given the limited effect of ketoconazole and rifampicin on lenvatinib pharmacokinetics, CYP3A4 metabolism does not seem to be of importance for lenvatinib metabolism. Therefore, there is no need to discuss its genetic polymorphism. *In vitro* data indicate that lenvatinib is a BCRP substrate, however, *in vivo* information concerning the involvement of this transporter in the pharmacokinetics of lenvatinib was lacking. From the available data, it is agreed that ketoconazole represents the 'worst case' scenario for BCRP inhibition. From the *in vivo* study with ketoconazole, even if the effect on the PK of lenvatinib was completely due to BCRP inhibition (and none to inhibition of P-gp), it is concluded that the effect was relatively small (15% and 19 % increase in AUC and C_{max}, respectively). In the same line, the effect of any BCRP polymorphism on lenvatinib PK would be equally or less than what has been observed with ketoconazole.

Lenvatinib is characterised by a moderate to high variability with regards to PK parameters in cancer patients, whereas in healthy volunteers variability appeared to be low. This could partially be explained by a variability in drug distribution due to changes in body size or to the ratio of fat to total mass (lenvatinib is a lipophilic drug) which could be different in patients vs. healthy subjects. It has been shown that weight has an impact on the pharmacokinetics of lenvatinib, although this was not considered to be clinical significant. An additional source of variability could be variable protein levels in cancer patients. Information on intra-patient variability, both in healthy subjects and patients has been provided and lenvatinib showed a high intra-subject variability for Cmax and a moderate intra-subject variability for AUC, both in patients and healthy volunteers.

No formal assessment of the dose proportionality of single and multiple doses was submitted. Interpretation of the data from Study E7080-E044-101 was difficult due to the low number of patients included and the high variability. In addition, there appeared to be non-linearity for C_{max} in study E7080-J081-103. Additional analysis was conducted to assess the PK nonlinearity using popPK analysis. When using data from the capsule and tablet formulation the dose effect on CL/F and F1 was confounded and, hence, the influence of dose was estimated to be more appropriately tested simultaneously on both CL/F and F1, as was performed in the final PK model. The nonlinearity on C_{max} was not supported by the results of the PopPK analysis.

Regarding time-dependency, the extent of accumulation was minimal in subjects with QD dosing of clinically relevant doses of lenvatinib.

Special populations

Subjects with severe renal impairment were predicted to have a 2.4-fold increase in exposure compared to the average exposure seen in subjects from a Phase 2 study who had ^{131}I-refractory, unresectable DTC. According to these results, an effect of mild and moderate renal impairment on lenvatinib pharmacokinetics appears negligible and no dose adjustment is judged necessary.

It is unknown whether there is a change in the plasma protein binding in renally impaired subjects. Considering that the within-study, relative comparisons of PK data based on unbound drug concentrations across groups, which may offset systematic error occurring in the sample analysis, do not rule out the possibility that patients with severe renal impairment may be exposed to higher unbound drug concentrations compared to other renal function groups. Therefore, patients with severe renal impairment should be carefully monitored, and a dose reduction is recommended. The recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended (see SmPC section 4.2 and 5.2).

The applicant is recommended to determine of unbound drug concentrations in patients with renal impairment, taking into account that the assessment of renal impairment should be based on free fraction.

Based on the results of study A001-006 (hepatic impairment), it is concluded that patients with mild or moderate hepatic impairment would most likely have the same benefit from the 24 mg dose as patients with no hepatic impairment. Therefore, no adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. For severe hepatic impairment (Child-Pugh C), a dose adjustment is proposed based on total drug concentrations and steady state projections. The recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability (see SmPC section 4.2 and 5.2). As for patients with renal impairment, it is unknown whether there is a change in the plasma protein binding in hepatically impaired subjects and the Applicant is recommended to provide the determination of unbound drug concentrations in patients with hepatic impairment.

Based on the population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age, sex, weight, and race (Japanese vs. other, Caucasian vs. other) had no significant effects on clearance (see SmPC sections 5.2 and 4.2). The higher incidence of AE in the Japanese population did not appear to be linked to changes in the lenvatinib exposure in this population, but rather to a higher sensitivity of Japanese patients to VEGF inhibition. No adjustment of starting dose is required on the basis of race and age (see SmPC section 4.2).

Subjects with body weight <60 kg had 36% higher exposure compared with subjects >60 kg and it is considered that this small effect of body weight on lenvatinib exposure does not warrant any dose adjustment. Simulations showed that there is an important effect of the combination of bodyweight and liver function on drug exposure. This effect surprisingly did not show any impact on neither hypertension nor proteinuria and the absence of a valid PKPD model for drug efficacy prevented for exploring the impact on drug efficacy. This is expected to be further explored based on the results of the planned study 211 (see RMP).

Lenvatinib must not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see non-clinical section and SmPC section 5.3). The safety and efficacy of lenvatinib in

children aged 2 to <18 years have not yet been established (see sections on clinical efficacy and clinical safety and SmPC section 5.1).

Pharmacokinetic interaction studies

Results from study Study E7080-A001-004 suggest that strong CYP3A and P-gp inhibitors have a small effect on lenvatinib exposure.

Like ketoconazole, rifampin is well established as an inhibitor of transporters including P-gp following single dose administration (Reitman et al., 2011). Overall, the data indicate that there is a small drug-drug interaction between lenvatinib and P-gp inhibitors and CYP3A inducers. Therefore, no dose adjustments are required when coadministering lenvatinib with known PXR agonists.

Co-administration of temozolomide with lenvatinib (24 mg QD) did not alter lenvatinib's PK parameters. Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the PK of any of these 3 drugs. The potential of drug-drug interaction study with a variety of other anti-neoplastic agents has been discussed by the applicant from a mechanistic perspective, especially the ones relevant for common concomitant medications. Based on the data provided, drug-drug interactions with other anti-cancer agents are not expected clinically.

In vitro, the proportion of the aldehyde oxidase (AOX) contribution to the lenvatinib metabolism is estimated to 17.4%, the proportion for CYP1A2 is 2.4% to 7.6% and for CYP2B6 is 3.0% to 6.7%. Little is still known about PK interaction of this enzyme AOX. However, its inhibition is observed with many drugs (Obach RS et al. 2004). Neither lenvatinib nor its metabolites have been shown to inhibit aldehyde oxidase (DMPKT2012-004), so there is no reason to expect that lenvatinib would lead to any effects on the clearance and so exposure of any coadministered drugs that are predominantly metabolised via aldehyde oxidase.

Results from *in vitro* studies with human microsomes have shown that lenvatinib exhibit time-dependent inhibition (TDI) of CYP3A4 (see non-clinical aspects). Due to insufficient data on the risk of induction at the intestinal level, the poor predictive value of the PBPK model for induction, the observed *in vitro* signal for inhibition and the major importance of CYP3A4 in the metabolism of drugs, the MAH will perform an *in vivo* study with midazolam as a probe substrate for CYP3A4 (see Risk Management plan) to investigate correctly the potential of lenvatinib for CYP3A4 inhibition/induction.

No data is available that can be used to exclude the risk that lenvatinib could be an inducer of CYP3A4 or Pgp in the gastrointestinal tract. This could potentially lead to decreased exposure to oral CYP3A4/Pgp substrates. This should be considered if co-administering oral CYP3A4/Pgp substrates for which retained efficacy is very important (see SmPC section 4.5). Awaiting the result of this DDI study, CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)) should therefore be administered with caution in patients receiving lenvatinib (See SmPC section 4.5).

For a drug intended for use in fertile women, the potential for drug interactions and common adverse events (e.g. thromboembolic events) with the oral contraceptives should always be considered. It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives. When the results of the midazolam study become available, the Applicant is recommended to discuss the potential interaction with oral contraceptives in light of these results and to consider the need for an additional DDI study with oral contraceptives. Awaiting these results, women using oral hormonal contraceptives should add a barrier method (see SmPC sections 4.5 and 4.6).

A minimal DDI risk for S- and R-Warfarin is expected when co-administered with lenvatinib. There is also a minimal DDI risk for lenvatinib when co-administered with thyroxine. For the effect of lenvatinib on

thyroxine, TSH is routinely monitored in patients with RR-DTC who are taking angiogenic TKIs and thyroxine doses are implemented or adjusted as needed. Therefore, even if this is known that angiogenic TKIs elevate levels of serum TSH, it is agreed that a drug-drug interaction study is not required.

Pharmacodynamic

Regarding genetic differences as assessed in tumor samples, although there was improved clinical benefit observed in the RAS mutated subset in Study 201, the small sample size in this single arm Phase 2 study does not allow to draw firm conclusions. Nevertheless, RAS mutations were identified as potential predictors of benefit. In the retrospective analysis conducted in the placebo-controlled Phase 3 study (Study 303), lenvatinib PFS benefit compared with placebo appeared to be maintained regardless of BRAF or RAS mutation status. However, the retrospective character of this subgroup analysis and limited number of patients do not allow drawing definitive conclusions on predictive value of particular mutational status for lenvatinib benefit. Even though activity of lenvatinib is claimed in all patients with RR-DTC irrespectively of molecular characteristics of tumours, targeting of multiple kinases and anti-proliferative activity in patients harbouring tumors with particular mutations would allow better individualization of benefit-risk assessment, what is particularly important in patients with higher risk of toxicities.

Genetic background of patients was associated with efficacy of anti-angiogenic agents in numerous studies. Therefore, analysis of host genetic factors that would predict efficacy and/or safety of lenvatinib is recommended. Prospective collection of constitutive DNA samples in clinical studies is recommended to enable retrospective genetic characterisation of potential predictive biomarkers of efficacy and of treatment-related safety issues (e.g. hypertension, proteinuria, serious liver injury cases, etc).

Many of undersirable effects of TKIs are on-target effects of these drugs given that tyrosine kinases are widely distributed with specific functional roles in different organs (Shah et al, 2013).

Although not studied directly with lenvatinib, the mechanism of action (MOA) for hypertension is postulated to be mediated by the inhibition of VEGFR2 in vascular endothelial cells. Similarly, although not studied directly, the MOA for proteinuria is postulated to be mediated by downregulation of VEGFR1 and VEGFR2 in the podocytes of the glomerulus. The mechanism of action for hypothyroidism is not fully elucidated (see SmPC section 5.1). Thyroid disfunction is among the most common endocrine sytem-related adverse events of thyrosine kinase inhibitors with several mechanisms proposed in relation to thyroid gland integrity, thyroid hormone transport and methabolism (Lodish, 2013; Illouz et al, 2014).

At least three serum biomarkers (VEGF, Ang2, and soluble Tie2 (sTie2)) investigated in the Phase 3 study appeared to be of value to predict lenvatinib treatment outcomes in DTC. However, further validation is needed. Changes in CAFs (in Studies 201 and 303) that correlated with lenvatinib exposure did not show consistent significant correlations with clinical outcome measures such as change in tumor size (maximum tumor shrinkage) PFS and OS. Combination of mutation status and serum biomarkers appears to improve their predictive value (Sherman et al, 2011).

No firm conclusions could be drawn for other types of biomarkers due to the limited number of patients, such as biomarkers of apoptosis, imaging biomarkers or circulating endothelial cells.

Further investigation of predictive value of serum biomarkers is expected in the planned clinical study 211 (see RMP). At least three of the biomarkers explored in the study 303 (VEGF, Ang2, and soluble Tie2) should be explored. A new PK/PD model, including data from study 211, is also expected and should ideally describe the effect of CAF on tumor size on a continuous time scale.

Given an inter-individual variability and heterogeneity in tumor response, monitoring of multiple biomarkers, rather than relying on a single biomarker, would be advantageous (Sharan and Woo, 2015). It seems unlikely that the use of single biomarker will be sufficient to predict efficacy and/or toxicity and

to account to tumor heterogeneity and genetic heterogeneity at tumor and host levels (Vasudev and Reynolds, 2014). It is important to translate candidate biomarkers into valid biomarkers to increase efficacy and decrease toxicity while improving overall guided personalised therapy.

With regard to the relationship between plasma concentration and effect, the applicant used an empirical and sequential approach to describe the changes in biomarkers and clinical endpoints related to drug efficacy. The approach was non informative for dose selection. An integrated and mechanism-based approach would have given more insight in the understanding of drug PK/PD and inform optimal dose selection. The final population PK model was used to derive individual PK parameters and lenvatinib exposures, which were then incorporated into the PK/PD datasets to be used in the subsequent population PK/PD analyses. An indirect model was used to describe tumor size and different predictors including exposure and CAF changes were tested using multiplicative models. The fact that drug exposure and CAF changes were concomitantly used as predictors was found to be an issue given their possible correlation. Overall, the model used was not considered valid and therefore no conclusion can be drawn on the correlation between reduction in tumour size and lenvatinib exposure and whether the effect of gender, ECOG, and baseline tumour size affected this relationship. The results of a new modeling as mentioned above is expected before valid concludions can be drawn in this regard.

In tumor growth inhibition model, correlation was shown between reduction in tumor size and lenvatinib exposure. However, given some limitations of the model used, a post marketing modelling study was recommended that will include some newly collected data in a study to be conducted (study 211).

PK/PD models were also developed to study the exposure response for hypertension and proteinuria. Hypertension is a known dose-related effect of VEGF/VEGFR-targeted therapies and it has been considered to be a biomarker of the efficacy of these agents (Chen and Cleck, 2009; Rixe, et al., 2009; Dienstmann, et al., 2011). A preliminary indirect model was developed only using data from study 201. Albeit not fully mechanistic, the indirect model used to describe drug effects on blood pressure from study 201 was considered acceptable and could be used for predictive purposes.

For the pooled data analysis for hypertension, the data were categorized and treated as a binary variable and a logistic model was developed to describe them. A number of issues regarding the model were discussed by the Applicant including the use of dose instead of presence of concomitant antihypertensive drugs, consideration of other (more mechanistic) model to describe their effects, justification of the choice of the parameter on which the effects were imputed and the addition of a markov element in case valid arguments could be provided to justify categorization of blood pressure in a binary variable. An indirect model instead of a logistic model would have been more adequate. Therefore no conclusion can be drawn at this stage and the company is requested to use the indirect instead of logistic model for blood pressure in the PK/PD modelling that will be conducted upon completion of study 211 (see RMP).

For the pooled data analysis for proteinuria, the data were treated as a categorical variable and a logistic model was developed to describe them. A Markov element was then added and endorsed. Based on the results from the model development stage, a PKPD model with Markov element and with logarithmic relationship for CAUC was superior to other exposure relationships. The PK/PD modelling that will be conducted upon completion of study 211 will provide further information on the dose-exposure-response relationships for drug safety including proteinuria.

Lenvatinib belongs to a class of drugs that potentially can prolong QT. However, the available clinical data, as well as the results of a published thorough QT study in healthy volunteers (Shumaker, 2014) showed only a minimal effect of lenvatinib on QT prolongation. Nevertheless, QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients

treated with placebo (see SmPC section 5.1). QTc prolongation is an important potential risk addressed in the Risk Management plan.

2.4.5. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of lenvatinib has been investigated to an acceptable extent. Overall, the potential for *in vivo* DDI with lenvatinib can be considered as low. *In vitro*, it was shown that lenvatinib inhibits CYP3A4, CYP2C8, UGT1A4, UGT1A1, OCT2, OATP1B1, OAT1, OAT3 but clinical relevant inhibition can be excluded.

An *in vivo* study with midazolam as a probe substrate for CYP3A4 is expected to provide further data on the potential of lenvatinib for CYP3A4 inhibition/induction (see RMP).

In order to correctly characterise the dose-exposure-response relationships for clinically relevant endpoints either for drug efficacy (PFS and response rate) or for drug safety (hypertension, proteinuria, hematology, etc) (see also clinical safety) and ultimately to optimise dose recommendation, additional PK/PD analyses should be done post-marketing based on already available and newly acquired data. An integrated and mechanism-based model should be used and blood pressure should be modelled as continuous variable when data from the study 211 will be available. The data analysis plan for PK/PD modelling including clear description of the study design optimization ensuring collection of informative data during this study will be provided at the time of submission of the clinical study 211 protocol. The results of the integrated and mechanism-based PK/PD modelling will be submitted at the time of submission of the CSR (see RMP).

2.5. Clinical efficacy

The clinical efficacy of lenvatinib (E7080, Lenvima), 4 mg and 10 mg capsules, for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC), is based on one pivotal Phase 3 study E7080-G000-303 (Study 303, the 'SELECT' trial). Supportive efficacy data for the RR-DTC indication were provided by:

- Study E7080-G000-201 (Study 201), a multicentre, international, open-label, single-arm Phase 2 study in subjects with advanced cancer (RR-DTC or MTC) and,

- Study E7080-J081-208 (Study 208), an ongoing, multicentre, open-label, single-arm Phase 2 study in Japanese subjects with advanced thyroid cancer (RR-DTC, MTC or ATC).

Table 20: Tabular listing and description of these 3 clinical studies

Study ID (Status)	**Indication**	**No. Study Centers (Location)**	**Dates - Study Start[a] / Clinical Cut-off / Database Lock**	**Study Design**	**Study Treatment: Dose, Route & Regimen**	**No. Subjects Treated / Ongoing (No. on Treatment at Clinical Cut-off)**
E7080-G000-303 (Double Blind Randomization Phase	RR-DTC	117 (Europe, North America,	05 Aug 2011 15 Nov 2013	Phase 3, randomized double-blind, placebo-controlled,	**Randomization Phase:** LENV 24-mg, Placebo	**Randomization Phase**: Treated: Total: 392

completed; Extension Phase ongoing[b] and OOL Lenvatinib Treatment Period of the Extension Phase[c] ongoing)		Asia Pacific, Japan, and Latin America)	24 Jan 2014	with OOL extension Randomization (2:1); Stratified by geographic region, age, and prior VEGF/VEGFR therapy	Capsules, oral, QD, continuously in 28-day cycles **OOL Extension Phase:** LENV 24-mg and 20-mg Capsules, oral, QD, continuously in 28-day cycles	LENV: 261 Placebo: 131 Ongoing[b]: Total: 130 LENV: 122 Placebo: 8 **OOL Extension Phase:** Placebo to LENV: 109[c]
E7080-G000-201 (Treatment Phase completed; Extension Phase ongoing[b])	Advanced thyroid cancer: RR-DTC, MTC	30 (United States, Europe, and Australia)	06 Nov 2008 11 Apr 2011 08 Apr 2013	Phase 2, open-label, single-arm with Treatment and Extension Phases; Stratified by histology	LENV 24-mg (2 RR-DTC subjects received LENV 10-mg BID) Tablets, oral, QD, continuously in 28-day cycles	Treated: Total: 117 (58 DTC[d], 59 MTC) Ongoing: 52 (23 DTC)
E7080-J081-208 (Ongoing[e])	Advanced thyroid cancer: RR-DTC, MTC, ATC	3 (Japan)	03 Sep 2012 15 Sep 2013[e] 21 Feb 2014	Phase 2, open-label, single-arm with Treatment and Extension Phases; Stratified by histology	LENV 24-mg Capsules, oral, QD, continuously in 28-day cycles	Treated: 35 (22 DTC, 4 MTC, and 9 ATC), as of cut-off date Ongoing[e]: 25 (19 DTC, 2 MTC, and 4 ATC)

ATC = anaplastic thyroid cancer, BID = twice daily, DTC = LENV = lenvatinib, IIR = independent imaging review, MTC = medullary thyroid cancer, OOL = optional open label, QD = once daily, RR-DTC = radioiodine refractory differentiated thyroid cancer, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.
a: Clinical start date is date of the first subject's signed informed consent.
b: At the clinical cut-off date (when data for the primary analysis were complete), subjects treated with lenvatinib who had not experienced disease progression could request to continue the same treatment at the same dose. The numbers of ongoing subjects reported are those still receiving treatment at the clinical cut-off date.
c: For Study 303, subjects receiving placebo who had confirmed progressive disease by the IIR and continued to satisfy inclusion and exclusion criteria could enter the OOL Lenvatinib Treatment Period in the Extension Phase and were treated with lenvatinib at a starting dose of 24 mg QD (prior to Protocol Amendment 04) or 20 mg QD (as of Protocol Amendment 04).
d: Includes 56 subjects who received lenvatinib 24 mg QD and 2 subjects treated with lenvatinib 10 mg BID.
e: Study 208 is still ongoing. Data cut-off date was set at 15 Sep 2013 for the submission.

2.5.1. Dose response studies

Four Phase 1 dose-finding studies (E7080-E044-101 (Study 101), E7080-A001-102 (Study 102), E7080-J081-103 (Study 103) and E7080-J081-105 (Study 105)) were conducted to determine the

maximum tolerated dose (MTD) of lenvatinib and the optimal dosing regimen. These studies examined escalating doses of lenvatinib administered QD or BID using continuous and interrupted dosing schedules.

Study 101

In Study 101, escalating doses of lenvatinib from 0.2 to 32 mg were given QD in continuous 28-day cycles to 82 patients with advanced solid tumours or lymphomas resistant or refractory to existing therapies or for whom no treatment was available.

In this study, a clear dose-response trend was observed with respect to partial response and progressive disease. However, there was also a clear relationship between dose and the probability of developing hypertension and proteinuria. Both the hypertension and proteinuria were manageable. Hypertension was managed with antihypertensive agents at the first occurrence of a diastolic BP >100 mmHg and dose reduction, if needed. Proteinuria was managed with dose interruption or reduction with no need for renal support. Dose reductions were required for 11% of the subjects with hypertension and for 17% of the subjects with proteinuria. As the dose increased, the number of patients requiring a dose reduction increased. Proteinuria was the dose-limiting toxicity, and the maximum tolerated dose (MTD) of lenvatinib was determined to be 25 mg QD. Dose reductions were required in 54% of subjects at the MTD of 25 mg QD.

Table 21: Number of Subjects (%) with Hypertension, Proteinuria, Dose Reduction, and Anti-tumour Activities – ITT/Safety Analysis Sets – Study 101

Parameters	**Doses of Lenvatinib (QD)**			
	0.2-6.4 mg (n=21)	**12-20 mg (n=30)**	**25 mg (n=24)**	**32 mg (n=7)**
	n (%)			
Treatment-emergent Hypertension	2 (9.5%)	12 (40.0%)	15 (62.5%)	4 (57.1%)
Grade 3	1 (4.8%)	3 (10.0%)	3 (12.5%)	2 (28.6%)
Treatment-emergent Proteinuria	3 (14.3%)	8 (26.7%)	7 (29.2%)	3 (42.9%)
Grade 3	0	2 (6.7%)	2 (8.3%)	2 (28.6%)
Dose Reduction	0	5 (16.7%)	13 (54.2%)	5 (71.4%)
Antitumor Activity (Tumour response based on RECIST 1.1 criteria)				
Partial Response (PR)	0	2 (6.7%)	3 (12.5%)	2 (28.6%)
Clinical Benefit Rate (PR+SD)	4 (19.0%)	17 (56.7%)	19 (79.2%)	5 (71.4%)
Progressive Disease	5 (23.8%)	7 (23.3%)	2 (8.3%)	0

Data from Study E7080 E044-101. In Study 101, escalating doses of lenvatinib from 0.2 to 32 mg were given QD in continuous 28-day cycles to 82 subjects with advanced solid tumours. The initial dose levels and number of subjects in each group were as follows: 0.2 mg (n = 4), 0.4 mg (n = 4), 0.8 mg (n = 4), 1.6 mg (n = 3), 3.2 mg (n = 3), 6.4 mg (n = 3), 12 mg (n = 12), 12.5 mg (n = 9), 16 mg (n = 6), 20 mg (n = 3), 25 mg (n = 24), and 32 mg (n = 7). Doses provided are the initial dose levels assigned.

ITT = intent-to-treat, QD = once daily, RECIST = Response Evaluation Criteria In Solid Tumours, SD = stable disease.

Study 102

Study 102 (monotherapy portion) was a dose escalation study with 2 dosing schedules examined (Schedule 1 - dose escalation from 0.1 mg BID to 3.2 mg BID in a 7 days on/7 days off schedule; then Schedule 2 - dose escalation from 3.2 mg BID to 12 mg BID with continuous daily dosing). The study was conducted in 77 patients with solid tumours or resistant/refractory lymphomas. The MTD was determined to be 10 mg BID with continuous dosing.

Study 102 recruited 6 subjects who had thyroid cancer (5 with MTC and 1 with DTC). Three subjects with MTC had a PR; the initial dose was lenvatinib 5 mg BID for one subject and was 8 mg BID for the 2 other subjects. One subject with MTC and the 1 subject with DTC had stable disease (SD).

Study 103

Study 103 was a dose-escalation study (0.5 to 20 mg BID) in which 27 Japanese subjects with advanced solid tumours were treated with lenvatinib BID in a 2 week on/1 week off schedule. The MTD was determined to be 13 mg BID.

Study 105

Study 105 was a dose-escalation study in which 9 Japanese patients with solid tumours who were resistant to standard therapies were treated with lenvatinib (20 and 24 mg) on a once daily dose schedule in 28-day cycles. No dose-limiting toxicities were reported in either the 20-mg or 24-mg QD group.

2.5.2. Main study(ies)

E7080-G000-303 (SELECT) (study 303)

Study E708-G000-303- (Study 303) was a multicenter, randomized, double-blind, placebo-controlled study in subjects who had RR-DTC and had radiographic evidence of disease progression within the prior 12 months.

Methods

The study was conducted in 3 phases: Pre-randomisation, Randomisation and Extension Phases. The design of Study 303 is depicted in the Figure below.

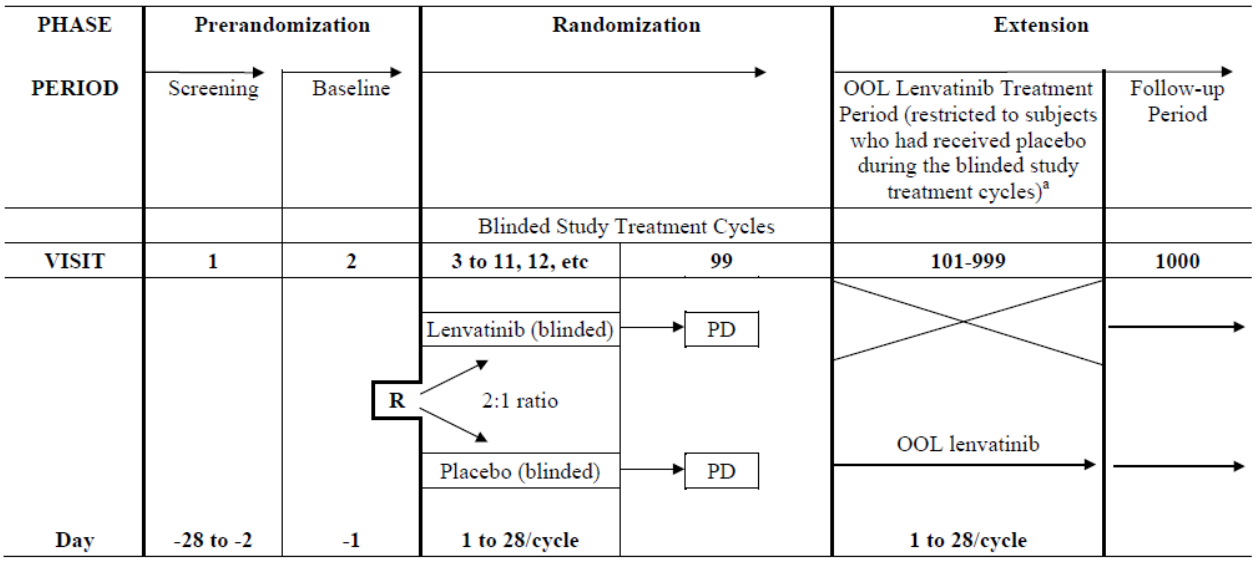


Figure 3: Design of the Study 303 ('SELECT')

OOL = optional open label, PD = progressive disease, R = randomisation

a: After confirmation of the progression of the disease, only subjects who requested to receive OOL lenvatinib were unblinded to the study drug administration. Only those subjects who received placebo as the blinded study drug could receive OOL lenvatinib. Subjects who did not wish to participate in the OOL Phase entered the Follow-up Period of the Extension Phase.

- *The Prerandomization Phase* included a screening period to establish subject eligibility and a baseline period to establish disease characteristics prior to treatment and to confirm eligibility.

- *The Randomization Phase* was the blinded study treatment phase, which began when the first subject was randomly assigned to treatment and ended at the time of the data cut-off for the primary study analysis (214 progression events or deaths prior to disease progression).

Subjects received blinded study drug until documentation of disease progression (confirmed by Independent Imaging Review (IIR)), development of unacceptable toxicity, or withdrawal of consent.

Subjects were evaluated for tumour response every 8 weeks or sooner if clinically indicated.

Subjects who discontinued treatment due to disease progression entered the Extension Phase. Subjects who discontinued treatment for any reason other than disease progression were followed in the Randomization Phase until disease progression or start of another anticancer treatment; these subjects then entered the Extension Phase for survival follow-up. All subjects on treatment at the time of the data cut-off for the primary analysis entered the Extension Phase.

- *The Extension Phase* included an optional, open-label (OOL) Lenvatinib Treatment Period and a Follow-up Period.

Subjects in the placebo arm who had disease progression confirmed by IIR could request to enter the OOL Lenvatinib Treatment Period and receive lenvatinib treatment. Subjects entering the OOL Lenvatinib Treatment Period have to have baseline tumour assessments re-established unless the last assessment in the Randomization Phase was performed within the following time periods before OOL Cycle 1/Day 1: 4 weeks for body and brain CT/MRI scans and 6 weeks for bone scans.

After the primary analysis was completed, subjects treated with lenvatinib who had not experienced disease progression could request to continue open-label lenvatinib at the same dose, according to the clinical judgment of the investigator.

Subjects taking placebo at the time of unblinding could be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or at the time of progression after a documented discussion of the risks and benefits with the investigator. Qualified subjects received lenvatinib treatment in the OOL Lenvatinib Treatment Period until disease progression (investigator's assessment), development of intolerable toxicity, or withdrawal of consent.

Subjects who had disease progression during the Randomization Phase and did not enter the OOL Lenvatinib Treatment Period and all subjects who discontinued lenvatinib treatment entered the Follow-up Period. Subjects were followed for survival, and all anticancer treatments were recorded until the time of death. The Follow-up Period will continue as long as study subjects are alive or until discontinuation of survival follow-up by the sponsor.

Independent Imaging Review (IIR)

Sites were required to submit all tumor assessment scans (CT/MRI/bone) to the IIR within 2 working days of acquisition. Scans submitted to the IIR were to be reconciled on an ongoing basis with entries in the

clinical electronic case report form (eCRF) for subject, date, anatomy, modality, and nominal time point. Once a time point was reconciled, it was to be read by 2 IIR radiologists.

Essentially, for a subject to be considered as having confirmed PD and therefore to stop therapy based on progression, a minimum of 2 readers (either both at the IIR or one each at the IIR and the investigator site radiologist) had to determine PD at the current time point.

Study Participants

Approximately 360 patients with RR-DTC and radiographic evidence of disease progression within the prior 12 months (+1 month screening window) were planned for randomization in this study.

Randomisation Phase

Table 22: Key Inclusion and Exclusion Criteria Study 303 ('SELECT')

Key inclusion criteria	**Key Exclusion criteria**
Histologically or cytologically confirmed -Papillary thyroid cancer (PTC): follicular variant and other variants (including Hürthle cell variant of papillary carcinoma, poorly differentiated) -Follicular thyroid cancer (FTC): Hürthle cell, clear cell, insular cell variants Measurable disease confirmed by central radiographic review: -at least 1 lesion of ≥ 1.0 cm in the longest diameter for a non-lymph node or ≥ 1.5 cm in the short-axis diameter for a lymph node according to RECIST 1.1 using CT/MRI. -if the only target lesion is a non-lymph node, it should have a longest diameter of ≥ 1.5 cm.	Anaplastic or medullary carcinoma of the thyroid.
≥ 18 years	Known intolerance to any of the study drugs (or any of the excipients).
ECOG performance status ≤2.	Prior treatment with lenvatinib.
Documented evidence of disease progression within 12 months (+1 month screening window, i.e., within ≤ 13 months) prior to signing informed consent, according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans	Any anticancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug and should have recovered from any toxicity related to previous anticancer treatment.
^{131}I-refractory / resistant as defined by at least one of the following: -≥ 1 measurable lesions that do not demonstrate iodine uptake on any radioiodine scan; -≥ 1 measurable lesions that has progressed by RECIST 1.1 within 12 months of ^{131}I therapy, despite	Major surgery within 3 weeks prior to the first dose of study drug.

demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning. These subjects must not be eligible for possible curative surgery; -cumulative activity of ^{131}I of > 600 mci or 22 GBq, with the last dose administered at least 6 months prior to study entry.	
Subjects may have received 0 or 1 prior VEGF/VEGFR-targeted therapy (for example sorafenib, sunitinib, pazopanib, etc.).	Two or more prior VEGF/VEGFR-targeted therapies or any ongoing treatment for ^{131}I-refractory DTC other than TSH-suppressive thyroid hormone therapy.
Subjects must be receiving thyroxine suppression therapy and thyroid stimulating hormone (TSH) should not be elevated (TSH should be ≤ 5.50 mcu/mL). When tolerated by the subject, thyroxine dose should be changed to achieve TSH suppression (TSH < 0.50 mcu/mL) and this dose can be changed concurrently upon starting lenvatinib.	Active malignancy (except for definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months.
Subjects with known brain metastases who have completed whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection, will be eligible if they have remained clinically stable, asymptomatic and off of steroids for one month.	Gastrointestinal malabsorption or any other condition that in the opinion of the investigator affect the absorption of lenvatinib.
All chemotherapy or radiation therapy related toxicities must have resolved to < Grade 2 severity, except alopecia and infertility.	Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.
Adequate renal, hepatic, blood coagulation and hematologic function. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤ 150/90 mmHg (corrected per Amendment 02) at screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1	Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment. Prolongation of QTc interval to > 480 ms. Subjects with urine protein ≥ 1 g/24h.
Females must not be lactating or pregnant at Screening or Baseline.	Active infection (any infection requiring treatment) Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial

Extension Phase - OOL Lenvatinib treatment period

Inclusion criteria

1. Placebo-treated subjects in the Randomisation Phase who had progressive disease (PD) confirmed by IIR, and who requested treatment with lenvatinib.

2. Subjects who continued to satisfy inclusion criteria 6-20 and exclusion criteria 4-16 as presented in the study protocol

3. Subjects with maximum interval between the day of confirmation of PD by IIR and Cycle 1/Day 1 of the OOL Lenvatinib Treatment Period of ≤3 months.

4. No systemic anticancer treatment during the interval between the day of confirmation of PD by the IIR and Cycle 1/Day 1 of the OOL Lenvatinib Treatment Period.

Treatments

Randomisation Phase

The starting dose of lenvatinib was 24 mg QD in the Randomization Phase. Lenvatinib 24 mg or matching placebo were taken orally as 2 capsules of 10 mg and one capsule of 4 mg, once daily (QD), continuously. A treatment cycle was defined as 28 consecutive days.

If a subject missed a dose, it could be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours elapsed from the time of the usual daily dose, study drug was to be taken the next day at the usual time in the morning. If the subject vomited after study drug administration, the subject was not to take another dose until the next scheduled dose.

Criteria for interruption of treatment, dose reduction, and resumption of treatment

Dose reductions occurred in succession based on the previous dose level (24, 20, 14, and 10 mg QD). Any dose reduction below 10 mg QD had to be discussed with the sponsor. Once the dose was reduced, it could not be increased at a later date.

Dose reduction and interruption instructions for subjects who experience treatment-related toxicity were as described in Table below:

Table 23: Study treatment dose reductions and interruption instructions

Treatment-Related Toxicity[a,b]	During Therapy	Adjusted Dose
Grade 1		
	Continue treatment	No change
Intolerable Grade 2[c] or Grade 3		
First occurrence	Interrupt until resolved to Grade 0-1 or return to baseline grade	20 mg orally once a day (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or return to baseline grade	14 mg orally once a day (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or return to baseline grade	10 mg orally once a day (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or return to baseline grade	Discuss with sponsor
Grade 4[d]	Discontinue Study Treatment	

Grading according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). All CTC grades of adverse events, decreasing and increasing, were collected.
a: A delay of study treatment for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment could be resumed.
b: Optimal medical management for nausea, vomiting, and diarrhea was initiated prior to any study treatment interruption or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject or physician to be intolerable.
d: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days prior to the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug were recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy were recorded. Any medication which was considered necessary for the subject's health and which was not expected to interfere with the evaluation of, or interact with, study drug could be continued during the study.

Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs) could be given at the discretion of the investigator, unless it was expected to interfere with the evaluation of, or to interact with, study drug.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and low molecular weight heparin (LMWH) were allowed but were to be used with caution. Granulocyte colony-stimulating factor (g-CSF) or equivalent could be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin could be used according to ASCO, institutional, or national guidelines, but the subject was to be carefully monitored for increases in red blood cell (RBC) counts.

If concomitant medication/therapy was administered for an AE, investigators recorded that AE on the Adverse Events CRF.

Objectives

Primary Objective

- To compare the progression free survival (PFS) of subjects with RR-DTC and radiographic evidence of disease progression within the prior 12 months treated with lenvatinib versus placebo

Secondary Objectives

- To compare objective response rate (ORR; complete and partial responses [CR and PR]) of subjects treated with lenvatinib versus placebo

- To compare overall survival (OS) of subjects treated with lenvatinib versus placebo
- To compare safety and tolerability of lenvatinib versus placebo
- To assess the pharmacokinetic (PK) profile of lenvatinib in subjects with DTC

Exploratory Objectives

- To compare disease control rate (DCR) (CR, PR, or stable disease [SD]), clinical benefit rate (CBR) (CR, PR + durable SD), and durable SD (duration of SD ≥23 weeks) of subjects treated with lenvatinib versus placebo
- To assess safety and efficacy (DCR, CBR and durable SD rate) of lenvatinib administered in the OOL Lenvatinib Treatment Period
- To identify and validate blood and tumor biomarkers that correlate with efficacy-related endpoints of this study
- To identify and validate DNA-sequence variants in genes influencing lenvatinib absorption, distribution, metabolism, excretion (ADME)

Outcomes / endpoints

Randomisation Phase

Primary efficacy endpoint

- PFS, defined as the time from the date of randomisation to the date of first documentation of disease progression or death (whichever occurred first) as determined by blinded Independent Imaging Review (IIR) conducted by the imaging core laboratory using RECIST 1.1

Secondary efficacy endpoints

- ORR, defined as the proportion of subjects who had best overall response (BOR) of CR or PR as determined by blinded IIR using RECIST 1.1
- OS measured from the date of randomisation until date of death from any cause.

Exploratory efficacy endpoints

- DCR, defined as the proportion of subjects who had a BOR of CR, PR, or SD. SD had to be achieved ≥7 weeks after administration of the first dose of study drug to be considered BOR.
- CB, defined as the proportion of subjects who had a BOR of CR, PR, or durable SD (duration ≥23 weeks)
- Durable SD rate, defined as the proportion of subjects with duration of SD ≥23 weeks

Extension Phase - OOL Lenvatinib treatment period

Exploratory efficacy endpoints

- DCR defined as the proportion of subjects who had BOR of CR or PR or SD, which had to be achieved ≥7 weeks after first study drug administration to be considered BOR.
- CBR defined as the proportion of subjects who had BOR of CR or PR or durable SD (duration ≥23 weeks)
- Durable SD rate defined as the proportion of subjects with duration of SD ≥23 weeks

Sample size

The sample size estimate was based on the primary endpoint, PFS, with the assumptions that survival follows an exponential distribution, an HR of 0.5714 corresponding to a 75% improvement when

comparing lenvatinib versus placebo (from a median of 8 months PFS for subjects treated with placebo to 14 months for those treated with lenvatinib), 2-tailed α = 0.01, 90% power, and an enrollment rate of 20 subjects per month.

Based on the above assumptions and the consideration of a 10% dropout rate, approximately 360 subjects were to be enrolled and randomized in a 2:1 ratio into the lenvatinib versus placebo arms, respectively.

A total of approximately 214 PFS events (progression, or deaths in the case of no progression) were required for the final analysis of PFS. The 214 PFS events were estimated to occur approximately 29 months (18 months, enrollment period; 11 months, follow-up period) after the start of the Randomisation Phase.

Randomisation

Randomisation Phase

Eligible subjects were randomly allocated in a 2:1 ratio to receive one of the 2 study drugs, administered continuously as QD oral dosing within 28-day treatment cycles: lenvatinib 24 mg or matched placebo. Randomisation was performed centrally by an interactive voice and web response system.

The randomisation scheme was stratified by region (Europe, North America, Other), age group (≤65 years or >65 years), and no prior VEGF/VEGFR targeted therapy vs one prior VEGF/VEGFR targeted therapy (0, 1).

Extension Phase - OOL Lenvatinib treatment period

Subjects randomized to placebo:

- who experienced disease progression (confirmed by IIR) during the randomisation phase could request to enter the OOL Lenvatinib Treatment Period and receive lenvatinib treatment

- at the time of unblinding due to the completion of the study primary analysis of PFS subjects could be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or at the time of progression after a documented discussion of the risks and benefits with the investigator.

Subjects randomized to lenvatinib: who had not experienced disease progression at the time of unblinding due to the completion of the study primary analysis could request to continue lenvatinib at the same dose.

Blinding (masking)

Subjects received blinded study drugs (lenvatinib or matching placebo) during the randomisation Phase of the study. The subject and all personnel involved with the conduct and the interpretation of the study, including investigators, study site personnel, and Sponsor staff, were blinded to treatment codes. Study drugs were packaged by the sponsor as double-blinded supplies for the Randomisation Phase of the study, and lenvatinib was packaged as open label drug for the Extension Phase of the study.

Statistical methods

General principles

Results were summarized using frequency and percentages for categorical data and mean, standard deviation (SD), median, minimum, maximum for continuous data. All analyses have been performed separately for Randomisation Phase and OOL Lenvatinib Treatment Period respectively except OS analysis.

Primary efficacy analysis

The primary endpoint, PFS, was compared between lenvatinib and placebo using the stratified log-rank test two-sided alpha level of 0.01 stratified by region (European, North America, Other), age group (≤ 65, > 65 years), and prior VEGF/VEGFR therapy (0, 1). The test was performed when the target number of 214 progression or deaths prior to disease progression occurred. The calculation of PFS as the primary analysis was based on disease progression as determined by tumour assessments performed by IIR. The unstratified log-rank test has been performed as supportive. The treatment effect was further characterized by the hazard ratio (HR, lenvatinib/placebo) with associated 2-sided 95% and 99% confidence intervals (CIs). This estimate has been provided using the Cox proportional hazards model stratified by region, age, and prior anti-VEGF/VEGF therapy. The median and quartiles for PFS, and the PFS rates at 6, 12, 18, and 24 months, were calculated using the Kaplan-Meier (K-M) product-limit estimates for each arm, and presented with 2-sided 95% CIs. The primary efficacy analysis was performed on the Intent to Treat analysis set with Per-Protocol analysis set as supportive. The following sensitivity analysis for the primary endpoint (PFS) were conducted:

1. Using the actual reported date of progression by IIR or death to define PFS regardless of missing assessments, treatment discontinuation, or use of new anticancer therapy

2. Using the radiologic assessment data from the investigator and death to define PFS

3. Using the uniform scheduled date of radiologic assessment to define the date of censoring and events depending on equivalence of radiologic assessment intervals between 2 treatment arms.

Secondary efficacy analyses

After achieving statistical significance at $\alpha = 0.01$ (2-sided) with primary endpoint, PFS, in favour of the lenvatinib arm, the secondary endpoints of ORR and OS were to be compared between the treatment arms by controlling the overall family-wise error rate at level $\alpha = 0.05$, using the fixed sequential testing procedure. The ORR was tested first at the 0.05 level. If the ORR achieved statistical significance at the 0.05 level (2-sided) in favour of the lenvatinib arm, then the OS was to be tested at the 0.05 level (2-sided).

- Objective Response Rate (ORR)

The null hypothesis of no difference in ORR between lenvatinib versus placebo was tested using the Cochran-Mantel-Haenszel (CMH) test at a 2-sided significance level of 0.05, stratified by region, age, and prior VEGF/VEGFR therapy. The ORR and corresponding 2-sided 95% CIs using asymptotic normal approximation was calculated by treatment arm. The 2-sided 95% CIs of the differences and odds ratio (lenvatinib versus placebo) in the ORRs between lenvatinib and placebo were calculated using asymptotic normal approximation.

- Overall Survival (OS)

Since placebo-treated subjects develop disease progression can crossover to active treatment, to estimate the true treatment effect on OS, the rank preserving structural failure time (RPSFT) model was planned to estimate OS curves as the primary analysis for survival. The difference in OS between the 2 treatment arms was evaluated using a bootstrap method. The adjusted K-M curves for the placebo arm with adjusted HR and 95% CI were estimated.

Overall survival curves were also estimated using an unadjusted K-M method and compared between treatment arms using the stratified log-rank test in the Intent-to-Treat Set. The Cox proportional hazards model was used to estimate the HR of lenvatinib versus placebo for OS and its 95% CI (stratified by the factors used for the PFS analysis). Additionally, the inverse probability of censoring weighted analysis was performed as a sensitivity analysis (see conduct of the study).

Results

Participant flow

Randomisation Phase

A total of 392 patients (n=261 lenvatinib, n=131 placebo) were randomized to receive treatment (ITT population). The Per Protocol (PP) population consisting of subjects who were randomised and received at least one dose of assigned study drug– IIR comprised 384 patients (n=257 lenvatinib, n=127 placebo).

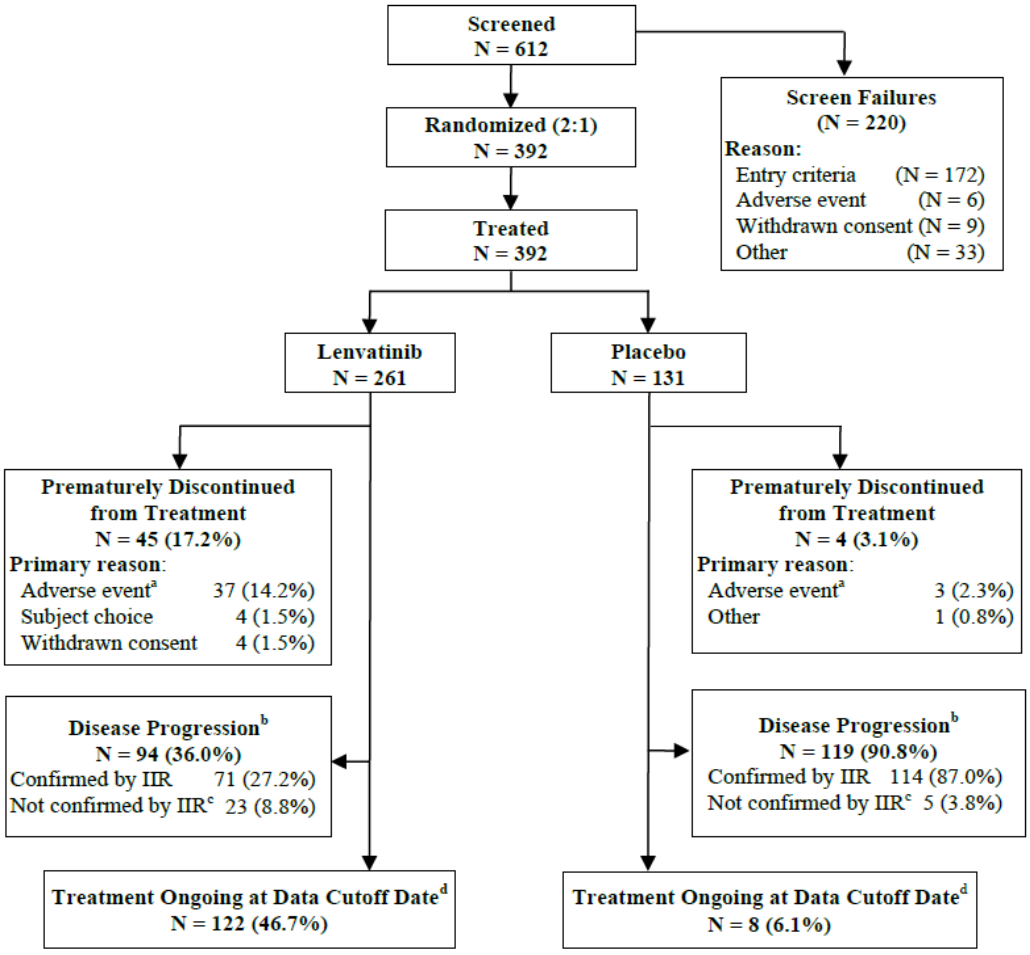


Figure 4: Flowchart of subject disposition in Randomisation Phase

a: Adverse events, including non-PD death, reported as the primary reason for discontinuation of treatment by the investigator. (This number does not include all AEs leading to study drug discontinuation, only those events recorded by the investigator as the primary reason for discontinuation.)
b: Disease progression reported by the investigator as the reason for withdrawal from the study. This differs from the number of subjects with progressive disease in the primary efficacy analysis, which followed FDA censoring guidelines for PFS and was determined by formal independent imaging review (IIR) by 2 radiologists, with adjudication where necessary.
c: Disease progression not confirmed by IIR includes subjects with disease progression as assessed by the investigator. In 7 cases (lenvatinib 3; placebo 4), postbaseline imaging scans were not performed, and in 21 cases (lenvatinib 20; placebo 1), postbaseline scans were available but IIR did not confirm disease progression; however, the investigator withdrew the subject from treatment.
d: Data cutoff date = 15 Nov 2013.

OOL Lenvatinib treatment period

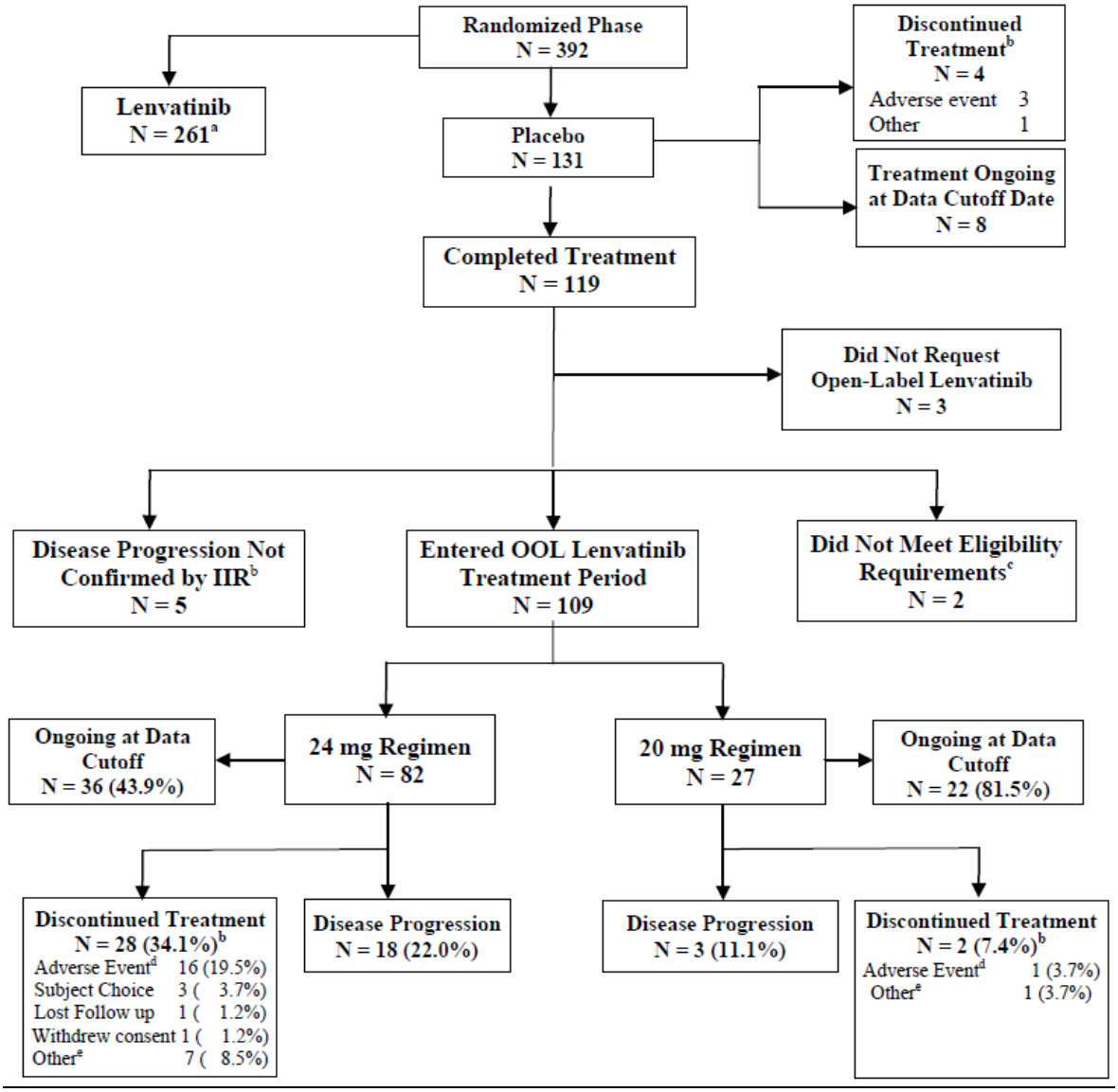


Figure 5: Flowchart of subject disposition in OOL Lenvatinib treatment period

AE = adverse events, CRF = case report form, IIR = independent imaging review, OOL = optional open-label lenvatinib.
a: Subjects not eligible for the OOL Lenvatinib Treatment Period and entered the Follow-up Period after completion of lenvatinib treatment as per protocol.
b: Reason given by the investigator for discontinuation from the trial (subject disposition CRF).
c: One subject did not meet inclusion criteria, and 1 subject was outside the 90 day maximum interval between the day of confirmation of progressive disease by IIR and Cycle 1/Day 1 of the OOL Lenvatinib Treatment Period.
d: AE reported as the primary reason for discontinuation of treatment by the investigator on the Subject Disposition CRF.
Additional AEs (3 on the 24 mg and 1 on the 20 mg regimen) were noted to have drug stopped as action taken but were not recorded by the investigator as the primary reason for discontinuation.
e: "Other" includes 3 subjects on the 24 mg regimen and 1 subject on the 20 mg regimen who died due to progressive disease while taking lenvatinib.

Data cutoff date = 15 Nov 2013

Recruitment

The study was conducted between 26 July 2011 (first enrolled subject gave informed consent) and 15 November 2013 (date of data cutoff for the primary analysis) at 117 study sites in Europe (60), North America (31), Asia Pacific (13), Japan (6), and Latin America (7). Data cutoff for the primary analysis

occurred on 15 November 2013 following the occurrence of 214 progression events or death events without disease progression.

Conduct of the study

Protocol Amendments

The original protocol was approved on 19 January 2011. There were 5 protocol amendments: Amendment 01 (08 January 2011), Amendment 02 (07 July 2011), Amendment 03 (10 April 2012), Amendment 04 (20 February 2013), and Amendment 05 (19 February 2014).

The main amendments are presented below.

Amendment 01 added an inclusion criterion specifying that eligibility must exclude possible curative surgery.

Amendment 02 led to the addition of an exploratory objective of efficacy and safety for the Optional Open Label E7080 Treatment Period, of the corresponding analysis set and clarification in regard to separate analysis of OLL data. Clarifications were provided in regard to a separation of biomarker assessments and pharmacogenetic/pharmacogenomics assessments to improve comprehension and clarification regarding planned analyses of gene mutations that may affect ADME.

Amendment 03 provided clarifications in regards to eligibility criteria in the OLL part, the timing of tumor assessments in randomisation and OLL phases, collection of tumor sample at any time during the study and in regard to the types of CT/MRI, bone, and brain scans to be used and the procedures for performing tumor assessments. Dose reduction and interruption instructions were modified to allow dose reductions at first occurrence of intolerable Grade 2 toxicity; clarified that each dose reduction is a one-level reduction and occurs in succession based on the previous dose level.

Amendment 04

• As of this amendment, subjects randomized to placebo who experienced disease progression and chose to enter the OOL Lenvatinib Treatment Period were enrolled at a 1-level dose reduction of lenvatinib, i.e., 20 mg QD, per Data Monitoring Committee (DMC) recommendation.

• After completion of the study primary analysis, at the time of unblinding, subjects treated with lenvatinib who had not experienced disease progression could request to continue lenvatinib at the same dose. Subjects taking placebo and who had radiographic evidence of disease progression could receive lenvatinib starting at 20 mg QD, per DMC recommendation.

Amendment 05 (implemented after the cutoff date for the primary analysis)

• Included guidance on the management of hepatotoxicity and thromboembolic events per agreement with the Voluntary Harmonisation Procedure (VHP).

• Required unblinding of all subjects remaining on randomized treatment after the data cutoff for the primary analysis.

• After having completed the primary analysis, subjects treated with lenvatinib who had not experienced disease progression could request to continue lenvatinib at the same dose, according to the clinical judgment of the investigator. Subjects taking placebo at the time of unblinding could be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or at the time of progression after a documented discussion of the risks and benefits with the investigator. The starting dose of lenvatinib was reverted back to 24 mg QD, because the results from the completed randomized provided definitive and

highly significant evidence of efficacy for the dose regimen starting with 24 mg, while maintaining a positive benefit/risk ratio.

Changes to the planned analyses

Before treatment unblinding

The definitions of the Per Protocol Analysis Set and Safety Analysis Set were changed from those stated in the protocol as follows:

• Per Protocol Analysis Set included those subjects who were randomized and received at least 1 dose of the assigned study drug and had no major protocol deviations. The population included those who had both baseline and at least 1 post-baseline tumor assessment, or those who died within 125 days after randomisation in the absence of post-baseline tumor assessment. This was the secondary analysis set for all tumor response related efficacy endpoints.

• Safety Analysis Set included all subjects who received any amount of study drug. This was the analysis set for all safety evaluations.

After treatment unblinding

Changes to the planned analyses after treatment unblinding included the following:

• The IPCW analysis (Robins and Finkelstein, 2000) was planned as a sensitivity analysis.

The analysis was tested but not fully implemented because the statistical model did not converge.

• Due to a limited amount of archived tumor tissue, the GEP, proteomic, and IHC analyses were not conducted.

• Ad hoc sensitivity analyses were requested by the Committee for Medicinal Products for Human Use (CHMP) as follows:

– PFS by time from most recent PD to the time of randomisation (of $\leq$ 3 or >3 months)

– Time to treatment failure (time from randomisation until objective tumor progression, use of new anticancer therapy, and treatment discontinuation due to any other reasons such as toxicity, withdrawal of consent, etc.)

– PFS using the worst case scenario when missing data were considered events. This analysis was not performed because in this study missing radiologic assessments were minimal and the treatment effect was large, therefore, worst case scenario would not change the overall result.

• Additional *ad hoc* analyses were performed to better characterize the benefit-risk profile of lenvatinib

– disposition, efficacy, and exposure by responder/non-responder status

– correlation of efficacy and safety with treatment-emergent hypertension

– time to dose reduction

– dose level at which response first reported

– AE rates before and after dose reduction

– AE rates by additional baseline and demographic subgroups

– weight change by body mass index (BMI)

• The PK data were summarized by actual concentration, not by dose-normalized concentrations as stated in the SAP. This was done to be consistent with a previous lenvatinib study (E7080-G000-204). The mean dose at each sample collection time point was added to the figure.

Protocol deviations

In the randomisation phase, major protocol deviations were reported for 4 (1.5%) subjects in the lenvatinib arm and 4 (3.1%) subjects in the placebo arm. One subject in the lenvatinib arm had 2 major protocol deviations: an overdose of study medication (144 mg) and deviation from eligibility criterion (subject had brain metastases and was not off steroids for 1 month prior to start of study drug). For two other patients eligibility criteria were not met (blood pressure outside the range; brain metastases and was not off steroids for 1 month prior to start of study drug) and one more subject had thoracocentesis for malignant pleural effusion. In placebo arm, eligibility criteria were not met for three patients and one patient received cytoreductive surgery and withdraw from the study.

One subject treated with 24 mg of lenvatinib in the OOL Treatment Period had a major protocol violation. This subject had radiotherapy during lenvatinib treatment.

Baseline data

Randomisation Phase

Demographic and baseline characteristics are summarised in Table 24.

Table 24: Demographic and baseline characteristics – Full analysis set

Parameter	Lenvatinib (N = 261)	Placebo (N = 131)	Total (N = 392)
Age (year)[a]			
n	261	131	392
Mean (SD)	62.1 (10.57)	61.5 (10.09)	61.9 (10.40)
Median	64.0	61.0	63.0
Min, Max	27, 89	21, 81	21, 89
Age group (year), n (%)			
≤65	155 (59.4)	81 (61.8)	236 (60.2)
>65	106 (40.6)	50 (38.2)	156 (39.8)
Sex, n (%)			
Male	125 (47.9)	75 (57.3)	200 (51.0)
Female	136 (52.1)	56 (42.7)	192 (49.0)
Region,[b] n (%)			
Europe	131 (50.2)	64 (48.9)	195 (49.7)
North America	77 (29.5)	39 (29.8)	116 (29.6)
Other	53 (20.3)	28 (21.4)	81 (20.7)
Race, n (%)			
White	208 (79.7)	103 (78.6)	311 (79.3)
Black or African American	4 (1.5)	4 (3.1)	8 (2.0)
Asian	46 (17.6)	24 (18.3)	70 (17.9)
Japanese	30 (11.5)	11 (8.4)	41 (10.5)
Other Asian	16 (6.1)	13 (9.9)	29 (7.4)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.3)
Other	2 (0.8)	0	2 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	10 (3.8)	9 (6.9)	19 (4.8)
Not Hispanic or Latino	251 (96.2)	122 (93.1)	373 (95.2)
TSH (μIU/mL), n (%)			
≤0.5	226 (86.6)	120 (91.6)	346 (88.3)
>0.5 to ≤2.0	25 (9.6)	10 (7.6)	35 (8.9)
>2.0 to ≤5.5	10 (3.8)	1 (0.8)	11 (2.8)
Weight (kg)			
n	261	131	392
Mean (SD)	75.7 (19.94)	78.3 (22.36)	76.6 (20.79)

Parameter	Lenvatinib (N = 261)	Placebo (N = 131)	Total (N = 392)
Median	73.3	74.0	73.5
Min, Max	33, 155	31, 165	31, 165
Height (cm)			
n	255	130	385
Mean (SD)	166.2 (10.68)	168.2 (11.71)	166.8 (11.07)
Median	166.0	168.0	166.4
Min, Max	138, 193	145, 198	138, 198
ECOG performance status, n (%)			
0	144 (55.2)	68 (51.9)	212 (54.1)
1	104 (39.8)	61 (46.6)	165 (42.1)
2	12 (4.6)	2 (1.5)	14 (3.6)
3	1 (0.4)	0	1 (0.3)
No. prior VEGF/VEGFR-targeted therapy, n (%)			
0	195 (74.7)	104 (79.4)	299 (76.3)
1	66 (25.3)	27 (20.6)	93 (23.7)

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
ECOG = Eastern Cooperative Oncology Group, Max = maximum, Min = minimum, SD = standard deviation, TSH = thyroid stimulating hormone, VEGF = vascular endothelial growth factor.
a: Age is calculated at date of informed consent.
b: North America includes Australia. Other includes Brazil, Chile, Japan, Republic of Korea, Russian Federation, and Thailand. Region was a stratification factor, not purely geographic.
Source: Table 14.1.4.1.

Disease history and characteristics

Summaries of the subject disease characteristics at study entry for the Full Analysis Set and of metastatic disease status at baseline for the Full Analysis Set as determined by IIR are presented in Tables below.

Table 25: Disease Characteristics – Full Analysis Set

Variable Category	Lenvatinib (N = 261)	Placebo (N = 131)	Total (N = 392)
I	30 (11.5)	10 (7.6)	40 (10.2)
II	12 (4.6)	12 (9.2)	24 (6.1)
≥45 years			
I	4 (1.5)	1 (0.8)	5 (1.3)
II	12 (4.6)	10 (7.6)	22 (5.6)
III	42 (16.1)	31 (23.7)	73 (18.6)
IV	150 (57.5)	65 (49.6)	215 (54.8)
IVA	57 (21.8)	21 (16.0)	78 (19.9)
IVB	5 (1.9)	1 (0.8)	6 (1.5)
IVC	88 (33.7)	43 (32.8)	131 (33.4)
Missing	11 (4.2)	2 (1.5)	13 (3.3)
Time from diagnosis of DTC to randomization (months)			
n	261	131	392
Mean (SD)	95.1 (90.48)	87.6 (69.34)	92.6 (83.99)
Median	66.0	73.9	67.5
Min, Max	0.4, 573.6	6.0, 484.8	0.4, 573.6
Time from metastatic diagnosis to randomization (months)			
n	260	131	391
Mean (SD)	54.5 (53.42)	55.6 (48.66)	54.8 (51.81)
Median	39.3	41.6	40.1
Min, Max	0.4, 433.1	3.3, 258.3	0.4, 433.1
Time from most recent disease progression to randomization (months)			
n	256	126	382
Mean (SD)	1.8 (2.20)	2.2 (2.56)	1.9 (2.33)
Median	0.7	1.1	0.9
Min, Max	0.2, 12.5	0.2, 13.6	0.2, 13.6

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
Max = maximum, Min = minimum, SD = standard deviation, TNM = tumor-mode-metastasis.
Source: Table 14.1.4.2.1.

Table 26: Baseline Metastatic Disease Status by Independent Review – Full Analysis Set

	Lenvatinib (N=261) n (%)	Placebo (N=131) n (%)
Locally advanced DTC[a]	4 (1.5)	0
Metastatic DTC[b]	257 (98.5)	131 (100)
Lung metastases	226 (86.6)	124 (94.7)
Lymph node metastases	138 (52.9)	64 (48.9)
Bone metastases	104 (39.8)	48 (36.6)
Pleural metastases	46 (17.6)	18 (13.7)
Liver metastases	43 (16.5)	28 (21.4)
Pericardium/intra-abdominal mass metastases	24 (9.2)	10 (7.6)
Musculoskeletal (non-bone)/skin metastases	10 (3.8)	5 (3.8)
Brain metastases[c]	9 (3.4)	7 (5.3)
Metastatic sites		
0	4 (1.5)	0
1	62 (23.8)	34 (26.0)
2	90 (34.5)	44 (33.6)
3	69 (26.4)	38 (29.0)
≥4	36 (13.8)	15 (11.5)

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
DTC = differentiated thyroid cancer
a: Local spread with no distant metastases.
b: Some subjects had metastases in multiple organ sites and are counted in more than one metastatic site category.
c: Subjects were eligible if their brain metastases were previously treated and had remained clinically stable, asymptomatic, and off of steroids for at least 1 month.
Source: Table 14.1.4.2.2.

One subject among the 4 patients identified with locally advanced disease was reported, based on further inspection, to have non target metastatic lesions in the lung as identified by the IIR.

Prior therapies

Overall, excluding cancer therapies, 90.4% of subjects in the lenvatinib arm and 84.7% of subjects in the placebo arm had received at least one prior medication (see Table below). The type and frequency of prior medications in the 2 treatment arms were comparable. The most frequently reported prior medications (>15% of subjects in either treatment arm) were in the following ATC classes: Alimentary Tract and Metabolism (67.4% lenvatinib; 58.0% placebo), Nervous System (52.1% lenvatinib; 48.9% placebo), Musculoskeletal System (31.8% lenvatinib; 26.0% placebo), Cardiovascular System (27.6% lenvatinib; 27.5% placebo), Blood and Blood Forming Organs (24.5% lenvatinib; 26.0% placebo), and Respiratory System (17.2% lenvatinib; 19.1% placebo).

Table 27: Prior cancer therapies and procedures – Full Analysis Set

	Lenvatinib (N=261)	Placebo (N=131)
Prior antithyroid cancer surgery		
Any prior antithyroid cancer surgery, n (%)	261 (100)	131 (100)
Prior radioiodine therapy		
Any prior radioiodine therapy,[a] n (%)	253 (96.9)	127 (96.9)
Reason for radioiodine therapy, n (%)		
Curative	188 (72.0)	86 (65.6)
Palliative	85 (32.6)	50 (38.2)
Other	29 (11.1)	17 (13.0)
Time from end of most recent radioiodine therapy to first dose of study drug (months), n (%)		
<6	31 (11.9)	12 (9.2)
6 to 12	37 (14.2)	21 (16.0)
≥12	185 (70.9)	94 (71.8)
Total dose of radioiodine therapy (GBq)		
n	249	126
Mean (SD)	16.108 (12.6034)	16.639 (11.7416)

	Lenvatinib (N=261)	Placebo (N=131)
Bone – skull/spine/thorax/pelvis/limbs	55 (21.1)	31 (23.7)
Bone – extremities	8 (3.1)	4 (3.1)
Skin	2 (0.8)	1 (0.8)
Musculoskeletal – soft tissue	16 (6.1)	6 (4.6)
Brain	9 (3.4)	7 (5.3)
Miscellaneous	7 (2.7)	2 (1.5)
Other	23 (8.8)	10 (7.6)
Progression of tumor lesion at the site since radiotherapy, n (%)		
Yes	58 (22.2)	32 (24.4)
No	58 (22.2)	26 (19.8)
Not evaluated	15 (5.7)	12 (9.2)
Time from end of most recent radiotherapy to first dose of study drug (months), n (%)		
<3	32 (12.3)	13 (9.9)
3 to 6	18 (6.9)	17 (13.0)
≥6	81 (31.0)	40 (30.5)

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
GBq = gigabecquerel, Max = maximum, Min = minimum, SD = standard deviation, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.
a: All subjects were documented to be ^{131}I refractory/resistant, including those subjects who did not receive radioiodine therapy because they had lesions that did not take up ^{131}I.
b: Subjects could be counted in multiple categories.
Source: Table 14.1.5.1, Table 14.1.5.2, Table 14.1.5.3, Table 14.1.5.4, Table 14.1.5.5.

	Lenvatinib (N=261)	Placebo (N=131)
Median	11.988	13.431
Min, Max	0.04, 70.00	1.85, 66.01
Prior VEGF/VEGFR-targeted therapy		
Any prior VEGF/VEGFR-targeted therapy, n (%)	66 (25.3)	27 (20.6)
Type of therapy, n (%)		
Sorafenib	51 (19.5)	21 (16.0)
Sunitinib	5 (1.9)	3 (2.3)
Pazopanib	3 (1.1)	2 (1.5)
Other	7 (2.7)	1 (0.8)
Duration of most recent VEGF/VEGFR-targeted therapy (months)		
n	66	27
Mean (SD)	14.17 (11.564)	13.67 (10.709)
Median	11.07	11.04
Min, Max	0.1, 61.7	2.5, 44.7
Time from end of most recent VEGF/VEGFR-targeted therapy to first dose of study drug (months), n (%)		
<3	30 (11.5)	10 (7.6)
3 to 6	18 (6.9)	4 (3.1)
≥6	18 (6.9)	13 (9.9)
Prior chemotherapy		
Any prior chemotherapy, n (%)	28 (10.7)	13 (9.9)
Prior regimens for metastatic disease, n (%)		
0	233 (89.3)	118 (90.1)
1	17 (6.5)	8 (6.1)
2	11 (4.2)	2 (1.5)
3	0	3 (2.3)
Prior Radiotherapy		
Any prior radiotherapy, n (%)	131 (50.2)	70 (53.4)
Reason for radiotherapy,[b] n (%)		
Curative	49 (18.8)	15 (11.5)
Prophylactic	16 (6.1)	6 (4.6)
Palliative	77 (29.5)	51 (38.9)
Concomitant with chemotherapy	4 (1.5)	4 (3.1)
Other	1 (0.4)	1 (0.8)
Site of prior radiotherapy, n (%)		
Lymph node – abdominal and pelvic adenopathy	1 (0.4)	0
Lymph node – neck adenopathy	30 (11.5)	12 (9.2)
Lymph node – thoracic adenopathy	14 (5.4)	10 (7.6)
Lymph node – other	11 (4.2)	2 (1.5)
Visceral – lung mass	3 (1.1)	6 (4.6)
Visceral – other	4 (1.5)	4 (3.1)

Numbers analysed

Randomisation Phase

All 392 subjects randomly assigned to treatment in the study were included in both the Full Analysis Set (Intent to-treat [ITT]) and the Safety Analysis Set. The Per Protocol Analysis Set excluded 8 subjects with major protocol violations (see above) and 1 subject who had no postbaseline assessments and comprised

383 (97.7%) subjects, 256 (98.1%) subjects in the lenvatinib arm and 127 (96.9%) subjects in the placebo arm. The Full Analysis Set was the primary analysis set used for efficacy analyses.

The analysis sets and the number of patients in each analysis set are summarised in Table below.

Table 28: Analysis sets

Analysis Set	Lenvatinib n	Placebo n	Total n
Full Analysis Set[a]	261	131	392
Per Protocol Analysis Set[b]	256	127	383
Safety Analysis Set[c]	261	131	392

Percentages are based on the number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
NA = not applicable, OOL = optional open label
a: All randomized subjects
b: Subjects who were randomized and treated, had no major protocol deviations, and had both baseline and at least 1 postbaseline tumor assessment or those who died within 125 days after randomization
c: All subjects who received any amount of the study drug in the Randomization Phase
Source: Table 14.1.3.1.

Extension Phase - OOL Lenvatinib treatment period

The OOL Lenvatinib Analysis Set included 109 of the 131 (83.2%) subjects in the placebo arm who entered the OOL Lenvatinib Treatment Period and crossed over to OOL lenvatinib.

As of the 15 Jun 2014 cutoff, of the 8 subjects who were receiving placebo in the randomization phase as of 15 Nov 2013, 6 subjects crossed over to the OOL Lenvatinib treatment phase.

Outcomes and estimation

Randomisation Phase

- **Primary efficacy endpoint - PFS (IIR-determined, Full analysis set)**

Table 29: PFS based on IRR and FDA censoring guidance – Full analysis set

	Lenvatinib (N=261)	Placebo (N=131)
Median PFS, months (95% CI)[a]	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Q1, Q3	7.4, NE	1.9, 6.7
Stratified Log-Rank Test (*P* value)[b]	*P*<0.0001	
Unstratified Log-Rank Test (*P* value)	*P*<0.0001	
Stratified Hazard Ratio (99% CI)[b,c]	0.21 (0.14, 0.31)	
PFS Rate, % (95% CI)[a]		
6 months	77.5 (71.7, 82.3)	25.4 (18.0, 33.6)
12 months	63.0 (56.5, 68.9)	10.5 (5.7, 16.9)
18 months	51.1 (43.3, 58.3)	3.8 (1.1, 9.2)
24 months	44.3 (35.1, 53.1)	NE (NE, NE)
Subjects with events, n (%)	107 (41.0)	113 (86.3)
Progressive disease[d]	93 (35.6)	109 (83.2)
Death	14 (5.4)	4 (3.1)
Censored subjects, n (%)	154 (59.0)	18 (13.7)
No baseline or postbaseline tumor assessment[e]	3 (1.1)	0
No progression	116 (44.4)	5 (3.8)
Death or progression after more than 1 missed assessment	1 (0.4)	0
New anticancer treatment started	0	0
Treatment discontinuation for reasons other than progressive disease[d]	34 (13.0)	13 (9.9)

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
CI = confidence interval, IxRS = interactive voice and web response system, NE = not estimable, PFS = progression-free survival, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.
a: The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
b: Stratified by region (Europe, North America, Other), age group (≤65, >65 years), and prior VEGF/VEGFR-targeted therapy (0, 1) from IxRS data.
c: The hazard ratio is expressed as lenvatinib/placebo and was estimated from a Cox proportional hazard model, stratified by IxRS randomization data.
d: Progressive disease for the determination of PFS for the primary analysis was based on confirmed tumor assessments by the IIR and FDA guidances on PFS censoring.
e: The 3 subjects in the lenvatinib arm were censored because they did not have a postbaseline tumor assessment as they were discontinued before the tumor assessment at 8 weeks. Subject 10201005 in the placebo arm, who did not have a post-baseline assessment, is included in the last row of the table (Listing 16.2.6.12.1 and Listing 16.2.1.2).
Source: Table 14.2.1.1.

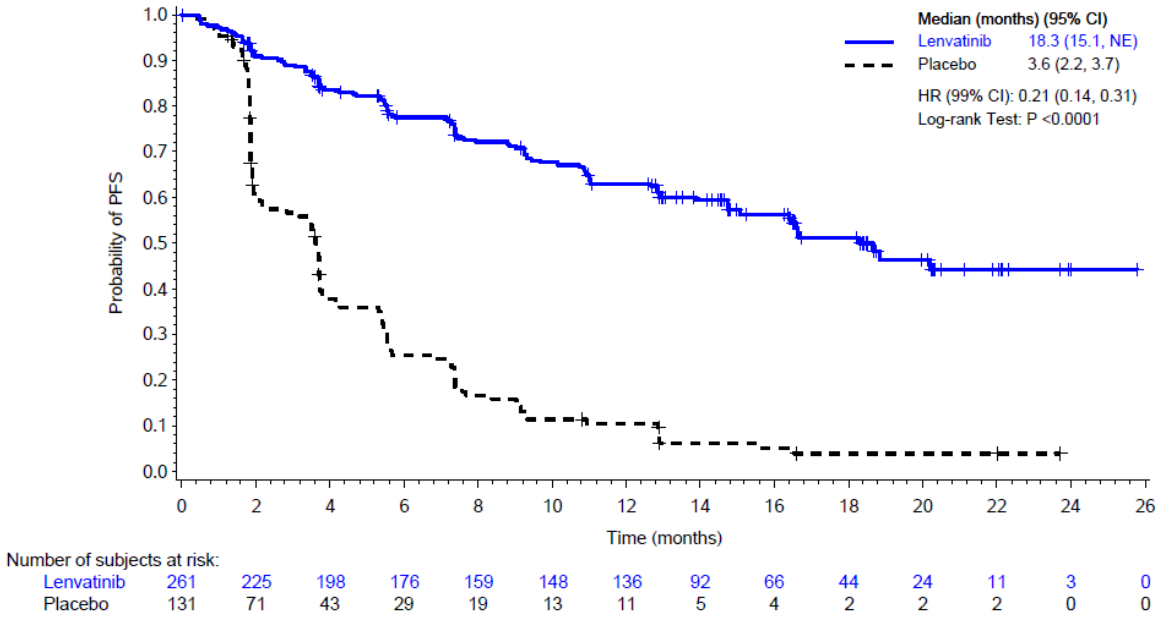


Figure 6: Kaplan-Meier Plot of PFS: IRR – Full analysis set

Data cutoff = 15 Nov 2013

Table 30: PFS: Sensitivity analyses – Full analysis set

	Primary Analysis Assessment by IIR		**Sensitivity Analysis A**[a] Assessment by IIR (all PDs and Deaths as Events)		**Sensitivity Analysis B**[b] Assessment by Investigator		**Sensitivity Analysis C**[c] Assessment by IIR (Uniform Time of Assessment)	
	Lenvatinib (N=261)	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**
Median PFS, mo (95% CI)[d]	18.3 (15.1, NE)	3.6 (2.2, 3.7)	16.6 (14.8, 20.3)	3.6 (2.2, 3.7)	16.6 (14.8, NE)	3.7 (3.5, 5.4)	18.4 (16.6, NE)	3.7 (NE, NE)
Q1, Q3	7.4, NE	1.9, 6.7	7.4, NE	1.9, 6.7	7.9, NE	1.9, 9.1	7.4, NE	1.9, 7.4
Stratified Log-Rank Test[e]	*P*<0.0001		*P*<0.0001		*P*<0.0001		*P*<0.0001	
Unstratified Log-Rank Test	*P*<0.0001		*P*<0.0001		*P*<0.0001		*P*<0.0001	
Stratified HR (99% CI)[e,f]	0.21 (0.14, 0.31)		0.22 (0.15, 0.32)		0.24 (0.16, 0.35)		0.24 (0.16, 0.35)	
Subjects with events, n (%)	107 (41.0)	113 (86.3)	119 (45.6)	114 (87.0)	107 (41.0)	110 (84.0)	107 (41.0)	113 (86.3)
Progressive disease	93 (35.6)	109 (83.2)	98 (37.5)	110 (84.0)	91 (34.9)	104 (79.4)	93 (35.6)	109 (83.2)
Death	14 (5.4)	4 (3.1)	21 (8.0)	4 (3.1)	16 (6.1)	6 (4.6)	14 (5.4)	4 (3.1)
Censored subjects, n (%)	154 (59.0)	18 (13.7)	142 (54.4)	17 (13.0)	154 (59.0)	21 (16.0)	154 (59.0)	18 (13.7)
Reasons for censoring								
No baseline or postbaseline tumor assessment	3 (1.1)	0	3 (1.1)	0	3 (1.1)	0	3 (1.1)	0
No progression	116 (44.4)	5 (3.8)	128 (49.0)	5 (3.8)	108 (41.4)	8 (6.1)	116 (44.4)	5 (3.8)
New anticancer treatment	0	0	11 (4.2)	12 (9.2)	0	0	0	0
Death or progression after more than 1 missing assessment	1 (0.4)	0	NA	NA	1 (0.4)	0	1 (0.4)	0
Treatment discontinued - reasons other than PD	34 (13.0)	13 (9.9)	NA	NA	42 (16.1)	13 (9.9)	34 (13.0)	13 (9.9)

	Primary Analysis Assessment by IIR		Sensitivity Analysis A[a] Assessment by IIR (all PDs and Deaths as Events)		Sensitivity Analysis B[b] Assessment by Investigator		Sensitivity Analysis C[c] Assessment by IIR (Uniform Time of Assessment)	
	Lenvatinib (N=261)	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**
PFS Rate % (95% CI)[a]								
6 months	77.5 (71.7, 82.3)	25.4 (18.0, 33.6)	77.3 (71.6, 82.0)	25.2 (17.7, 33.2)	80.3 (74.7, 84.8)	29.9 (22.2, 38.1)	77.8 (72.1, 82.5)	26.5 (18.8, 34.7)
12 months	63.0 (56.5, 68.9)	10.5 (5.7, 16.9)	61.5 (55.0, 67.3)	10.3 (5.6, 16.7)	64.1 (57.5, 69.9)	15.0 (9.4, 22.0)	63.3 (56.8, 69.2)	11.0 (6.0, 17.5)
18 months	51.1 (43.3, 58.3)	3.8 (1.1, 9.2)	47.9 (40.5, 55.0)	3.8 (1.1, 9.1)	49.7 (41.8, 57.0)	9.8 (4.6, 17.3)	52.8 (45.4, 59.6)	4.2 (1.3, 9.8)
24 months	44.3 (35.1, 53.1)	NE (NE, NE)	39.7 (30.5, 48.6)	NE (NE, NE)	44.1 (34.9, 52.9)	NE (NE, NE)	47.2 (38.7, 55.2)	NE (NE, NE)

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
CI = confidence interval, HR = hazard ratio, IIR = independent imaging review, IxRS = interactive voice and web response system, NA = not applicable, NE = not estimable, PD = progressive disease, PFS = progression-free survival, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.
a: Sensitivity Analysis A = All disease progression and deaths events were used to determine PFS even if a subject had missing assessments or treatment discontinuation due to reasons other than PD. All events before the use of new anticancer therapies, crossover to OOL lenvatinib treatment, or data cutoff date were used.
b: Sensitivity Analysis B: The radiologic assessment data for disease progression from the investigator and death was used to determine PFS.
c: Sensitivity Analysis C: The uniform scheduled date of radiologic assessment was used to define the date of censoring and events depending on equivalence of radiologic assessment intervals between 2 treatment arms.
d: The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
e: Stratified by region (Europe, North America, Other), age group (≤65, >65 years), and prior VEGF/VEGFR-targeted therapy (0, 1) from IxRS data.
f: The hazard ratio is expressed as lenvatinib/placebo and was estimated from a Cox proportional hazard model, stratified by IxRS randomization data.
Source: Table 14.2.1.1, Table 14.2.1.4, Table 14.2.1.5, and Table 14.2.1.6.

- **Secondary efficacy endpoint - overall survival**

Using a stratified Cox proportional hazard model without making any adjustments for placebo-treated subjects who crossed over to treatment with open-label lenvatinib, the HR was 0.73 (95% CI: 0.50, 1.07, p=0.1032) at the time of the primary efficacy analysis. The median OS had not been reached for either the lenvatinib group or the placebo group. The OS rates were numerically higher in the lenvatinib arm compared with the placebo arm (12 months: 81.6% vs 75.4%, respectively; 18 months: 72.3% vs 62.5%, respectively; 24 months: 58.2% vs 54.6%, respectively).

Updated OS analysis at data cutoff date June 2014 is presented below.

Table 31: Overall survival – unadjusted - FAS

Overall Survival - Unadjusted
Full Analysis Set

	Lenvatinib (N = 261)	Placebo (N = 131)
Stratified Cox Model Hazard Ratio (95% CI)[a, b]	0.80 (0.57, 1.12)	
Stratified Log-rank Test P-value[a, b]	0.1993	
Death, n (%)	93 (35.6)	55 (42.0)
Censored Subjects, n (%)	168 (64.4)	76 (58.0)
Lost to follow-up	0 (0.0)	0 (0.0)
Withdrawal of consent	15 (5.7)	3 (2.3)
Alive	153 (58.6)	73 (55.7)
Median Overall Survival (months) (95% CI)[c]	NE (30.9, NE)	NE (21.7, NE)
Q1, Q3	16.3, NE	13.1, NE
Median Follow-up (months) (95% CI)[c]	23.6 (22.7, 24.5)	24.1 (22.2, 26.1)
Q1, Q3	21.2, 27.3	21.4, 27.1

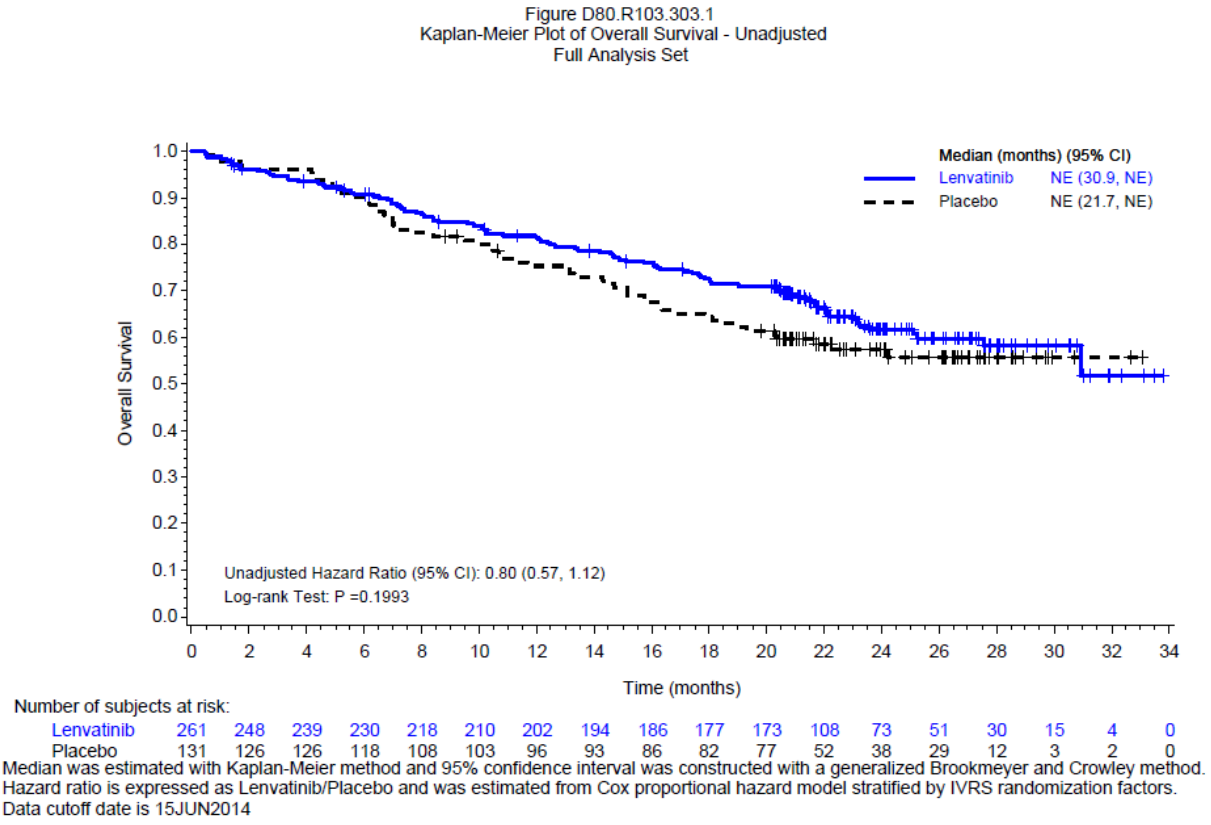


Figure 7: Kaplan-Meier Plot of Overall Survival - Unadjusted Model – Full Analysis Set (15 June 2014)

As at data cutoff date June 2014 and with adjustment for crossover by using the Rank Preserving Structural Failure Time model, there was a significant difference in overall survival between the treatment groups (HR=0.53; 95%CI: 0.34, 0.82, p=0.0051). The difference had already bordered statistical significance at the data cutoff for the primary efficacy analysis (see Table 32).

Table 32: Overall survival data for Study 303 as of the original cutoff date (15 Nov 2013) for the Marketing Authorization Application (MAA) and the updated cutoff date of 15 June 2014 (adjusted analysis)

Parameter	Study 303[a]			
	Lenvatinib (N=261)		Placebo (N=131)	
	Cutoff date:		Cutoff date:	
	15 Nov 2013	15 Jun 2014	15 Nov 2013	15 Jun 2014
No. of subjects who crossed over, n (%)	NA	NA	109 (83.2)	115 (87.8)
No. of subjects who died, n (%)	71 (27.2)	93 (35.6)	47 (35.9)	55 (42.0)
No. of subjects who were censored, n (%)	190 (72.8)	168 (64.4)	84 (64.1)	76 (58.0)
Median follow-up, months(95% CI)	17.1 (16.0, 17.6)[b]	23.6 (22.7, 24.5)[b]	17.4 (15.9, 19.0)[b]	24.1 (22.1, 26.1)[b]
Hazard Ratio (95% CI)	0.62[b] (0.40, 1.00)	0.53[c] (0.34, 0.82)	-	-
P value	P=0.0510	P=0.0051		
Median OS, months (95% CI)	NE (22.0, NE)[d]	NE (30.9, NE)	NE (14.3, NE)[b]	19.1 (14.3, NE)[b]

CI = confidence interval; DTC = differentiated thyroid cancer; HR: hazard ratio; ITT = intent-to-treat; NA = not applicable; NE = not estimable; OS = overall survival.

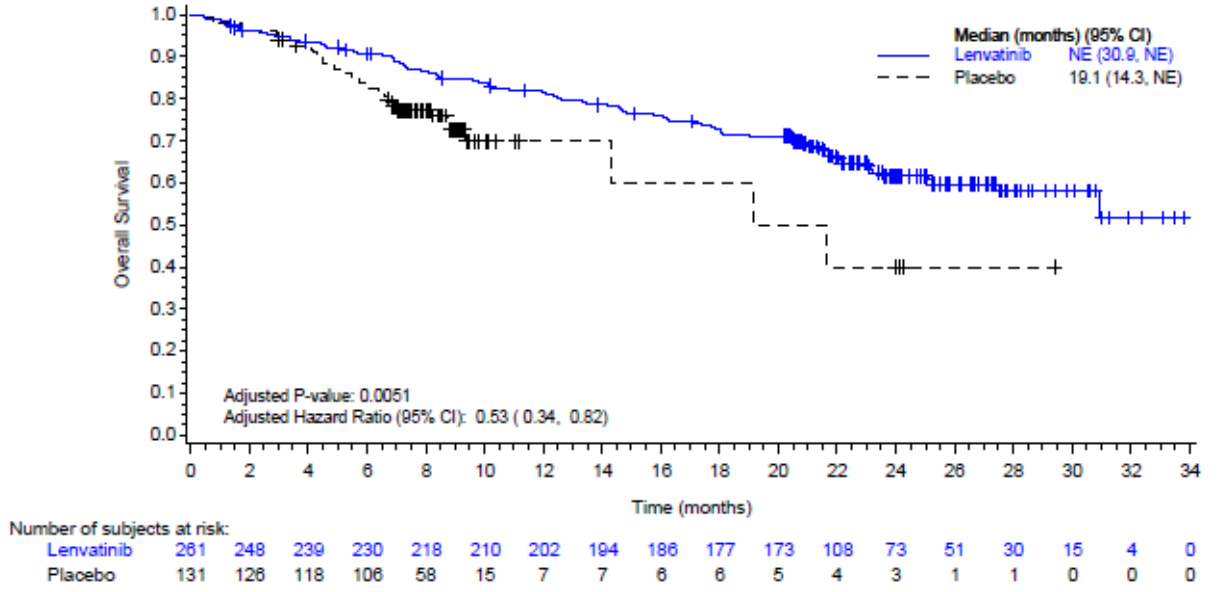
a: Overall survival data for Study 303 shown here were adjusted using a planned Rank-Preserving Structural Failure Time (RPSFT) model to correct for the bias due to treatment crossover from placebo to lenvatinib and to

estimate the treatment effect of lenvatinib on OS. The p-value and 95% CI of the adjusted hazard ratio are from bootstrapping.

b: The RPSFT HR is expressed as lenvatinib/placebo.

c: The HR is expressed as lenvatinib/placebo and the CI is from bootstrapping. The unadjusted HR is 0.80 (0.57, 1.12).

d: Median OS was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.



RPSFT: Rank-Preserving Structural Failure Time model
Median was estimated with Kaplan-Meier method and 95% confidence interval was constructed with a generalized Brookmeyer and Crowley method.
Hazard ratio is expressed as Lenvatinib/Placebo and was estimated from unstratified Cox proportional hazard model.
The p-value and 95% CI of adjusted hazard ratio are from bootstrapping.
Data cutoff date is 15JUN2014

Figure 8: Kaplan-Meier Plot of Overall Survival Adjusted with RPFST Model

Secondary efficacy endpoint - response rate

Table 33: Objective response: IIR and investigators review – Full analysis set

	Assessment by the IIR		Assessment by the Investigator	
	Lenvatinib (N=261)	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**
Objective response rate (CR + PR)				
n (%)	169 (64.8)	2 (1.5)	155 (59.4)	3 (2.3)
95% CI[a]	(59.0, 70.5)	(0.0, 3.6)	(53.4, 65.3)	(0.0, 4.9)
Rate difference lenvatinib vs placebo (95% CI)[a]	63.2 (57.1, 69.4)		57.1 (50.6, 63.6)	
Odds ratio (95% CI)[b]	28.87 (12.46, 66.86)		25.81 (11.34, 58.71)	
P value (lenvatinib vs placebo)[b]	*P*<0.0001		*P*<0.0001	
No. of responders (CR + PR)	**(n=169)**	**(n=2)**	**(n=155)**	**(n=3)**
Duration of Objective Response (months)				
Median (95% CI)[c]	NE (16.8, NE)	NE (NE, NE)	NE (13.3, NE)	NE (NE, NE)
Q1, Q3	9.4 , NE	NE, NE	11.1, NE	NE, NE
Time to First Objective Response (months)				
Median (95% CI)[c]	2.0 (1.9, 3.5)	5.6 (1.8, 9.4)	3.5 (1.9, 3.7)	9.4 (1.8, 11.0)
Q1, Q3	1.9, 3.7	1.8, 9.4	1.9, 4.9	1.8, 11.0
	(N=261)	**(N=131)**	**(N=261)**	**(N=131)**
Best Overall Tumor Response, n (%)				
CR	4 (1.5)	0	3 (1.1)	0
PR	165 (63.2)	2 (1.5)	152 (58.2)	3 (2.3)
SD	60 (23.0)	71 (54.2)	81 (31.0)	77 (58.8)
Durable stable disease	40 (15.3)	39 (29.8)	59 (22.6)	51 (38.9)
Progressive disease	18 (6.9)	52 (39.7)	10 (3.8)	45 (34.4)
Not evaluable[d]	1 (0.4)	2 (1.5)	2 (0.8)	2 (1.5)
Unknown[e]	13 (5.0)	4 (3.1)	13 (5.0)	4 (3.1)

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013. As described in Section 11.4.1, 9 subjects (all in the lenvatinib arm) did not have a confirmatory bone scan after response.
Tumor assessment was based on RECIST 1.1 criteria. Objective response rate = CR + PR. Durable SD = SD with duration ≥23 weeks. Stable disease must have been ≥7 weeks after randomization.
BOR = best overall response, CI = confidence interval, CR = complete response, IxRS = interactive voice and web response system, PR = partial response, RECIST = Response Evaluation Criteria In Solid Tumors, SD = stable disease.
a: 95% CI calculated using asymptotic normal approximation.
b: *P* value and odds ratio were calculated using Cochran Mantel-Haenszel test, stratified by region (Europe, North America, Other), age group (≤65, >65 years), and prior VEGF/VEGFR-targeted therapy (0, 1) from IxRS data.
c: The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
d: A BOR of "not evaluable" applied when a subject had a response of NE at a scheduled tumor assessment time point followed by progressive disease, or for a subject with stable disease achieved <7 weeks after randomization.
e: A BOR of "unknown" occurred when a subject did not have a postbaseline tumor assessment.
Source: Table 14.2.3.1 and Table 14.2.3.2.

An analysis of concordance of the BOR between tumor assessments by the IIR and by investigator for each subject using a weighted Kappa coefficient for interrater agreement, showed substantial agreement; the Kappa observed was 0.69 for the lenvatinib arm and 0.70 for the placebo arm, where 0 is no agreement and 1 is perfect agreement.

The ORR, based on the IIR assessments, in the per protocol analysis set, was consistent with the ORR based on the IIR assessments in the full analysis set. The ORR, based on the IIR assessments, in the per protocol analysis set, was 65.2% (95% CI: 59.4, 71.1) in the lenvatinib arm and 0.8% (95% CI: 0.0, 2.3) in the placebo arm. The difference between the 2 arms was 64.4% (95% CI: 58.4, 70.5). The odds ratio was 29.20 (95% CI: 12.25, 69.59), which was statistically significant (p<0.0001) in favour of lenvatinib treatment.

Exploratory efficacy endpoints

Table 34: Exploratory efficacy analyses: assessments by IIR and investigator review – Full analysis set

	Assessment by the IIR		Assessment by the Investigator	
	Lenvatinib (N=261)	**Placebo (N=131)**	**Lenvatinib (N=261)**	**Placebo (N=131)**
Disease Control Rate (CR + PR + SD), n (%)	229 (87.7)	73 (55.7)	236 (90.4)	80 (61.1)
95% CI[a]	(83.8, 91.7)	(47.2, 64.2)	(86.9, 94.0)	(52.7, 69.4)
Rate difference lenvatinib vs placebo, % (95% CI)	32.0 (22.6, 41.4)		29.4 (20.3, 38.4)	
Odds Ratio (95% CI)	5.05 (2.98, 8.54)		4.98 (2.81, 8.82)	
P value[b]	*P*<0.0001		*P*<0.0001	
Clinical Benefit Rate (CR + PR + durable SD), n (%)	209 (80.1)	41 (31.3)	214 (82.0)	54 (41.2)
95% CI[a]	(75.2, 84.9)	(23.4, 39.2)	(77.3, 86.7)	(32.8, 49.7)
Rate difference lenvatinib vs placebo, % (95% CI)	48.8 (39.5, 58.1)		40.8 (31.1, 50.4)	
Odds Ratio (95% CI)	7.63 (4.55, 12.79)		6.32 (3.84, 10.39)	
P value[b]	*P*<0.0001		*P*<0.0001	
Duration of Stable Disease (months)				
Median (95% CI)[c]	9.3 (5.7, 16.5)	5.6 (5.3, 7.4)	9.6 (7.9, 14.7)	5.7 (5.5, 7.4)
Q1, Q3	5.5, 16.5	3.7, 9.0	6.3, NE	3.9, 10.8

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
Tumor assessment was based on RECIST 1.1 criteria. Objective response = CR + PR. Disease control response = CR + PR + SD. Clinical benefit response = CR + PR + durable SD. Durable SD = SD with duration ≥23 weeks. Stable disease must have been ≥7 weeks after randomization.
CI = confidence interval, CR = complete response, IxRS = interactive voice and web response system, PR = partial response, NE = not estimable, RECIST = Response Evaluation Criteria In Solid Tumors, SD = stable disease.
a: 95% CI calculated using asymptotic normal approximation.
b: *P* value and odds ratio were calculated using Cochran Mantel-Haenszel test, stratified by region (Europe, North America, Other), age group (≤65, >65 years), and prior VEGF/VEGFR-targeted therapy (0, 1) from IxRS data.
c: The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
Source: Table 14.2.3.1 and Table 14.2.3.2.

Ancillary analyses

Randomisation Phase

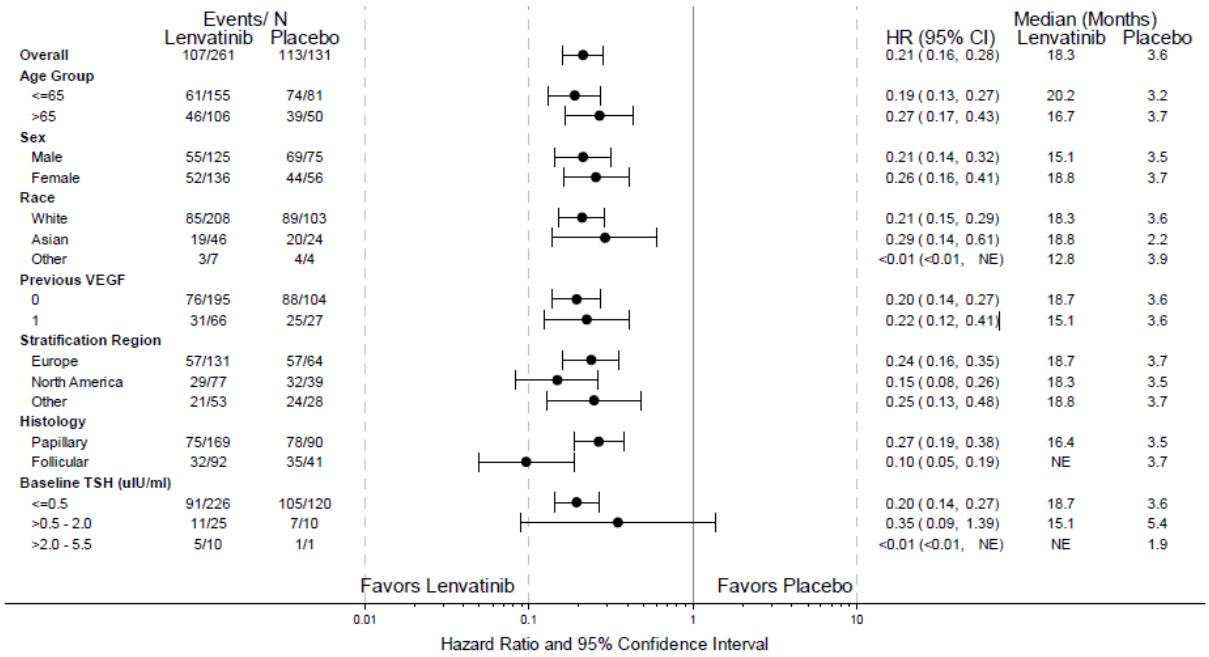
- *Ad hoc analyses requested by CHMP*

Table 35: Time to treatment failure and additional sensitivity analyses for PFS – IRR – Full analysis set

	Time to Treatment Failure[a]		PFS - Primary Analysis – Full Analysis Set[b]		PFS Based on Time From Most Recent Assessment of PD to Randomization[c]			
					<3 months		≥3 months	
	Lenv (N=261)	Placebo (N=131)	Lenv (N=261)	Placebo (N=131)	Lenv (N=215)	Placebo (N=100)	Lenv (N=46)	Placebo (N=31)
Median, mo (95% CI)[d]	13.8 (10.8, 16.6)	3.5 (2.1, 3.7)	18.3 (15.1, NE)	3.6 (2.2, 3.7)	18.7 (15.1, NE)	3.6 (1.9, 3.7)	16.6 (8.8, NE)	3.7 (1.9, 6.7)
Stratified log-rank test[e]	*P*<0.0001		*P*<0.0001		*P*<0.0001		*P*<0.0001	
Stratified HR[e,f]	0.26 (99% CI: 0.18, 0.37)		0.21 (99% CI: 0.14, 0.31)		0.19 (95% CI: 0.14, 0.27)		0.35 (95% CI: 0.17, 0.74)	

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date = 15 Nov 2013.
CI = confidence interval, HR = hazard ratio, IxRS = interactive voice and web response system, Lenv = lenvatinib, NA = not applicable, NE = not estimable, PD = progressive disease, PFS = progression-free survival, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.
a: Time to treatment failure: time from randomization until objective tumor progression, use of new anticancer therapy, and treatment discontinuation due to any other reasons such as toxicity, withdrawal of consent, etc.
b: The primary analysis was based on the Full Analysis Set (see Table 17).
c: PFS was determined for subgroups based on the time from the most recent assessment of PD before study entry to the time of randomization (≤ or >3 months).
d: The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
e: Stratified by region (Europe, North America, Other), age group (≤65, >65 years), and prior VEGF/VEGFR-targeted therapy (0, 1) from IxRS data.
f: HR expressed as lenvatinib/placebo and was estimated from a Cox proportional hazard model, stratified by IxRS data.
Source: Table 14.2.1.1, Table 14.2.5.1, Table 14.2.5.2, and Figure 14.2.5.1.8.

- *Subgroup analysis*



Other Race group includes Black or African American, Native Hawaiian or other Pacific Islander, and Other
Median was estimated with Kaplan-Meier method and 95% confidence interval was constructed with a generalized Brookmeyer and Crowley method.
Hazard ratio is expressed as Lenvatinib/Placebo and was estimated from Stratified Cox proportional hazard model.
Program: R:\projects\e7080\g000-303\csr2014comb\dev\pg\g_fas_forest_pfs.sas Data cutoff date 15NOV2013 20MAR2014 23:38

Figure 9: Forest plots of hazard ratio for lenvatinib versus placebo for PFS in subgroups: IIR – Full analysis set

- *Tumour shrinkage*

Additional ad hoc analyses were conducted to explore the time of the tumour shrinkage. Lenvatinib induced a rapid onset of tumour shrinkage, with an initial large reduction (median reduction >20%) in the sum of the diameters of target lesions at the first tumour assessment (8 weeks after randomisation), followed by a slower decline that continued despite dose interruptions or dose reductions. The maximum percentage of tumour shrinkage was correlated with longer treatment duration. In subjects who had a dose reduction due to toxicity, the majority of tumour shrinkage occurred during treatment with the 24 mg dose, prior to the first dose reduction.

- *Efficacy outcome(s) to subsequent treatments*

Study 303 was not planned or designed to evaluate subsequent lines of therapy, i.e., progression-free survival 2 (PFS2) or end-of-next-line-treatment. There was no further radiology data collected after lenvatinib discontinuation. Therefore, PFS2, in this situation, is estimated by end of next treatment.

A total of 108 lenvatinib subjects and 10 placebo subjects discontinued due to PD and did not enter the OOL treatment period (lenvatinib subjects were not eligible for the OOL treatment period). Only 40 (37%) lenvatinib and 4 (40%) placebo subjects received next-line anticancer therapy. Median PFS2 (as end-of-next-line therapy) for the lenvatinib subjects was 16.1 months (95% CI: 12.6, 19.7) and was 4.2 months (95% CI: 0.3, 11.6) for the placebo subjects. Further, a total of 48 lenvatinib and 5 placebo subjects discontinued treatment due to reasons other than PD. Of these subjects, 17 lenvatinib (35.4%) and no placebo subjects received next-line anticancer treatment. Median time to progression or death for the lenvatinib subjects was 16.4 months (95% CI: 8.9, NE). Four of the 5 placebo subjects died; median time to progression or death was 6.7 months (95% CI: 4.9, NE).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36: Summary of efficacy for trial 303

Title: Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (The 'SELECT' Trial) A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer		
Study identifier	E7080-G000-303, NCT01231554, 2010-02378-41	
Design	multicenter, multinational, randomized, double-blind, placebo-controlled	
	Duration of Main phase:	until confirmed disease progression (by Independent Imaging Review [IRR]), development of unacceptable toxicity, or withdrawal of consent 26 Jul 2011- 15 Nov 2013 (data cut-off)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	until disease progression (by investigator's assessment), development of unacceptable toxicity, or withdrawal of consent 03 Oct 2011- 15 Nov 2013 (data cut-off)
Hypothesis	Superiority (main phase), Exploratory (extension phase)	

Treatments groups	lenvatinib		Main Phase: 24 mg (two 10-mg capsules and one 4-mg capsule), once daily, oral dosing, continuously with 28-day treatment cycles N=261 Extension Phase: 24 mg (two 10-mg capsules and one 4-mg capsule), once daily, oral dosing, continuously with 28-day treatment cycles As of Amendment 4 (from 16 Feb 2013), lenvatinib at a dose of 20 mg (two 10-mg capsules) QD. Lenvatinib 24 mg: n=82 Lenvatinib 20 mg: n=27 N=109
	placebo		Main Phase: matching placebo capsule, once daily, oral dosing, continuously with 28-day treatment cycles N=131 Extension Phase: n/a
Endpoints and definitions	Primary endpoint (main phase)	Progression Free Survival (PFS)	Time from randomization to first documentation of disease progression or death as determined by blinded IIR conducted by the imaging core laboratory using RECIST 1.1 The robustness of the primary efficacy analysis (Full analysis set) was supported by using multiple sensitivity and secondary efficacy (Per Protocol analysis set) analysis.
	Secondary endpoints (main phase)	Objective Response Rate (ORR)	Proportion of subjects who had best overall response (BOR)of complete response (CR) or partial response (PR) as determined by blinded IRR using RECIST1.1
		Overall Survival (OS)	Time from randomization until death from any cause
	Exploratory efficacy endpoints (main and extension phases)	Disease Control Rate (DCR)	Proportion of subjects who had BOR of CR, PR or stable disease (SD). SD had to be achieved ≥ 7 weeks after administration of first dose of study drug.
		Clinical Benefit Rate (CBR)	Proportion of subjects who had BOR of CR, PR or durable SD (duration ≥23 weeks).
		Durable SD rate	Proportion of subjects with duration of SD ≥23 weeks

	Ad hoc as requested by CHMP (main phase)	Time to Treatment Failure (TTP) PFS based on:	Time from randomization until objective tumour progression, use of new anticancer therapy, and treatment discontinuation due to any other reasons as toxicity, withdrawal of consent, etc. Time from most recent assessment of Progressive Disease before study entry to time of randomization (<3 or ≥3 months).
Database lock	15 November 2013		

<u>Results and Analysis</u> (Main Phase)

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (Intent-to-Treat) consisting of all randomized subjects – IIR **15 November 2013**		
Descriptive statistics and estimate variability	**Treatment group**	**Lentavinib**	**placebo**
	Number of subject	**261**	**131**
	PFS (median, in months)	18.3	3.6
	95% CI	15.1, NE	2.2, 3.7
	ORR (N (%))	169 (64.8)	2 (1.5)
	95% CI	59.0, 70.5	0.0, 3.6
	OS – adjusted (median, in months)	Not estimable (NE)	NE
	95% CI	22.0, NE	14.3, NE
	OS – unadjusted (median, in months)	NE	NE
	95% CI	22.0, NE	20.3, NE
	DCR (N (%))	229 (87.7)	73 (55.7)
	95% CI	83.8, 91.7	47.2, 64.2
	CBR (N (%))	209 (80.1)	41 (31.3)
	95% CI	75.2, 84.9	23.4, 39.2
	Durable SD rate (N (%))	40 (15.3)	39 (29.8)
	95% CI	n/a	n/a
	TTP (median, in months)	13.8	3.5
	95% CI	10.8, 16.6	2.2, 3.7
	Number of subject	**215**	**100**

	PFS ad hoc <3 months (median, in months)	18.7	3.6
	95% CI	15.1, NE	1.9, 3.7
	Number of subject	**46**	**31**
	PFS ad hoc ≥3 months (median, in months)	16.6	3.7
	95% CI	8.8, NE	1.9, 6.7
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	lenvatinib vs placebo
		Stratified HR	0.21
		99% CI	0.14,0.31
		P-value Stratified Unstratified	 <0.0001 <0.0001
	Secondary endpoint ORR	Comparison groups	lenvatinib vs placebo
		Odds ratio	28.87
		95% CI	12.46, 66.86
		P-value	<0.0001
	Secondary endpoint OS	Comparison groups	lenvatinib vs placebo
		HR adjusted	0.62
		95% CI	0.40, 1.00
		P-value	0.0510
		HR unadjusted	0.73
		95% CI	0.50, 1.07
		P-value	0.1032
	Exploratory endpoint DCR	Comparison groups	lenvatinib vs placebo
		Odds ratio	5.08
		95% CI	2.98, 8.54
		P-value	<0.0001
	Exploratory endpoint CBR	Comparison groups	lenvatinib vs placebo
		Odds ratio	7.63
		95% CI	4.55, 12.79
		P-value	<0.0001
	Ad hoc endpoint TTF	Comparison groups	lenvatinib vs placebo
		Stratified HR	0.26
		95% CI	0.18, 0.37
		P-value	<0.0001
	Ad hoc endpoint PFS >3 months	Comparison groups	lenvatinib vs placebo
		Stratified HR	0.19
		95% CI	0.14, 0.27
		P-value	<0.0001
	Ad hoc endpoint PFS≥3 months	Comparison groups	lenvatinib vs placebo
		Stratified HR	0.35
		95% CI	0.17, 074

		P-value	<0.0001
Notes	Effect Estimate Comparison of exploratory endpoint 'durable SD rate': n/a		
Analysis population and time point description	Full analysis set (Intent-to-Treat) consisting of all randomized subjects **15 June 2014**		
Descriptive statistics and estimate variability	**Treatment group**	**Lentavinib**	**placebo**
	Number of subject	**261**	**131**
	OS – adjusted (median, in months)	Not estimable (NE)	19.1
	95% CI	30.9, NE	14.3, NE
	OS – unadjusted (median, in months)	NE	NE
	95% CI	30.9, NE	21.7, NE
Effect estimate per comparison	Secondary endpoint OS	Comparison groups	lenvatinib vs placebo
		HR adjusted	0.53
		95% CI	0.34, 0.82
		P-value	0.0051
		HR unadjusted	0.80
		95% CI	0.57, 1.12
		P-value	0.1993
Analysis description	**Secondary analysis**		
Analysis population and time point description	Per Protocol analysis consisting of subjects who were randomized and received at least one dose of assigned study drug– IIR **15 November 2013**		
Descriptive statistics and estimate variability	**Treatment group**	**Lentavinib**	**placebo**
	Number of subject	**257**	**127**
	PFS (median, in months)	18.3	3.6
	95% CI	15.1, NE	2.2, 3.7
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	lenvatinib vs placebo
		Stratified HR	0.21
		99% CI	0.14, 0.31
		P-value Stratified Unstratified	 <0.0001 <0.0001

Supportive studies

Study 303- Optional Open-Label part

Subjects in the placebo arm of the Randomization Phase who had disease progression confirmed by IIR could request open-label lenvatinib treatment in the OOL Lenvatinib Treatment Period (see study 303, method).

All efficacy analyses for the OOL Lenvatinib Treatment Period were descriptive only. All efficacy endpoints for the OOL Lenvatinib Treatment Period using the OOL analysis set were considered exploratory.

Results

Data cutoff date: 15 Nov 2013

Patients' disposition is presented in Figure 6.

More subjects have received the 24 mg starting dose of lenvatinib, and these subjects received lenvatinib treatment for a longer duration than those whose starting dose was 20 mg. Median duration of treatment was more than 2 times longer in subjects taking the 24 mg regimen than in those taking the 20 mg regimen: 8.9 months (range: 0 to 25 months) and 3.9 months (range: 0 to 8 months), respectively.

- The median PFS, as assessed by the investigators, for all subjects in the OOL Lenvatinib Treatment Period was 10.1 months and was 12.4 months for those who received the 24 mg lenvatinib regimen. The median was not yet reached at the time of data cutoff for those who received the 20 mg regimen due to the short follow-up time. The PFS curves appeared similar for the 24 mg and for the 20 mg regimens through the end of follow-up for the 20 mg regimen.
- The BOR for the OOL subjects included CR in 1 subject (1.2%) and PR in 44 subjects (53.7%) taking the 24 mg regimen and PR in 12 subjects (44.4%) taking the 20 mg regimen. This resulted in an ORR of 52.3% (95% CI: 42.5, 61.9) for all the OOL subjects combined and an ORR of 54.9% (95% CI: 43.5, 65.9) for the 24 mg regimen and 44.4% (95% CI: 25.5, 64.7) for the 20 mg regimen.
- The DCR was 72.5% for the OOL subjects combined and was 76.8% for the 24 mg regimen and 59.3% for the 20 mg regimen. The CBR was 67.0% for all the OOL subjects combined and was 72.0% for the 24 mg regimen and 51.9% for the 20 mg regimen.

Although comparisons between the dose regimens are difficult to make due to differences in subject numbers, exposure to lenvatinib, and length of follow-up, the ORR, DCR, and CBR were numerically greater for the 24 mg regimen compared to rates achieved for subjects treated with the 20 mg regimen.

Data update – data cutoff date: 15 Jun 2014

A total of 115 subjects were treated with lenvatinib in the OOL treatment period as of the 15 Jun 2014 cutoff, since of the eight (8) subjects who were receiving placebo in the Randomization Phase as of 15 Nov 2013 six (6) subjects crossed over to the OOL lenvatinib treatment phase (3 subjects each received OOL lenvatinib 24 mg or 20 mg). Subjects who received the 20-mg regimen represented a small (n=30) subset of the overall population. The remaining 85 subjects received lenvatinib at a starting dose of 24 mg.

Furthermore, only placebo-treated subjects who had confirmed disease progression (by IIR) during the Randomization Phase and who met protocol-specified eligibility criteria were treated with lenvatinib in the OOL phase of the study. Consequently, these patients were further advanced in the course of their disease, since they had experienced 2 sequential, confirmed disease progressions (by IIR)—the first before randomization at the time of study entry and the second during treatment with study drug in the Randomization Phase.

Because the allocation of patients to the OOL phase of the study happened sequentially and was not randomized, major intergroup differences were observed. Baseline patient characteristics, previous treatments, geographical allocation, on-study placebo exposure, lenvatinib exposure in the OOL phase, as well as median follow up times vary considerably for these 2 dose regimens. Therefore, the 30 subjects

who received the 20-mg regimen represent a different population compared with those subjects who received the 24-mg regimen in both the Randomization Phase and the OOL lenvatinib treatment phase.

All 6 placebo-treated subjects who crossed over were still receiving OOL lenvatinib treatment as of 15 Jun 2014. Of the 58 placebo-treated subjects who were ongoing in the OOL lenvatinib treatment phase as of 15 Nov 2013, 49 subjects were still receiving OOL lenvatinib (31 subjects started at a 24-mg dosage and 18 started at a 20-mg dosage) as of 15 Jun 2014 and 9 subjects had ended treatment (6 for radiographic PD, and 1 each for AE, withdrawal of consent, and clinical progression with death).

For all 115 subjects combined, the median PFS as of 15 Jun 2014, based on investigator assessments in the OOL Lenvatinib treatment period, was 22.1 months (95% CI: 9.4, NE). Median PFS was 17.5 months (95% CI: 8.3, NE) for subjects in the 24-mg regimen and not estimable (95% CI: 10.9, NE) for subjects in the 20-mg regimen. PFS rate at 6 months was 74.9% vs 71.1% and at 12 months – 68.1% vs 53.2%, respectively. The ORR (CR+PR) was 52.9% (95% CI: 41.8, 63.9) for subjects in the 24-mg cohort and 60.0% (95% CI: 40.6, 77.3) in the 20-mg cohort. The estimated PFS rates for all 115 subjects were as follows: 72.1% at 6 months, 56.7% at 12 months, 52.7% at 18 months, and 47.4% at 24 months. Almost all subjects at the ≥ 12-month time points were receiving the 24-mg regimen.

The BOR as of 15 Jun 2014 for all subjects combined was as follows: CR in 1 (0.9%) subject (who received the 24-mg regimen), partial response (PR) in 62 subjects (53.9%), and stable disease (SD) in 26 subjects (22.6%). This resulted in an ORR (CR+PR) of 54.8% (95% CI: 45.2, 64.1) for all of the subjects in the OOL treatment period combined. The ORR was 52.9% (95% CI: 41.8, 63.9) for subjects in the 24-mg cohort and 60.0% (95% CI: 40.6, 77.3) in the 20-mg cohort.

Study 201

Study 201 was a multicenter, multinational, open-label, single-arm Phase 2 study. The purpose of this study was to evaluate the safety and efficacy of lenvatinib in subjects with advanced thyroid cancer stratified by histological subtypes RR-DTC and MTC.

At the start, eligible subjects were dosed with one 10 mg tablet BID. The starting dose was changed to 24 mg QD as per Protocol Amendment 01. The basis for the increase in the starting dose was the PK/PD analyses of the results of the 2 Phase 1 studies (Study 101 and Study 102). Of the 58 subjects in the RR-DTC cohort, 2 subjects were treated with lenvatinib 10 mg BID and 56 subjects with lenvatinib 24 mg QD given continuously in 28-day cycles.

The Treatment Phase began at the time that the first subject began study drug administration and ended at the time at the time of the data cutoff for the primary study analysis (when all enrolled subjects completed 8 cycles of treatment or discontinued study treatment prior to the eighth cycle). All subjects then entered the Extension Phase. The Extension Phase consisted of a Treatment Period and a Follow-up Period. The Extension Phase began immediately after the Treatment Phase ended and included all subjects who were either still receiving treatment or in follow-up. For subjects who discontinued treatment due to disease progression, survival was followed during the Follow-up Period of the Extension Phase.

At the time of DCO (11 April 2011), of the 58 RR-DTC subjects who received lenvatinib, 23 (39.7%) subjects continued treatment in the Extension Phase and 35 (60.3%) subjects were discontinued from the treatment in the Treatment Phase (including the 2 subjects who received one 10-mg tablet BID); 18 (31.0%) due to disease progression, 14 (24.1%) with an AE(s) as the primary reason for discontinuation, 3 subjects (5.2%) discontinued due to other reasons including subject choice and withdrawal of consent. The median duration of exposure was 12.9 months (range: 0.7 - 17.7 months).

The median total amount of drug (total dose) taken per subject was 5,350 mg (range: 480 - 11,880 mg). The median dose intensity (mg/day) per subject was 19.5 mg/day (range: 7 - 24 mg/day).

The primary efficacy endpoint of the study, the ORR based on assessments by the IIR, was 50.0% (95% CI: 36.6, 63.4). No subject had a BOR of CR. PR was observed in 50.0% of subjects and SD in 43.1% of subjects. Durable SD (SD for a minimum of 23 weeks) was observed in 27.6% of subjects.

The median duration of response for the responders (n=29) was 12.7 months (95% CI: 8.8, NE).

Secondary efficacy results were as follows:

- The median estimate of PFS was 12.6 months based on assessment by the IIR.
- The 6-month and 12-month PFS rates were 77.7% and 54.7%, respectively.
- The median OS based could not be reliably estimated due to a relatively short follow-up time for OS. The median follow-up time was 16.1 months (range: 15.0 - 16.6). The OS rate at 12 months was 85.8% and at both 18 and 24 months was 77.9%.
- Based on assessments by the IIR, the DCR was 93.1% (95% CI: 83.3, 98.1) and the CBR was 77.6% (95% CI: 64.7, 87.5).
- The median time to response for responders in the Efficacy Evaluable Population (n=28) was 3.6 months.

Results for secondary efficacy endpoints based on the investigators' assessments were similar to those based upon IIR.

The efficacy variables were also evaluated separately for subjects who received prior VEGF/VEGFR-targeted therapy and those who did not. The numbers of subjects with or without prior VEGF/VEGFR-targeted treatment were small which limited the comparisons of the results, however the following was observed. The ORR, based on assessments by the IIR, was 58.8% (95% CI: 32.9, 81.6) in subjects with prior VEGF/VEGFR-targeted treatment (n=17) and was 46.3% (95% CI: 30.7, 62.6) in subjects without prior VEGF therapy (n=41).

As of the 15 Jun 2014 cutoff, 7 RR-DTC subjects were still receiving treatment and 37 (63.8%) subjects with RR-DTC had died.
After a median follow-up time of 51.6 months, the median OS was 32.3 months (95% CI: 23.3, 35.8) compared with 27.7 months [95% CI: 27.7, NE]) as of the cutoff date of 15 Sep 2013.

Study 208

Study 208 is an ongoing, multicenter, open-label, single-arm Phase 2 study. The purpose of this study is to evaluate the safety and efficacy of lenvatinib in Japanese subjects with advanced thyroid cancer, stratified by histological subtypes i.e. RR-DTC, MTC and ATC. The evaluation of efficacy is a secondary objective. Secondary efficacy outcomes are PFS, OS, ORR, DCR and CBR. Eligible subjects are to receive lenvatinib 24 mg by continuous QD dosing given continuously in 28-day cycles.

The study start date was 03 Sep 2012. An interim CSR, based on the DCO date of 15 Sep 2013, has been provided.

Tumour assessments using RECIST 1.1 are to be performed by the investigators during the Pre-treatment Phase and then every 8 weeks after the first dose for RR-DTC subjects.

At the time of DCO, 22 subjects with RR-DTC received at least 1 dose of lenvatinib. Nineteen subjects (86.4%) were still receiving study drug at the DCO date, and 3 (13.6%) had discontinued: 2 (9.1%) due to disease progression and 1 (4.5%) due to subject choice.

At the time of DCO, the median duration of exposure was 4.5 months (range: 0.7 - 11.0 months). The median total amount of drug (total dose) taken per subject was 1487 mg (range: 332 - 5832 mg). The median dose intensity (mg/day) per subject was 13.8 mg/day (range: 7.5 - 20.3 mg/day).

- The median PFS was not estimable at the DCO date, as 2 subjects had disease progression and 20 subjects were censored without events.
- At the time of DCO, the response rate was evaluated in 21 subjects, as 1 subject did not have a post-baseline tumour assessment reported during the study.
- No subjects had a complete response, 10 of 21 subjects (47.6%) had a BOR of PR.
- The ORR was 47.6% (95% CI: 25.7, 70.2).
- Eleven subjects (52.4%) had a BOR of SD.
- At the time of DCO, the disease control rate (DCR= CR+PR+SD) was 100.0% (21/21) and the Clinical benefit rate (CBR=CR+PR+durable SD) was 78.6% (11/14).
- The median OS could not be estimated at the DCO date for subjects as only 1 RR-DTC subject.

As of the 15 June 2014 cutoff, 23 RR-DTC subjects had been treated with lenvatinib, which includes one additional RR-DTC subject enrolled since the cutoff date of 15 Sep 2013. Treatment was still ongoing for 20 subjects with RR-DTC. One of 23 subjects had died.

The ORR (CR+PR) based on investigator's assessments was 69.6%, the disease control rate (CR+PR+SD) was 100.0%, and the best overall response was PR in 16 subjects (69.6%) and SD in 7 subjects (30.4%).

Median PFS had not yet been reached, and median OS was not estimable.

Comparison of efficacy results of lenvatinib Phase 3 Study 303 and sorafenib Phase 3 DECISION Study

An indirect comparison of the key efficacy data of the lenvatinib Phase 3 Study 303 and the sorafenib Phase 3 DECISION Study is shown in table below.

Table 37: Comparison of key efficacy parameters in lenvatinib Phase 3 Study 303 and sorafenib Phase 3 DECISION Study

	SELECT TRIAL		DECISION Trial	
	Lenvatinib (N=261)	**Placebo (N=131)**	**Sorafenib (N=207)**	**Placebo (N=210)**
Median PFS (95% CI)[a] (months)	18.3 (15.1, NE)	3.6 (2.2, 3.7)	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)
Stratified Hazard Ratio (99% or 95% CI)[b,c]	0.21 (0.14, 0.31)		0.59 (0.45, 0.76)	
Stratified Log-Rank Test (*P* value)[b]	*P*<0.0001		*P*<0.0001	
	(N=261)	**(N=131)**	**(n=196)**	**(n=201)**
Best Overall Tumor Response[d], n (%)				
Complete response (CR)	4 (1.5)	0	0	0
Partial response (PR)	165 (63.2)	2 (1.5)	24 (12.2)	1 (0.5)
Objective Response Rate[e] (CR + PR), n (%)	169 (64.8)	2 (1.5)	24 (12.2)	1 (0.5)
95% CI[e]	(59.0, 70.5)	(0.0, 3.6)	(7.6, 16.8)	(0.01, 2.7)
Median Duration of Objective Response (95% CI) (months)	NE (16.8, NE)	NE	10.2 (7.4, 16.6)	NE
	(N=261)	**(N=131)**	**(N=207)**	**(N=210)**
No. of subjects who received open-label active treatment[f], n (%)	-	109 (83.2)	61 (29.5)	157 (74.8)
Number of Deaths[f]	71 (27.2)	47 (35.9)	66 (31.9)	72 (34.3)
Median OS[g] (95% CI) (months)	NE (22.0, NE)	NE (20.3, NE)	NE	36.5 (32.2, NE)
Adjusted Stratified Hazard Ratio (95% CI)[h]	0.62 (0.40, 1.00)		Not calculated	
P value[h]	*P*=0.0510		Not calculated	
Unadjusted Stratified Hazard Ratio (95% CI)[i]	0.73 (0.50, 1.07)		0.88 (95% CI: 0.63-1.24)	
P value[i]	*P*=0.1032		*P*=0.47	

Percentages are based on the total number of subjects in the relevant treatment arm.
CI = confidence interval, CR = complete response, PR = partial response, NE = not estimable, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, RECIST = Response Evaluation Criteria In Solid Tumors VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.

a: The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
b: For Study 303, a 2-sided log-rank test was stratified by region (Europe, North America, Other), age group (≤65, >65 years), and prior VEGF/VEGFR-targeted therapy (0, 1). For the DECISION trial, a 1-sided log-rank test was stratified by region (Europe, North America, Asia) and age group (<60, ≥60 years).
c: For both studies, the hazard ratio is expressed as active/placebo and was estimated from a Cox proportional hazard model, stratified by randomization data.
d: For Study 303, tumor responses were evaluated based on RECIST 1.1 criteria. For the DECISION trial, tumor responses were evaluated based on modified RECIST 1.0 criteria. Tumor assessments were performed every 8 weeks for both studies.
e: For both studies, the ORR was assessed with the Cochran-Mantel-Haenszel test and the 95% CI calculated using asymptotic normal approximation.
f: The number of subjects receiving open-label sorafenib, the number of placebo subjects crossed over to active treatment, and the number of deaths are those that had occurred at the cutoff time for the following OS analyses; for Study 303, the OS analysis was conducted at the time of the primary analysis, and for the DECISION trial, the OS analysis was conducted 9 months after the data cutoff for the final PFS analysis (Sorafenib US Package Insert).
g: For both studies, the median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method. For Study 303, the OS analysis was estimated at the time of the primary analysis. For DECISION trial, the OS analysis was conducted 9 months after the data cutoff for the final PFS analysis.
h: *P*-value and 95% CI of the adjusted hazard ratio were determined using the rank preserving structural failure time model.
i: For both studies, the statistics were not adjusted for the crossover of placebo subjects to the open-label phase. The hazard ratio was estimated from a stratified Cox proportional hazard model.
Source: Study 303 Table 14.2.1.1, Table 14.2.2.1.1, Table 14.2.2.1.2, Table 14.2.3.1; Brose, et al., 2014; Sorafenib US Package Insert.

Clinical studies in special populations

Elderly

The tables below summarise the efficacy in elderly.

Table 38: Efficacy in Special Populations: Elderly – All DTC Subjects

	Age 65-74 (older subjects number)	**Age 75-84 (older subjects number)**	**Age 85+ (older subjects number)**	**Total (total number of subjects)**
Controlled Trials				
E7080-G000-303 (L) [b]	89	27	2	261
E7080-G000-303 (P) [b]	45	9	0	131
Non Controlled Trials				
E7080-G000-201[a]	24	1	0	58
E7080-J081-208[a]	6	0	0	22
E7080-G000-303 (OOL)[b]	39	5	0	109
Total of lenvatinib-exposed RR-DTC subjects:	**158**	**33**	**2**	**450**

L = Lenvatinib; P = placebo; OOL = open label extension

a: At a data cutoff of 15 Sep 2013

b: At a data cutoff 15 Nov 2013 (time of primary efficacy analysis). Two further subjects aged <65 years crossed over from the placebo arm of Study 303 into the OOL phase as at the data cutoff for the pooled safety analysis to give a total of 452 lenvatinib-exposed RR-DTC subjects as at 15 Mar 2014.

Source: Table D80.R139.99.01

Table 39: Efficacy in Special Populations: Elderly – Non-DTC Monotherapy Subjects

	Age 65-74 (older subjects number)	Age 75-84 (older subjects number)	Age 85+ (older subjects number)	Total (total number of subjects)
Non-Controlled Trials				
E7080-E044-101	**13**	**2**	**0**	**82**
E7080-A001-102	**17**	**10**	**1**	**59**
E7080-E044-104	**0**	**0**	**0**	**6**
E7080-J081-105	**0**	**0**	**0**	**9**
E7080-G000-201a	**12**	**0**	**0**	**59**
E7080-G000-203	**15**	**2**	**0**	**113**
E7080-G000-204	**40**	**13**	**0**	**133**
E7080-G000-206	**43**	**24**	**0**	**182**
E7080-J081-208b	**7**	**0**	**0**	**13**
Total:	**147**	**51**	**1**	**656**

ATC = anaplastic thyroid cancer; MTC = medullary thyroid cancer, a: Includes MTC subjects, b: Includes MTC and ATC subjects. Source: Table D120.R139.01.03

Paediatric population

Paediatric Investigation Plan was first agreed with the EMA Paediatric Committee (PDCO) on 28 May 2013 (EMEA-001119-PIP-01-11). Measure 5 of the PIP related to the treatment of papillary and follicular thyroid cancer (which together comprise differentiated thyroid cancer) includes an open-label, multi-centre, non-controlled trial to evaluate pharmacokinetics, pharmacodynamics, tolerability and safety of lenvatinib in children from 2 years to less than 18 years of age with a relapsed or refractory solid malignant tumour and, in patients with osteosarcoma, an extension phase to evaluate lenvatinib in combination with ifosfamide and etoposide.

No other separate clinical studies have been undertaken to investigate the clinical efficacy of lenvatinib in special populations. Mostly PK data were provided by studies in patients with renal and hepatic impairment.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose-finding

The initial clinical experience with lenvatinib in thyroid cancer came from the Phase 1 Study 102.

A population pharmacokinetic/pharmacodynamics (PK/PD) analysis of the results of the two Phase 1 studies (Study 101 and Study 102) indicated that PFS and response (PR or durable SD) significantly increased with higher lenvatinib exposure. With a half-life of 28 hours, the steady state would be achieved within 5 days. Therefore, given the totality of the data from Study 101, a starting dose of lenvatinib 25 mg QD was proposed. Lenvatinib 25 mg QD maximizes efficacy (antitumor activities) while inducing a degree of hypertension controllable by administration of antihypertensive therapy.

To simplify drug administration in view of the two strengths developed (10 mg and 4 mg capsules), a dosage of 24 mg QD (two 10-mg capsules plus one 4-mg capsule) was selected for continued lenvatinib development.

Based on the results of the Phase 2 studies, the Phase 3 Study 303 was designed using a lenvatinib dosage of 24 mg QD given continuously in 28-day cycles, with a dose interruption and reduction management plan implemented based on observed adverse events (AE). Standard supportive therapies would also be used to treat the AEs. Thus, the dose of lenvatinib was individualised for each subject over the course of the study to maximize anti-tumour response and minimize adverse events.

Clinical efficacy

The primary evidence for the efficacy of lenvatinib for the target indication comes from one pivotal Phase 3 study, E7080-G000-303 (Study 303), and is supported by data from a Phase 2 study, E7080-G000-201 (Study 201) and an ongoing Phase 2 Study, E7080-J081-208 (Study 208).

Protocol assistance from the CHMP was solicited throughout the development program for lenvatinib. The design and methodology of the pivotal study was reviewed and considered adequate. Since at the time of this study protocol initiation and until recently, there was no authorised effective therapy for RR-DTC, the use of placebo as control in the pivotal Study 303 is considered acceptable.

The independence of the confirmation of progressive disease status at study entry and of disease progression prior to discontinuation of therapy in the randomization phase, and the independence of tumour assessments review for the primary analysis of PFS were reassuring the quality and reliability of the study data.

The claimed indication for lenvatinib is the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC). The definition of RR-DTC was congruent with that used for the sorafenib pivotal Phase 3 study and is considered appropriate.

All but 3 subjects in the lenvatinib arm had metastatic disease. These 3 subjects had locally advanced disease that met inclusion criteria. The response to treatment (efficacy and safety) of these 3 subjects with locally advanced disease was clinically apparent (one subject achieved complete response) and was consistent with that observed for the overall study population and the majority of subjects who had metastatic disease (data not shown).

Follicular thyroid cancer includes oncocytic follicular (Hürthle) cell carcinoma, which is associated with a poorer outcome, less favourable response to RAI and distinct molecular features. A post-hoc analysis in Hürtle cell subtype population, however, showed that the efficacy and safety in these patients are in line with those in the overall population (data not shown).

The inclusion and exclusion criteria for Study 303 appropriately reflect the target population of the indication sought. In addition, subjects having had one previous VEGF/VEGFR targeted therapy were eligible. As this subpopulation of patients was excluded from therapy with sorafenib and with an unmet medical need, the inclusion of such patients is endorsed. In Study 303, approximately one-fourth of the randomized subjects have had a previous VEGF/VEGFR targeted therapy, mainly consisting of sorafenib (approximately 77 %).

The use of a blinded and independent radiological assessment of PFS in order to reduce possible investigator bias and the conduction of sensitivity analyses in order to assess the robustness of the PFS results in accordance with current EMA guideline (EMA/CHMP/27994/2008/Rev.1) are endorsed.

Randomization was stratified according to geographic region, age and prior VEGF/VEGFR-targeted therapy in order to minimize the potential for imbalance between the treatment groups with respect to pre-treatment characteristics that may influence treatment response.

Cross-over to lenvatinib was optional for subjects initially randomized to placebo either at the time of disease progression during the Randomization Phase or at the time of the completion of the study primary analysis of PFS and mandatory unblinding of treatment assignment.

The use of concomitant supportive medication and use of an algorithm of dose interruptions/reductions to manage toxicity outlined in the study protocol is endorsed.

Efficacy data and additional analyses

The subject demographic and baseline characteristics of Study 303 (randomization phase), were generally well balanced between both treatment arms. The percentage of subjects with an ECOG PS of 0, 1 or 2 was similar across treatment arms. One subject in the lenvatinib arm had an ECOG PS of 3, which was considered a minor protocol deviation.

Prior cancer therapies and procedures were similar in the two treatment arms. The subject disease characteristics at study entry were generally balanced between both treatment arms. A higher percentage of subjects had a histological diagnosis of PTC (66.1% overall, 64.8% lenvatinib, 68.7% placebo vs subjects with a diagnosis of FTC: 33.9% overall, 35.2% lenvatinib, 31.3% placebo). The type and frequency of metastatic disease were similar in the two treatment arms. Approximately half of all subjects (56.3% lenvatinib, 56.5% placebo) had hypertension at baseline. Subgroup analysis showed consistent results between patients with papillary thyroid cancer (66.1%) and other subgroups, such as in patients with follicular thyroid cancer (33.9%) which included Hürthle cell 14.8% and clear cell 3.8%. The estimation of benefit becomes more difficult in smaller patients populations, especially when considering such groups as separate pathological entities with potentially distinct activity due to differences in pathogenic pathways involved. From this point of view, types of DTC (papillary/ follicular/ Hürthle cell) are specified in the indication (see SmPC section 4.2).

RR-DTC is characterized by very heterogeneous clinical behaviour as relative to size; location and growth dynamics of metastases. All patients included into the pivotal study had progressive disease but the rate of tumour growth was not known. No personalized therapeutic strategies could be proposed based on available data and decision when to start therapy would depend on benefit/risk assessment in individual patients.

RR-DTC patients are generally asymptomatic at the time of progression. Symptomatic disease was not a requirement for a start of therapy. Given that symptomology and PRO collection were not a part of pivotal study design, no data are available to date. The CHMP recommends collecting such data, along with adherence safety and efficacy data in the planned Study 211.

Study 303 met its primary objective of a statistically significant and clinically meaningful benefit of lenvatinib as measured by PFS. Based on blinded IIR and FDA guidance on PFS censoring, lenvatinib prolonged median PFS by 14.7 months compared with placebo (18.3 months vs 3.6 months, respectively). The HR was 0.21 (stratified Cox proportional hazard model, 99% CI: 0.14, 0.31) in favour of lenvatinib. The difference in PFS between lenvatinib and placebo was highly significant ($p<0.0001$) using both stratified and unstratified log-rank tests.

The results of the PFS analysis in the per protocol analysis set and of all 3 planned sensitivity analyses using different progression events were all consistent with the primary analysis. The HRs for all the analyses were comparable (0.21 to 0.24). The log-rank tests all showed a statistically significant difference between lenvatinib treatment and placebo ($p<0.0001$).

Analyses of the secondary endpoints ORR and OS support the demonstrated efficacy of lenvatinib for the primary efficacy endpoint of PFS.

ORR, based on IRR assessments in the full analysis set, was significant higher with lenvatinib treatment compared with placebo (64.8% vs 1.5%; OR: 28.87, p<0.0001). The ORR, based on investigator's assessment in the full analysis set, was consistent with the ORR based on IRR assessment. Moreover, the ORR based on the IIR assessments in the per protocol analysis set, was consistent with the ORR based on the IIR assessments in the full analysis set.

The overall survival analysis did not show a statistically significant difference between treatments but this is not surprising given the study was not powered for it. The results are also confounded by the fact that the majority of placebo subjects crossed over to lenvatinib after disease progression. Nevertheless the survival results are numerically better for lenvatinib than placebo and there is certainly no evidence of a detrimental effect of treatment.

As of the most recent cutoff date of 15 Jun 2014, the OS analysis still showed a numerical superiority for lenvatinib with an HR of 0.80 (95% CI: 0.57, 1.12; P=0.1993). The RPSFT-adjusted HR was 0.53 (95% CI: 0.34, 0.82), in favour of the lenvatinib arm. The difference in OS between the 2 treatment arms became statistically significant as determined using the resampling method (bootstrapping) (P=0.0051). With a median follow-up period of 23.6 months in the lenvatinib arm, the median OS was not yet reached. In the placebo crossover arm with a median follow-up of 24.1 months, the median OS was 19.1 months (95% CI: 14.3, not estimable [NE]). Although RPSFT model is one of the most commonly methods used to estimate survival time after treatment switching, it has some serious limitations. The main assumption in this model is that treatment effect is the same regardless of when the experimental treatment is initiated, e.g. delayed start of experimental treatment has the same effect as starting upfront. However, this structural assumption is untestable and, bearing in mind how a patient's prognosis changes after disease progression, it is also likely to be untrue. This adjustment is therefore likely to result in a treatment effect over-estimation. The results are also sensitive to the method used for determination of acceleration factor F and the re-censoring is applied to all censored patients irrespectively of switch. Bearing all this in mind, the results from the adjusted model can only be used as supportive.

The results of the analyses of exploratory efficacy endpoints of Study 303 (DCR, CBR and durable SD rate) overall further support the clinical effectiveness of lenvatinib.

Hypertension is a known dose-related effect of VEGF/VEGFR-targeted therapies and it has been reported to be a biomarker of the efficacy of these agents. Therefore, ad hoc analyses were conducted to investigate the relationship between the treatment-emergent AE of hypertension and the effectiveness of lenvatinib treatment (data not shown). The various ad hoc analyses (PFS, OS, ORR and tumour shrinkage) overall further support the concept that the treatment-emergent AE of hypertension can be a predictive biomarker of tumour response and target inhibition. However no conclusions can be drawn at this stage on the predictivity of such biomarkers for the activity of lenvatinib.

At a request of CHMP during protocol assistance, the Applicant did a comparative analysis of the efficacy and safety of lenvatinib and the recently approved tyrosine kinase inhibitor for the treatment of RR-DTC sorafenib. Whereas the baseline demographic characteristics were in general similar for both Phase 3 studies, a number of differences in study design and disease characteristics suggest that subjects in Study 303 had a slightly poorer prognosis. The differences in populations might have contributed to the differences observed between the placebo arms of the two studies. Nevertheless, broadly, both the pivotal study 303 for lenvatinib and the sorafenib pivotal trial had similar eligibility criteria and endpoints.

In both studies, the active treatment highly significantly improved PFS (p<0.0001) compared with placebo. However, the difference in median PFS between the active treatment and placebo arms was 14.7

months in Study 303 and 5.0 months in the DECISION study. The CIs of the HR of lenvatinib versus placebo in Study 303 (0.21; 99% CI: 0.14, 0.31) were lower than, and did not overlap compared with those of sorafenib versus placebo in the DECISION trial (0.59; 95% CI: 0.45, 0.76).

Study 303 was not planned or designed to evaluate subsequent lines of therapy, i.e., progression-free survival 2 (PFS2) or end-of-next-line-treatment. PFS2 was estimated by end of next treatment. The data shown were therefore limited in quantity and represented an ad-hoc exploratory evaluation. Overall, the PFS2 analyses do not allow drawing valid conclusions. It is recommended to include PFS2 estimation in the planned study 211.

In the OOL phase, efficacy between the starting doses of 24 mg and 20 mg was compared. Similar results in terms of PFS and ORR were observed for the starting doses of 24 mg and 20 mg. Overall, considering the small number of patients, and possible confounding factors, firm conclusions could not be based on the results provided (see discussion on starting dose under clinical safety).

2.5.4. Conclusions on the clinical efficacy

Overall, the efficacy of lenvatinib in the proposed indication has been shown. Lenvatinib (24 mg QD) demonstrated statistically ($p<0.0001$) and clinically meaningful prolongation of PFS by 14.7 months compared to placebo, as assessed by IIR. The HR was 0.21 (99% CI: 0.14, 0.31). The PFS results were robust, as established by using multiple sensitivity and secondary efficacy analyses.

At the time of primary PFS analysis, there was no obvious sign of detrimental effect in OS. However, the OS data were immature. An updated OS analysis still showed a numerical superiority for lenvatinib with an HR of 0.80, although non-significant. Exploratory analyses of OS to correct for cross-over did not reveal any concerns in terms of a possible detriment in terms of OS.

2.6. Clinical safety

Patient exposure

The safety profile of lenvatinib is based on a pooled analysis of data from 1108 subjects from completed studies who had received single agent lenvatinib on a continuous basis. It includes 452 subjects with RAI-refractory DTC who received the recommended dose in the pivotal Phase 3 SELECT trial and two Phase 2 clinical trials.

Ten clinical studies in cancer patients, who received single-agent lenvatinib continually, including Study 303, were pooled for the integrated safety analysis (see table below).

Table 40 : Clinical Studies included in the lenvatinib safety analysis

Study	phase	type	number of subjects treated		safety set name
			Lenvatinib 24 mg (or 20 mg)	placebo	
303	3	randomized	261	131	DTC randomized
303	3	open label (OOL)	84 (27)		DTC Non randomized
201	2	open label	56 (2)		DTC Non randomized
208	2	open label	22		DTC Non randomized
201	2	open label	59		Non DTC
208	2	open label	13		Non DTC
101	1	open label	82		Non DTC
102	1	open label	59		Non DTC

104	1	open label	6		Non DTC
105	1	open label	9		Non DTC
203	2	open label	113		Non DTC
204	2	open label	133		Non DTC
206	2	open label	182		Non DTC

The safety cut-off date for these studies was 15 September 2013, except for Study 303 (safety cut-off date was 15 March 2014). The main analyses of safety were based on the following 4 safety sets for the pooled studies, with emphasis on the studies in patients with RR-DTC.

1) DTC Randomized Safety Set (N=392): Placebo-treated (N=131) and lenvatinib-treated (N=261) subjects from the randomized portion only of Study 303

2) DTC Non-randomized Safety Set (N=191): Lenvatinib-treated subjects with DTC from Studies E7080-G000-201 and E7080-J081-208, and the optional open-label (OOL) portion of Study 303

3) All DTC Lenvatinib Safety Set (N=452): Lenvatinib-treated subjects from Studies 201, 208, and 303 (both the randomized and the OOL portions of the study)

4) Non-DTC Monotherapy Safety Set (N=656): All subjects who received single-agent lenvatinib continually in cancer studies, excluding DTC: Studies E7080-E044-101, E7080-A001-102 (monotherapy cohort/continuous dosing), E7080-E044-104, E7080-J081-105, 201 (subjects with medullary thyroid cancer [MTC] only), E7080-G000-203 (monotherapy cohort), E7080-G000-204, E7080-G000-206, and 208 (subjects with MTC or anaplastic thyroid cancer [ATC] only)

Table 41: Summary of Demographics – all safety sets

	Safety Sets				
	DTC Randomized		DTC Nonrandomized	All DTC Lenvatinib	Non-DTC Monotherapy
Parameter Statistic	Placebo (N=131)	Lenvatinib (N=261)	Lenvatinib (N=191)	Lenvatinib (N=452)	Lenvatinib (N=656)
Age, years					
Mean (SD)	61.5 (10.09)	62.1 (10.57)	60.6 (9.60)	61.5 (10.18)	57.1 (12.93)
Median	61.0	64.0	61.0	63.0	59.0
Q1, Q3	55, 69	55, 69	55, 69	55, 69	49, 66
Min, Max	21, 81	27, 89	21, 81	21, 89	22, 85
Age Group, n (%)					
<65 years	77 (58.8)	143 (54.8)	116 (60.7)	259 (57.3)	457 (69.7)
≥65 - <75 years	45 (34.4)	89 (34.1)	69 (36.1)	158 (35.0)	147 (22.4)
≥75 years	9 (6.9)	29 (11.1)	6 (3.1)	35 (7.7)	52 (7.9)
Sex, n (%)					
Male	75 (57.3)	125 (47.9)	111 (58.1)	236 (52.2)	312 (47.6)
Female	56 (42.7)	136 (52.1)	80 (41.9)	216 (47.8)	344 (52.4)
Ethnicity, n (%)					
Hispanic or Latino	9 (6.9)	10 (3.8)	16 (8.4)	26 (5.8)	24 (3.7)
Not Hispanic or Latino	122 (93.1)	251 (96.2)	175 (91.6)	426 (94.2)	535 (81.6)
Missing	0	0	0	0	97 (14.8)

Race, n (%)					
White	103 (78.6)	208 (79.7)	134 (70.2)	342 (75.7)	593 (90.4)
Black	4 (3.1)	4 (1.5)	7 (3.7)	11 (2.4)	15 (2.3)
Asian	24 (18.3)	46 (17.6)	48 (25.1)	94 (20.8)	32 (4.9)
Other	0	3 (1.1)[a]	2 (1.0)	5 (1.1)	16 (2.4)
Geographic Region, n (%)					
Europe	64 (48.9)	131 (50.2)	75 (39.3)	206 (45.6)	196 (29.9)
North America[b]	39 (29.8)	77 (29.5)	68 (35.6)	145 (32.1)	408 (62.2)
Other[c]	28 (21.4)	53 (20.3)	48 (25.1)	101 (22.3)	52 (7.9)
Baseline Weight, kg					
Mean (SD)	78.3 (22.36)	75.7 (19.94)	79.1 (22.50)	77.2 (21.10)	79.0 (19.56)
Median	74.0	73.3	75.3	74.0	76.3
Q1, Q3	62.0, 93.0	61.0, 88.0	61.1, 93.0	61.1, 90.3	65.0, 90.9
Min, Max	31, 165	33, 155	31.0, 165.2	31.0, 165.2	37.8, 177.5
Baseline Weight Group, n (%)					
< 60 kg	28 (21.4)	62 (23.8)	41 (21.5)	103 (22.8)	94 (14.3)
≥60 kg	103 (78.6)	199 (76.2)	150 (78.5)	349 (77.2)	562 (85.7)

Table 42 : Patient exposure – safety analysis set (cut-off date 15 September 2013, except for study 303: 14 March 2014)

	Patients exposed, number (%)	Patients exposed to the proposed 24 mg dose	Patients with ≥6 months safety data	Patients with ≥12 months safety data	Patients with ≥24 months safety data
Placebo-controlled (DTC Randomized set)	261 (100)	261 (100)	185 (70.9)	135 (51.7)	13 (5)
Open studies (DTC Nonrandomized set) *	191 (100)	162 (84.8)	104 (54.5)	59 (30.9)	12 (6.3)
All RR-DTC patients *	452 (100)	423 (93.6)	289 (63.9)	194 (42.9)	25 (5.5)
Other Cancers (Non-DTC monotherapy)**	656 (100)	508 (77.4)	177 (27)	79 (12)	24 (3.7)
Totals patients	1108 (100)	931 (84)	466 (42.1)	273 (24.6)	49 (4.4)

* The lenvatinib starting dose was 24 mg QD except for 29 subjects (27 subjects from the OOL part of Study 303 had a starting dose of 20 mg QD and 2 subjects from Study 201 were treated with 10 mg BID).
** The lenvatinib starting dose was <14 mg (93 subjects), ≥14 -<20 mg (12 subjects), ≥20 -<24 mg (12 subjects), 24 mg (508 subjects), and >24 mg (31 subjects).

A summary of study drug exposure for all safety sets is presented below.

Table 43 : Summary of Study Drug Exposure – All Safety Analysis Sets

	Safety Analysis Set				
	DTC Randomized		**DTC Nonrandomized**	**All DTC Lenvatinib**	**Non-DTC Monotherapy**
Parameter Statistic	**Placebo N=131**	**Lenvatinib N=261**	**Lenvatinib N=191**	**Lenvatinib N=452**	**Lenvatinib N=656**
Duration of Treatment[a], months					
Mean (SD)	6.1 (5.47)	13.7 (8.24)	10.8 (9.35)	12.5 (8.84)	6.1 (8.25)
Median	3.9	16.1	8.2	11.1	3.5
Q1, Q3	2.1, 8.1	5.9, 19.6	3.9, 15.4	4.7, 18.8	1.6, 7.4
Min, Max	0, 28	0, 31	0.1, 45.9	0.1, 45.9	0.0, 89.6
Treatment, SY[b]	67.1	298.8	171.2	470.0	331.1
Exposure, SY[c]	65.4	269.5	154.0	423.4	304.9

Parameter Statistic	Safety Analysis Set				
	DTC Randomized		DTC Nonrandomized	All DTC Lenvatinib	Non-DTC Monotherapy
	Placebo N=131	Lenvatinib N=261	Lenvatinib N=191	Lenvatinib N=452	Lenvatinib N=656
Average Daily Dose[d], mg/day					
Mean (SD)	23.3 (1.74)	16.9 (5.13)	17.5 (4.81)	17.2 (5.00)	18.8 (6.00)
Median	24.0	16.2	18.0	16.8	20.5
Q1, Q3	23.8, 24.0	13.4, 21.5	14.1, 21.2	13.7, 21.5	15.2, 24.0
Min, Max	14, 24	6, 25	6.9, 24.0	5.8, 25.5	0.2, 32.0
Dose Most Frequently Received[e,f]					
>24	NA	NA	NA	NA	17 (2.6)
24	127 (96.9)	111 (42.5)	78 (40.8)	189 (41.8)	376 (57.3)
20	2 (1.5)	30 (11.5)	47 (24.6)	77 (17.0)	85 (13.0)
>14 - <20	NA	NA	NA	NA	22 (3.4)
14	2 (1.5)	66 (25.3)	41 (21.5)	107 (23.7)	46 (7.0)
>10 - <14	NA	NA	NA	NA	34 (5.2)
10	0	40 (15.3)	18 (9.4)	58 (12.8)	38 (5.8)
<10	0	14 (5.4)	7 (3.7)	21 (4.6)	38 (5.8)

DTC = differentiated thyroid cancer, Max = maximum, Min = minimum, NA = not applicable, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, SY = subject-years.

a: Duration of treatment (in months) is defined as (Last dose date – First dose date + 1) × (12÷365.25).

b: Subject-years of treatment = sum of duration of treatment (in years) for all subjects in each category, including dose interruptions.

c: Duration of exposure is defined as number of days a subject actually received a dose, excluding dose interruptions. Subject-year = sum of duration of exposure (in years) for all subjects in each category.

d: Average daily dose is calculated as total dose (mg) ÷ duration of treatment (days).

e: The dose most frequently received during the treatment period was defined as the mode of all dose levels received. The highest dose was chosen if there was a tie in the number of dose levels most frequently received.

f: Subjects in the thyroid cancer studies followed a planned treatment and individualized dose reduction algorithm for toxicity as follows: 24 mg → 20 mg → 14 mg → 10 mg.

Dose interruptions and reductions were integral to the management of lenvatinib-related toxicities. Following a starting dose of 24 mg, subjects could have sequential, stepwise dose reductions to 20 mg (first reduction), 14 mg (second dose reduction), or 10 mg (third dose reduction) on an individual basis as needed for AEs. Across all safety sets, exposure to lenvatinib was highest for the 24-mg dose (89.71 SY, 146.20 SY, and 127.42 SY for the DTC Randomized, All DTC Lenvatinib, and Non-DTC Monotherapy Safety Sets, respectively) compared with each of the lower doses administered. Exposure to the 20-mg dose and 14 mg dose were 50.8 SY and 71.8 SY respectively. When considering starting dose of 24 mg, the median dose intensity was lower for lenvatinib-treated subjects in Study 303 (16.8 mg/day/subject) compared with those in Study 201 and open label part of the Study 303 (19.5 and 19.4 mg/day/subject, respectively). With the starting dose of 20 mg/day, the median dose intensity was 20 mg/day/subject.

A shorter duration of exposure in some patient subpopulations, (those older than 75 years, Asians, and subjects with renal impairment) were observed in the lenvatinib treated subjects across safety sets. Such patients had lower exposure, shorter median duration of treatment and lower median cumulative dose, lower relative dose intensity, and sometimes lower average daily dose across all safety sets. These differences were not observed for the respective subgroups in the placebo arm of the DTC Randomized safety set.

Japanese subjects had a shorter duration of treatment vs. non-Japanese subjects (median of 8.1 vs. 11.9 months in the All DTC Lenvatinib Safety Set) and received a lower average daily dose of lenvatinib (median of 11.3 mg vs. 17.9 mg in the All DTC Lenvatinib Safety Set). However, median duration of lenvatinib treatment was similar (16.9 vs. 16.0 months) between Japanese and non-Japanese subjects,

respectively, in the DTC Randomized Safety Set, although total dose and dose intensity were lower for Japanese subjects.

Lenvatinib-treated subjects who received prior VEGF-targeted therapy had a numerically shorter duration of treatment than subjects who had not received prior VEGF-targeted therapy (median, 11.1 vs 16.9 months); however, no meaningful differences in other exposure parameters were seen in the DTC Randomized Safety Set. A decrease in the duration of treatment (median, 3.6 vs 4.2 months) was also seen in subjects who received prior VEGF-targeted therapy in the placebo group.

Lenvatinib-treated subjects with ECOG ≥1 or hepatic impairment had lower exposure, shorter duration of treatment and lower cumulative dose across safety sets; however, the same trend was observed in the placebo group in the DTC Randomized safety set.

Adverse events

Nearly 100% of lenvatinib-treated subjects across all Safety Sets and 90% of placebo-treated subjects in the DTC Randomized Safety Set had at least 1 treatment emergent adverse event (TEAE). More lenvatinib-treated subjects had a TEAE with maximum CTCAE Grade of 3 or greater (range 72% to 87% across all Safety Sets) than did placebo-treated subjects (30%).

Table 44 : Overview of Treatment-Emergent Adverse Events – All Safety Sets

	Safety Sets				
	DTC Randomized		DTC Non-randomized	All DTC Lenvatinib	Non-DTC Monotherapy
Subjects with at least 1 of the following:	**Placebo (N=131) n (%)**	**Lenvatinib (N=261) n (%)**	**Lenvatinib (N=191) n (%)**	**Lenvatinib (N=452) n (%)**	**Lenvatinib (N=656) n (%)**
TEAE	118 (90.1)	260 (99.6)	191 (100)	451 (99.8)	647 (98.6)
Treatment-related TEAE[a]	80 (61.1)	254 (97.3)	185 (96.9)	439 (97.1)	610 (93.0)
TEAE with maximum CTCAE Grade of[b]					
1	27 (20.6)	1 (0.4)	3 (1.6)	4 (0.9)	25 (3.8)
2	52 (39.7)	32 (12.3)	37 (19.4)	69 (15.3)	147 (22.4)
3	28 (21.4)	183 (70.1)	123 (64.4)	306 (67.7)	367 (55.9)
4	5 (3.8)	24 (9.2)	16 (8.4)	40 (8.8)	56 (8.5)
5	6 (4.6)	20 (7.7)	12 (6.3)	32 (7.1)	52 (7.9)[c]
SAE[d]	31 (23.7)	139 (53.3)	98 (51.3)	237 (52.4)	314 (47.9)
Fatal AE	6 (4.6)	20 (7.7)	12 (6.3)	32 (7.1)	54 (8.2)[c]
Nonfatal SAE	30 (22.9)	136 (52.1)	95 (49.7)	231 (51.1)	289 (44.1)
TEAE leading to treatment discontinuation	6 (4.6)	46 (17.6)	42 (22.0)	88 (19.5)	168 (25.6)
TEAE leading to study drug modification					
Dose Reduction and/or Interruption	25 (19.1)	234 (89.7)	155 (81.2)	389 (86.1)	404 (61.6)
Dose Reduction[e]	6 (4.6)	178 (68.2)	107 (56.0)	285 (63.1)	186 (28.4)
Dose Interruption[e]	24 (18.3)	217 (83.1)	128 (67.0)	345 (76.3)	364 (55.5)

For each row category, a subject with two or more adverse events in that category is counted only once.
AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, SAE = serious adverse event, TEAE = treatment-emergent adverse event.
a: Treatment-related TEAEs includes those reported by the investigator to be possibly or probably related to study drug or for which causality was missing.
b: If a subject had more than one TEAE, the subject is only counted once at the maximum grade.
c: There are 2 more fatal AEs than there are CTCAE Grade 5 TEAEs for Non-DTC Monotherapy Safety Set because in Study 101 2 subjects each had a fatal AE for which severity was recorded by the investigator as being CTCAE Grade 2.
d: A subject may be counted in both categories if the subject had both a fatal and a nonfatal SAE.
e: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Treatment-emergent adverse events that occurred in at least 5% of subjects with a between-treatment difference of at least 5% higher for any CTCAE grade or at least 2% for subjects with TEAEs of CTCAE Grade 3 or 4 were summarized by MedDRA SOC and preferred term for the DTC Randomized Safety Set (see Table 45).

Table 45 : Per-Subject Incidence of Treatment-Emergent Adverse Events Occurring in 5% or More of Subjects With a Between-Treatment Difference of at Least 5% for All CTCAE Grades or at Least 2% for CTCAE Grades 3 and 4 by MedDRA System Organ Class and Preferred Term – DTC Randomized Safety Set

MedDRA System Organ Class Preferred Term	Placebo (N=131) n (%)		Lenvatinib (N=261) n (%)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Blood and Lymphatic System Disorders				
Lymphopenia	2 (1.5)	0	19 (7.3)	3 (1.1)
Thrombocytopenia	3 (2.3)	0	23 (8.8)	4 (1.5)
Endocrine Disorders				
Hypothyroidism	0	0	14 (5.4)	0
Gastrointestinal Disorders				
Abdominal pain	5 (3.8)	1 (0.8)	43 (16.5)	4 (1.5)
Abdominal pain upper	10 (7.6)	0	41 (15.7)	2 (0.8)
Constipation	20 (15.3)	1 (0.8)	75 (28.7)	1 (0.4)
Diarrhoea	22 (16.8)	0	176 (67.4)	24 (9.2)
Dry Mouth	11 (8.4)	0	44 (16.9)	1 (0.4)
Dyspepsia	5 (3.8)	0	34 (13.0)	1 (0.4)
Flatulence	1 (0.8)	0	16 (6.1)	0
Glossodynia	0	0	18 (6.9)	1 (0.4)
Nausea	33 (25.2)	1 (0.8)	122 (46.7)	6 (2.3)
Oral Pain	1 (0.8)	0	25 (9.6)	1 (0.4)
Stomatitis	9 (6.9)	0	96 (36.8)	11 (4.2)
Vomiting	19 (14.5)	0	93 (35.6)	5 (1.9)
General Disorders and Administration Site Conditions				
Asthenia	17 (13.0)	3 (2.3)	66 (25.3)	16 (6.1)
Fatigue	32 (24.4)	2 (1.5)	111 (42.5)	12 (4.6)
General physical health deterioration	1 (0.8)	0	11 (4.2)	7 (2.7)
Malaise	0	0	14 (5.4)	0
Oedema peripheral	10 (7.6)	0	54 (20.7)	1 (0.4)
Infections and Infestations				
Urinary tract infection	7 (5.3)	0	30 (11.5)	3 (1.1)
Investigations				
Alanine aminotransferase increased	0	0	20 (7.7)	4 (1.5)
Aspartate aminotransferase increased	2 (1.5)	0	18 (6.9)	5 (1.9)
Blood creatinine increased	2 (1.5)	0	19 (7.3)	0
Blood TSH increased	0	0	17 (6.5)	0
Electrocardiogram QT prolonged	2 (1.5)	0	23 (8.8)	4 (1.5)
Platelet count decreased	0	0	17 (6.5)	1 (0.4)
Weight decreased	19 (14.5)	1 (0.8)	134 (51.3)	35 (13.4)
Metabolism and Nutrition Disorders				
Decreased appetite	24 (18.3)	1 (0.8)	142 (54.4)	18 (6.9)
Dehydration	3 (2.3)	1 (0.8)	23 (8.8)	6 (2.3)
Hypoalbuminaemia	2 (1.5)	0	25 (9.6)	1 (0.4)
Hypocalcaemia	0	0	33 (12.6)	13 (4.9)
Hypokalaemia	5 (3.8)	0	36 (13.8)	9 (3.4)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	9 (6.9)	1 (0.8)	68 (26.1)	1 (0.4)

Back Pain	12 (9.2)	0	46 (17.6)	5 (1.9)
Musculoskeletal pain	11 (8.4)	1 (0.8)	42 (16.1)	1 (0.4)
Myalgia	6 (4.6)	0	50 (19.2)	4 (1.5)
Pain in extremity	9 (6.9)	2 (1.5)	40 (15.3)	3 (1.1)
Nervous System Disorders				
Dizziness	12 (9.2)	0	40 (15.3)	1 (0.4)
Dysgeusia	4 (3.1)	0	47 (18.0)	0
Headache	15 (11.5)	1 (0.8)	100 (38.3)	8 (3.1)
Psychiatric Disorders				
Insomnia	4 (3.1)	0	31 (11.9)	0
Renal and Urinary Disorders				
Proteinuria	4 (3.1)	0	88 (33.7)	28 (10.7)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	23 (17.6)	0	62 (23.8)	0
Dysphonia	7 (5.3)	0	82 (31.4)	3 (1.1)
Epistaxis	1 (0.8)	0	31 (11.9)	0
Oropharyngeal pain	2 (1.5)	0	41 (15.7)	1 (0.4)
Skin and Subcutaneous Tissue Disorders				
Alopecia	7 (5.3)	0	32 (12.3)	0
Hyperkeratosis	2 (1.5)	0	18 (6.9)	0
PPE	1 (0.8)	0	84 (32.2)	9 (3.4)
Rash	2 (1.5)	0	49 (18.8)	1 (0.4)
Vascular Disorders				
Hypertension	20 (15.3)	5 (3.8)	181 (69.3)	112 (42.9)
Hypotension	3 (2.3)	0	23 (8.8)	4 (1.6)

Table includes those AEs that occurred in 5% or more of subjects provided there was a between-treatment difference of at least 5% for All CTCAE Grades or at least 2% for Grades 3 and 4. Subjects with 2 or more TEAEs reported for the same preferred term were counted only once using the highest CTCAE grade.
Percentages are based on the total number of subjects in the relevant treatment arm.
AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, PPE = palmer-plantar erythrodysesthesia syndrome, TEAE = treatment-emergent adverse event, TSH = thyroid stimulating hormone.

TEAEs adjusted by treatment duration

There was a large difference in duration of exposure between treatment arms in the DTC Randomized Safety Set, where the lenvatinib arm had a median duration of exposure 4 times that of the placebo arm (see patient exposure). The rate of TEAEs was also adjusted by treatment duration.

Treatment duration was defined as time of last dose minus first dose plus 1, and included treatment interruptions, unlike exposure duration, which did not include treatment interruptions. Depending on the pattern of occurrence over time and whether the AEs occurred spontaneously or were derived from scheduled assessments, it was determined whether the incidence or treatment duration-adjusted analysis was more appropriate for evaluating a specific AE.

Treatment-emergent AEs that occurred at a duration-adjusted rate of greater than 0.20 episodes per SY in the lenvatinib arm of the DTC Randomized Safety Set are presented in table below. The frequency order of TEAE episodes based on AE rate was similar to that observed for subject incidence in the lenvatinib treatment arm in Table 45, although vomiting occurred at a higher rate and weight decrease occurred at a lower rate than would have been predicted by the subject incidence.

Table 46 : Treatment-Emergent Adverse Events That Occurred at a Duration-Adjusted Rate Greater Than 0.20 Episodes per Subject-Year in the Lenvatinib Arm – DTC Randomized Safety Set

MedDRA Preferred Term	Placebo (N=131) Treatment SY[a]=67.1		Lenvatinib (N=261) Treatment SY[a]=298.8	
	Episodes	AE Rate[b]	Episodes	AE Rate[b]
All TEAE Episodes[c]	1050	15.66	6883	23.04
Diarrhoea	26	0.39	451	1.51
Hypertension	25	0.37	334	1.12
Decreased appetite	29	0.43	228	0.76
Nausea	45	0.67	209	0.70
Vomiting	24	0.36	183	0.61
Headache	18	0.27	172	0.58
Fatigue	35	0.52	164	0.55
Weight decreased	19	0.28	160	0.54
Stomatitis	10	0.15	139	0.47
Proteinuria	4	0.06	127	0.43
Palmar-plantar erythrodysaesthesia syndrome	1	0.01	126	0.42
Asthenia	19	0.28	100	0.33
Constipation	23	0.34	98	0.33
Dysphonia	7	0.10	94	0.31
Arthralgia	14	0.21	93	0.31
Cough	31	0.46	78	0.26
Myalgia	7	0.10	72	0.24
Oedema peripheral	11	0.16	72	0.24
Abdominal pain	7	0.10	71	0.24
Rash	3	0.04	64	0.21

Preferred terms are sorted based on the AE rate in the lenvatinib treatment arm. In the event of a tie, they are sorted alphabetically. The 0.20 cut-off is based on the AE rate in the lenvatinib treatment arm.
AE = adverse event, DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, SY = subject-years, TEAE = treatment-emergent adverse event.
a: Total Treatment Subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: AE Rate (episodes/subject-year) = total occurrence of AE episode (n) divided by total subject-years for the respective treatment group.
c: TEAE episode is based on MedDRA lower level term. A single episode is defined from onset through resolution or, if ongoing, to the end of the reporting period.

Regarding Grade 3 or 4 TEAEs that occurred at a duration-adjusted rate of 0.02 episodes per SY or higher in the lenvatinib arm of the DTC Randomized Safety Set, the frequency order of Grade 3 or 4 TEAE episodes based on AE rate was similar to that observed for subject incidence in the lenvatinib treatment arm in table 45. The episodes per SY for lenvatinib-treated subjects were approximately twice that for the placebo-treated subjects.

Clinically Significant Adverse Events (CSEs)

CSEs are briefly summarized below and important findings noted.

Hypertension and proteinuria

The 2 most frequently reported CSEs observed with lenvatinib were hypertension and proteinuria, both of which tended to occur early during treatment. Hypertension and proteinuria were both frequently reported as Grade 3 events.

In the pivotal Phase 3 SELECT trial, hypertension (including hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) was reported in 72.8% of lenvatinib-treated patients and 16.0% of patients in the placebo-treated group. The median time to onset in lenvatinib-treated patients was 16 days. Reactions of Grade 3 or higher (including 1 reaction of Grade 4)

occurred in 44.4% of lenvatinib-treated patients compared with 3.8% of placebo-treated patients. The majority of cases recovered or resolved following dose interruption or reduction, which occurred in 13.0% and 13.4% of patients, respectively. In 1.1% of patients, hypertension led to permanent treatment discontinuation.

Proteinuria was reported in 33.7% of lenvatinib-treated patients and 3.1% of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 reactions occurred in 10.7% of lenvatinib-treated patients and none in placebo-treated patients. The majority of cases had an outcome of recovered or resolved following dose interruption or reduction, which occurred in 16.9% and 10.7% of patients, respectively. Proteinuria led to permanent treatment discontinuation in 0.8% of patients.

The incidence of hypertension, including Grade 3-4 events, was higher in female, Japanese, and elderly subjects. Grade 3 or 4 hypertension was also reported more frequently in subjects with baseline hepatic or renal function impairment.

In study 303, the presence of hypertension at Baseline correlated with the development of renal events during treatment with lenvatinib with an odds ratio of 3.26 (95% CI: 1.43, 7.4.3) compared with subjects who did not have hypertension at Baseline. The development of hypertension during lenvatinib treatment appeared to be correlated with the development of proteinuria with an odds ratio of 3.00 (95% CI: 1.51, 5.96) compared with subjects who did not develop hypertension.

The evolution of the average number of days a subject reported an AE per treatment cycle was defined as the total number of days with the specific AE (e.g., hypertension) for all subjects who were treated at each cycle (4 weeks) divided by the number of subjects at risk. The evolution of the average number of days with hypertension started with 6 days for the first cycle, reached its maximum of 10.5 days at cycle 2 and then slowly declined to a plateau of about 4.5 days hypertension per cycle between cycle 15 and cycle 24. The evolution of the average number of days with proteinuria started with 0.8 days for the first cycle, reached a maximum of 4.5 days of proteinuria at cycle 6 and then declined slowly to a plateau of about 2 days of proteinuria between cycles 17 and 24. Both these patterns suggested that the protocol of dose reduction / discontinuation was successful at controlling the adverse reactions of, respectively, hypertension and proteinuria.

Posterior reversible encephalopathy syndrome is a rare event known to be linked to hypertension (Chen and Cleck, 2009). Three confirmed cases of PRES occurred, all within the first 6 months of exposure to lenvatinib.

Thromboembolic events

Certain thromboembolic events are known to occur with VEGF/VEGFR-targeted therapies. For purposes of analysis, these were separated into arterial and venous thromboembolic events, based on literature reports that the 2 have different risk factors and that venous thromboembolism is not linked to VEGFR-targeting agents, but rather to the patients' hypercoagulable state secondary to the ongoing malignancy.

Venous thromboembolism per sponsor-generated query (SGQ) analysis occurred at similar rates with lenvatinib across safety sets, and occurred at a similar rate to that for placebo in the DTC Randomized Safety Set on a duration-adjusted basis (lenvatinib, 0.05; placebo, 0.09 episodes/SY). There were four Grade 5 venous thromboembolic events in lenvatinib-treated subjects (2 DTC, 2 non-DTC) and none in placebo-treated subjects.

Arterial thromboembolic events per SGQ analysis were also uncommon, but occurred at a slightly higher rate with lenvatinib than with placebo on a duration-adjusted basis (0.07 vs. 0.04 episodes/SY) in the

DTC Randomized Safety Set. Arterial thromboembolic events were distributed throughout the duration of treatment. A total of 7 (1.5%) lenvatinib-treated DTC subjects prematurely discontinued treatment for the event.Serious arterial thromboembolic events were reported for 1.5% and 3.8% of subjects, respectively, in the placebo and lenvatinib arms of the DTC Randomized Safety Set, and in 3.8% of subjects in the All DTC Lenvatinib Safety Set. Across all safety sets, there were five Grade 5 arterial thromboembolic events in lenvatinib-treated subjects (2 DTC, 3 Non-DTC). While other factors may well have contributed to these events, based on similar occurrences with other VEGF/VEGFR-targeted agents, it is not possible to exclude lenvatinib as a causal agent.

Renal impairment/failure

Although renal events per SMQ analysis occurred more frequently with lenvatinib than with placebo on a duration-adjusted basis, almost all subjects who developed renal failure/impairment had 1 or more contributory factors. The majority of renal events were mild to moderate, with Grade 3-4 events occurring at a very low rate (0.02 episodes per SY in lenvatinib-treated DTC subjects). In the DTC Randomized Safety Set, most renal events were reversible and resolved with hydration, and did not lead to premature discontinuation.

There were 5 renal events associated with a fatal outcome in lenvatinib-treated subjects (1 DTC, 4 Non-DTC) and none in placebo-treated subjects. All of the reported renal-related deaths occurred in the setting of progression of the underlying malignancy.

Liver injury/failure

In the SELECT trial, the most commonly reported liver-related adverse reactions were hypoalbuminaemia (9.6% lenvatinib vs. 1.5% placebo) and elevations of liver enzyme levels, including increases in alanine aminotransferase (7.7% lenvatinib vs. 0 placebo), aspartate aminotransferase (6.9% lenvatinib vs. 1.5% placebo), and blood bilirubin (1.9% lenvatinib vs. 0 placebo). The median time to onset of liver reactions in lenvatinib-treated patients was 12.1 weeks. Liver-related reactions of Grade 3 or higher (including 1 Grade 5 case of hepatic failure) occurred in 5.4% of lenvatinib-treated patients compared with 0.8% in placebo-treated patients. Liver-related reactions led to dose interruptions and reductions in 4.6% and 2.7% of patients, respectively, and to permanent discontinuation in 0.4%.

Across safety sets, hepatic events per SGQ analysis were reported at higher rates with lenvatinib than with placebo, adjusted for treatment duration. Most hepatic events were related to liver enzyme elevations or hypoalbuminemia, and were Grade 1 or 2. Grade 3-4 hepatic events occurred in 5% or fewer of lenvatinib-treated DTC subjects. Four subjects met the laboratory screening criteria for potential Hy's Law cases. However, upon thorough evaluation, these subjects had medical conditions that accounted for the laboratory findings; therefore, they did not represent true Hy's Law cases. Hepatic events were controlled with dose interruptions and reductions, and only 1 DTC subject discontinued lenvatinib treatment due to a hepatic TEAE. There were 4 deaths due to a hepatic-related TEAE in lenvatinib–treated subjects (1 subject in the DTC Randomized Safety Set and 3 subjects in the Non-DTC Monotherapy Safety Set).

Amongst 1108 patients treated with lenvatinib, there were 3 cases (0.3%) of hepatic failure, all with a fatal outcome. One occurred in a patient with no liver metastases. There was also a case of acute hepatitis in a patient without liver metastases.

A higher incidence of liver events occurred in Asian subjects (primarily Japanese) compared with white subjects.

GI perforation and fistula formation events

Across the DTC safety sets, GI perforation and fistula formation (per SGQ analysis) occurred at similar rates for lenvatinib and placebo, adjusted for treatment duration. The incidence of dose modifications was low, and only 2 DTC subjects discontinued lenvatinib treatment due to the event.

Hypocalcemia

In the pivotal Phase 3 SELECT trial, hypocalcaemia was reported in 12.6% of lenvatinib-treated patients vs. no cases in the placebo arm. The median time to first onset in lenvatinib-treated patients was 11.1 weeks. Reactions of Grade 3 or 4 severity occurred in 5.0% of lenvatinib-treated vs 0 placebo-treated patients. Most reactions resolved following supportive treatment, without dose interruption or reduction, which occurred in 1.5% and 1.1% of patients, respectively; 1 patient with Grade 4 hypocalcaemia discontinued treatment permanently.

Across DTC safety sets, hypocalcemia per SGQ analysis occurred at higher rates with lenvatinib compared with placebo, adjusted for treatment duration. Hypocalcemia events tended to be mild to moderate, although 7 lenvatinib-treated subjects (5 DTC, 2 Non-DTC) had a nonfatal serious AE (SAE) versus none for placebo.

Similar findings were observed based on laboratory data, with Grade 3-4 low calcium values reported in 8.8% of lenvatinib-treated subjects and 1.5% of placebo-treated subjects (all Grade 3) in the DTC Randomized Safety Set, 7.2% of those in the All DTC Lenvatinib Safety Set, and 1.9% of those in the Non-DTC Monotherapy Safety Set. The underlying mechanism is unknown, although an increase in the incidence of hypocalcemia has been reported with another TKI, sorafenib (Brose, et al., 2014). Hypocalcemia was manageable with the use of concomitant medication and dose modifications.

Hemorrhage

The risk of bleeding has been reported to be increased in patients treated with VEGF/VEGFR-targeted therapies.

In the pivotal Phase 3 SELECT trial, haemorrhage was reported in 34.9% of lenvatinib-treated patients versus 18.3% of placebo-treated patients. Reactions that occurred at an incidence of ≥0.75% above placebo were: epistaxis (11.9%), haematuria (6.5%), contusion (4.6%), gingival bleeding (2.3%), haematochezia (2.3%), rectal haemorrhage (1.5%), haematoma (1.1%), haemorrhoidal haemorrhage (1.1%), laryngeal haemorrhage (1.1%), petechiae (1.1%), and intracranial tumour haemorrhage (0.8%). When adjusted to account for the 4-fold greater duration of exposure in the lenvatinib versus the placebo arm, the following reactions occurred less frequently on lenvatinib than placebo: haemoptysis (0.05 episodes/subject-year on lenvatinib vs. 0.21 episodes/subject-year on placebo) and pulmonary haemorrhage (0.02 episodes/subject-year on lenvatinib vs. 0.09 episodes/subject-year on placebo).

The median time to first onset in lenvatinib-treated patients was 10.1 weeks versus 3.9 weeks in the placebo arm. No differences between lenvatinib- and placebo-treated patients were observed in the incidences of serious reactions (3.4% vs. 3.8%), reactions leading to premature discontinuation (1.1% vs. 1.5%), or reactions leading to dose interruption (3.4% vs. 3.8%) or reduction (0.4% vs. 0).

Across the DTC safety sets, haemorrhage occurred at similar rates for lenvatinib and placebo when adjusted for treatment duration; the majority of events were Grade 1.

In the All DTC Lenvatinib Safety Set, the incidence of dose modifications was low, and only 1.3% of subjects discontinued treatment for hemorrhage. The most frequently reported serious bleeding event was intracranial tumour haemorrhage. The SAE rate for hemorrhage per SMQ was similar between lenvatinib- (2.7% to 4.0%) and placebo-treated (3.8%) subjects. Grade 5 hemorrhagic events occurred in 5 lenvatinib treated subjects (3 DTC and 2 Non-DTC), and in 1 placebo-treated subject.

Overall, amongst 1108 patients treated with lenvatinib, 3 patients (0.3%) had a Grade 4 haemorrhage and 5 patients (0.5%) had a Grade 5 reaction including arterial haemorrhage, haemorrhagic stroke, intracranial tumour haemorrhage, haemoptysis and tumour haemorrhage.

Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome is characteristic of VEGF/VEGFR-targeted agents (Brose, et al., 2014). The incidence (32.2%) in Study 303 was lower than that reported for sorafenib, and the majority of events were mild or moderate. The incidence of PPE was higher among females, Japanese, and subjects with baseline hepatic function impairment treated with lenvatinib. The incidence of PPE in Japanese subjects (74.2% vs. 27.4% for non-Japanese in the All DTC Lenvatinib Safety Set) was consistent in Study 303 and the Japan-only study, Study 208, suggesting an underlying mechanism that makes Japanese individuals more susceptible to this effect of lenvatinib. However, PPE did not appear to be dose-limiting for lenvatinib, and no subjects discontinued treatment because of it.

QTc prolongation

QTc prolongation has been observed with VEGF/VEGFR-targeted therapies. The evaluation of QTc prolongation in lenvatinib clinical studies included both an analysis of QTc prolongation based on AE reports (per SMQ) and an analysis of actual QT measurements from electrocardiograms. Collectively, electrocardiogram data and AE reports of QTc prolongation indicated that, in patients with advanced malignancy and associated complications (many of which result in electrolyte imbalance), there appears to be a numerically higher incidence of QTc-prolongation events with lenvatinib.

In the DTC Randomized Safety Set, a higher incidence of TEAEs for QTc prolongation per standardized MedDRA query (SMQ) was reported in the lenvatinib arm (8.8%) than the placebo arm (1.5%). Additionally, a higher incidence of QTc prolongation was reported in the All DTC Lenvatinib Safety Set (7.5%) than in the Non DTC Monotherapy Safety Set (1.5%). However, there were no deaths, serious adverse events (SAEs), or Grade 4 occurrences of QTc prolongation in any of the Safety Sets and only one subject in the All DTC Lenvatinib Safety Set discontinued treatment due to QTc prolongation among all the Safety Sets.

Based on electrocardiogram (ECG) data, 10.0% of lenvatinib-treated subjects and 3.1% of placebo-treated subjects in the DTC Randomized Safety Set had a maximum increase from baseline Fridericia's corrected QT interval (QTcF) of >60 ms. The maximum postbaseline QTcF value was >500 ms in 2.7% and 0.8% of subjects, respectively.

There were no reported episodes of ventricular tachycardia or Torsades de Pointes or deaths due to QT prolongation. Most events for QTc prolongation per SMQ were sporadic and resolved; there was no recurrence when the lenvatinib dose was reduced and no other intervention was required.

Many subjects had electrolyte alterations (e.g., hypocalcaemia and hypokalemia) at the time of the QTc prolongation event. In the DTC Randomized Safety Set, hypokalemia occurred in 36 subjects (13.8%, any grade) in the lenvatinib arm. Of these, 9 (3.4%) Grade 3 events, no Grade 4 events, 1 (0.4%) serious adverse event of hypokalemia, and no deaths due to hypokalemia were reported in the lenvatinib arm. No subjects discontinued treatment due to hypokalemia in the DTC Randomized Safety Set.

Across the entire lenvatinib-treated subject safety set (N = 1108 subjects), the TEAE of hypokalemia was reported in 92 subjects (8.3%) with the following frequencies: Grade 1 = 55 (59.8%), Grade 2= 15 (16.3%), Grade 3 = 17 (18.5%), Grade 4 = 5 (5.4%). There were 5 SAEs of hypokalemia reported and no outcome of death due to hypokalemia was reported.

Among these 92 subjects with a TEAE of hypokalemia as described above, 66 subjects (71.7%) had concurrent TEAE of diarrhea; 13 subjects (14.1%) also reported a TEAE of QTc prolongation; and 10 subjects (10.9%) reported combined and concurrent TEAEs of hypokalemia, diarrhea and QTc prolongation. There were 3 SAEs of hypokalemia (n=66) in subjects with hypokalemia and diarrhea and no SAEs or deaths were reported in the 10 subjects with combined TEAEs of hypokalemia, diarrhea and QTc prolongation.

With regards to the use of thiazides as a concomitant medication, 26 of 92 subjects (28.3%) with a TEAE of hypokalemia; 18 of 66 subjects (27.3%) with combined TEAEs of hypokalemia and diarrhea; 5 of the 13 (38.5%) subjects with combined TEAEs of hypokalemia and QTc prolongation; and 3 of the 10 (30%) subjects with combined TEAEs of hypokalemia, diarrhea and QTc prolongation, respectively had a concomitant medication of thiazides.

With regards to other GI toxicities such as vomiting, 42 of 92 subjects (45.7%) with a TEAE of hypokalemia also had a TEAE of vomiting. Among these, 6 subjects (6.5%) had a combined TEAE of hypokalemia, vomiting and QTc prolongation and only 2 (2.2%) of these subjects had a concomitant medication of thiazides.

Left ventricular ejection fraction decrease and cardiac failure events

Cardiomyopathy and congestive heart failure (CHF) have been reported with the use of VEGF/VEGFR targeted therapies, including sunitinib (Di Lorenzo et al., 2009; Richards, et al., 2011); however, refractory CHF with a fatal outcome has rarely been reported. In a retrospective study, Klein Hesselink et al. (2013) showed that the risk of cardiovascular mortality was increased 3.3-fold in individuals with DTC compared with controls, independent of age, sex, and cardiovascular risk factors, and that lower TSH levels were independently associated with an increased risk of cardiovascular mortality. The authors suggested that the increased risk of cardiovascular mortality in individuals with DTC may be due to long-term exposure to thyroid hormone suppression therapy rather than to the underlying cancer.

A report of echocardiographic parameters in Study E7080-G000-204 (Study 204) showed that changes in LVEF were small and the results did not suggest a direct cardiotoxic effect of lenvatinib. In Study 303, median percentage changes in LVEF from baseline to postbaseline nadir values were small (-5.0% and -1.5% for lenvatinib and placebo, respectively). No placebo-treated subjects had a significantly decreased LVEF value. In the lenvatinib arm, however, 2.3% and 1.5% of subjects had either a decrease of more than 20% from Baseline or a postbaseline nadir value below 40%, respectively. None of these subjects had cardiac failure clinically. In the All DTC Lenvatinib Safety Set, 2 subjects with decreased LVEF per echocardiogram had a reported TEAE of cardiac failure; both recovered after a dose interruption and continued lenvatinib treatment at a reduced dose.

The preferred term “ejection fraction (EF) decreased” was captured in the analysis of cardiac failure per SMQ. In the DTC Randomized Safety Set, “ejection fraction decreased” was the most common TEAE reported for cardiac failure per SMQ (14/17 subjects) and was mostly Grade 1 or 2. This finding indicated that most reports of cardiac failure AEs per SMQ were, in fact, decreased EF events. None of the subjects who experienced a TEAE of “ejection fraction decreased” had any other AE associated with cardiac failure per SMQ. Adjusted for treatment duration, the incidence of decreased EF per SGQ was similar for lenvatinib-treated subjects across all safety sets (0.03 to 0.05 episodes/SY), but slightly higher than that for placebo-treated subjects (0.01 episodes/SY).

Overall, these results suggest that lenvatinib has a small effect on LVEF.

Weight decrease

Weight loss has been reported as an AE with other VEGF/VEGFR targeted therapies, including sorafenib and motesanib (Haraldsdottir and Shah, 2014). A population PK/PD analysis showed that lenvatinib exposure significantly increased the probability of experiencing weight loss. Weight loss and decreased appetite were frequently reported TEAEs with lenvatinib in clinical studies. In the DTC Randomized Safety Set, weight loss was cumulative over time for lenvatinib-treated subjects. At the end of treatment, median weight loss was greater in the lenvatinib arm compared with placebo (lenvatinib, -5.3 kg; placebo, -1.0 kg). However, weight loss primarily occurred in subjects with higher BMI (i.e., the overweight and obese BMI categories) Weight loss in the lowest BMI quartile was minimal.

Cytopenia

Bone marrow hypoplasia was observed in nonclinical studies of lenvatinib, and is a known effect of VEGF inhibition. In the lenvatinib clinical studies, however, the incidence of cytopenias (anemia, leukopenia, neutropenia, thrombocytopenia) reported as TEAEs was low and similar in the All DTC Lenvatinib and Non-DTC Monotherapy Safety Sets. Grade 3-4 cytopenias were reported infrequently with lenvatinib in Study 303 (<2% of subjects). However, the incidence of thrombocytopenia was higher in female and Japanese subjects.

Blood thyroid stimulating hormone changes

In the pivotal Phase 3 SELECT trial, 88% of all patients had a baseline TSH level less than or equal to 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 57% of lenvatinib-treated patients as compared with 14% of placebo-treated patients.

Hypothyroidism manifesting as changes in hormone levels is a known AE of anti-angiogenic agents and was observed in patients with intact thyroid and in thyroidectomised patients. In the Study 303 all patients had prior anti-thyroid cancer surgery and a TEAE of blood TSH increased was reported in 17 (6.5%) subjects in the lenvatinib arm and no subjects in the placebo arm. Consistently, hypothyroidism was reported as a TEAE in 14 (5.4%) subjects in the lenvatinib arm and no subjects in the placebo arm and in 6 (5.5%) of subjects in the overall OOL group. There were no Grade ≥3 events of blood thyroid stimulating hormone increased or hypothyroidism.

Interstitial lung disease-like events (ILD)

The incidence of ILD-like events reported with lenvatinib was low: in the DTC randomised set with lenvatinib 2 (0.8%) for pneumonitis and 1 (0.4%) for lung infiltration; no cases have been reported with placebo. Incidences in the All DTC lenvatinib and the non-DTC monotherapy set were similar. In the DTC indication events were of grade 1 or 2; 1 grade 3 event was reported with lenvatinib in a non-DTC indication.

Adverse drug reactions

The methodology used to characterise an AE as related to lenvatinib is described below. The comparative incidence of events on lenvatinib compared with placebo in the DTC Randomized Safety Set was reviewed and:

• AEs with an incidence greater than or equal to 5% higher than placebo (any CTC grade) were included.

• A lower threshold was used for Clinically Significant Events (CSEs) and events were assigned as ADRs if the reported incidence was greater than placebo by at least 0.75% (i.e. a minimum 2 subject difference).

• Additional ADRs (e.g. PRES) were identified from a manual review of all other events which occurred more frequently on lenvatinib than placebo, and for which it was concluded there was a reasonable

possibility of a causal relationship taking into account factors such as the medical importance of the event and biological plausibility.

Subsequently synonymous terms were combined, and other groups of terms were grouped together and the frequency of the grouped term computed. Examples of such terms are “haemorrhagic events”, “renal failure events”, “Gastrointestinal and abdominal pain”.

In most cases (except lymphopenia, cerebrovascular accident, monoparesis, myocardial infarction, cardiac failure, hypotension, and hepatocellular damage), the final frequency category for the All DTC Safety Set was the same as that for the DTC Randomized Safety Set.

Based on this the following are considered adverse drug reactions:

Very common: Urinary tract infection, Thrombocytopeniaa, Hypocalcaemia, Hypokalaemia, Weight decreased, Decreased appetite, Insomnia, Dizziness, Headache, Dysgeusia, Haemorrhaged, Hypertensione, Hypotension, Dysphonia, Diarrhoea, Gastrointestinal and abdominal pains, Vomiting, Nausea, Oral inflammation, Oral pain, Constipation, Dyspepsia, Dry mouth, Palmar-plantar erythrodysaesthesia syndrome, Rash, Alopecia, Back pain, Arthralgia, Myalgia, Pain in extremity, Musculoskeletal pain, Proteinuria, Fatigue, Asthenia, Oedema peripheral.

Common: Lymphopenia, Hypothyroidism, Blood thyroid stimulating hormone increased, Dehydration, Hypomagnesaemia, Hypercholesterolaemia, Cerebrovascular accident, Myocardial infarctionc, Cardiac failure, Electrocardiogram QT prolonged, Ejection fraction decreased, Pulmonary embolism, Anal fistula Flatulence, Aspartate aminotransferase increased, Hypoalbuminaemia, Alanine aminotransferase increased, Blood alkaline phosphatase increased, Hepatic function abnormal, Gamma-glutamyltransferase increased, Blood bilirubin increased, Hyperkeratosis, Renal failure cases, Renal impairment, Blood creatinine increased, Blood urea increased and Malaise.

Uncommon: Perineal abscess, Splenic infarction, Posterior reversible encephalopathy syndrome Monoparesis, Transient ischaemic attack, hepatocellular damage/hepatitis.

Overdose

The highest tested doses of lenvatinib in clinical studies were 32 mg QD and 20 mg BID. Accidental medication errors resulting in single doses of 40 to 48 mg have also occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE.

There have also been reports of overdose with lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of lenvatinib (i.e., renal and cardiac failure), or were without adverse reactions.

There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, lenvatinib should be withheld and appropriate supportive care given as required (see SmPC section 4.9).

Comparison of the main adverse effects of Sorafenib and Lenvatinib

Table 47 : Comparison of the main adverse effects of Lenvatinib and Sorafenib in placebo controlled trials

MedDRA Preferred Term[a]	Study SELECT Lenvatinib arm N = 261 n (%)	Study DECISION Sorafenib arm N = 207 n (%)
Hypertension	**181 (69,3)**	84 (40,6)

Diarrhoea	173 (66,3)	142 (68,6)
Decreased appetite (anorexia)	**139 (53,3)**	66 (31,9)
Weight decreased (weight loss)	132 (50,6)	97 (46,9)
Nausea	**121 (46,4)**	43 (20,8)
Fatigue	110 (42,1)	103 (49,8)
Headache	**100 (38,3)**	37 (17,9)
Stomatitis (oral mucositis)	**93 (35,6)**	48 (23,2)
Vomiting	**92 (35,2)**	23 (11,1)
PPE syndrome	84 (32,2)	**158 (76,3)**
Proteinuria (*)	**84 (32,2)**	6 (2,9)
Dysphonia (voice changes)	**82 (31,4)**	25 (12,1)
Constipation	**74 (28,4)**	31 (15)
Asthenia (*)	**65 (24,9)**	25 (12,1)
Cough	58 (22,2)	32 (15,5)
Rash (rash or desquamation)[c]	48 (18,4)	**104 (50,2)**
Back pain	**45 (17,2)**	22 (10,6)
Abdominal pain (abdominal pain NOS)	42 (16,1)	29 (14)
Pain in extremity	40 (15,3)	28 (13,5)
Dyspnoea	39 (14,9)	30 (14,5)
Pyrexia (fever)	35 (13,4)	23 (11,1)
Hypocalcaemia	34 (13)	39 (18,8)
Alopecia	32 (12,3)	**139 (67,1)**
Oral pain (pain, throat, pharynx or larynx)	24 (9,2)	21 (10,1)
ALT increased	19 (7,3)	26 (12,6
Blood TSH increased (serum TSH increased[b])	17 (6,5)	**69 (33,3)**
AST increased	17 (6,5)	23 (11,1)
Pruritis	13 (5)	**44 (21,3)**
Pain (pain, other)	4 (1,5)	**22 (10,6)**

main source: table 2.7.4-80 of the SCS appendices (summary-clin-safety-appendices-00 pg 147)

Table includes AEs with an incidence of ≥10% in the sorafenib arm of the DECISION study, with the exception of proteinuria. Table contains only data from the double-blind phase of the studies.

Data for the sorafenib Phase 3 DECISION study were obtained from Brose et al., 2014;

(*) for proteinuria the data comes from the clinical study report of sorafenib cut off 31/08/2012 table 14.3.3/18 page 355 and for asthenia the data come from table 2-4 (study 14295), pg 62 of the SCS of sorafenib.

The data cutoff date for the lenvatinib 303 (SELECT) study was 15 Nov 2013.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BID = twice daily, Gr = grade, MedDRA = Medical Dictionary for Regulatory Activities,NA = not available, NC = not calculated, NOS = not otherwise specified, PPE = palmar-plantar erythrodysaesthesia, QD = once daily, TEAE = treatment-emergent adverse event, TSH = thyroid-stimulating hormone.

a: AE terms used in the sorafenib DECISION study, if different from those for the lenvatinib study, are shown in parentheses.

b: For the sorafenib DECISION study, TSH concentrations higher than 0.5 mIU/L (a study-specific AE) are included within this category, and are reported according to MedDRA version 15.1.

c: For Study 303, the term "rash" does not include the preferred terms of rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, orash pruritic.

Serious adverse events and deaths

Serious adverse events

Across safety sets, nonfatal SAEs occurred in 44.1% to 52.1% of subjects in the lenvatinib groups across all safety sets and 22.9% of subjects in the placebo group in DTC Randomized safety set. For the DTC Randomized Safety Set, the incidence of SAEs, adjusted for treatment duration, was slightly higher for the lenvatinib arm (0.93 episodes/SY) compared with the placebo arm (0.78 episodes/SY).

Table 48 : Nonfatal Serious Adverse Events That Occurred in 2% or More of Subjects – All Safety Sets

MedDRA Preferred Term	Safety Sets			
	DTC	DTC Non-	All DTC	Non-DTC

	Randomized		randomized	Lenvatinib	Monotherapy
	Placebo (N=131) n (%)	Lenvatinib (N=261) n (%)	Lenvatinib (N=191) n (%)	Lenvatinib (N=452) n (%)	Lenvatinib (N=656) n (%)
Subjects with at least 1 nonfatal SAE	30 (22.9)	136 (52.1)	95 (49.7)	231 (51.1)	289 (44.1)
Pneumonia	3 (2.3)	10 (3.8)	5 (2.6)	15 (3.3)	12 (1.8)
Dehydration	0	7 (2.7)	7 (3.7)	14 (3.1)	19 (2.9)
Hypertension	0	9 (3.4)	3 (1.6)	12 (2.7)	18 (2.7)
Hypotension	0	4 (1.5)	5 (2.6)	9 (2.0)	9 (1.4)
Pulmonary embolism	2 (1.5)	5 (1.9)	4 (2.1)	9 (2.0)	15 (2.3)
Malignant pleural effusion	1 (0.8)	3 (1.1)	5 (2.6)	8 (1.8)	0
General physical health deterioration	0	6 (2.3)	1 (0.5)	7 (1.5)	2 (0.3)
Asthenia	0	2 (0.8)	4 (2.1)	6 (1.3)	7 (1.1)
Atrial fibrillation	0	2 (0.8)	4 (2.1)	6 (1.3)	2 (0.3)
Decreased appetite	0	2 (0.8)	4 (2.1)	6 (1.3)	8 (1.2)
Abdominal pain	0	1 (0.4)	4 (2.1)	5 (1.1)	21 (3.2)
Dyspnoea	5 (3.8)	3 (1.1)	2 (1.0)	5 (1.1)	8 (1.2)
Vomiting	0	4 (1.5)	1 (0.5)	5 (1.1)	19 (2.9)
Dysphagia	3 (2.3)	3 (1.1)	1 (0.5)	4 (0.9)	2 (0.3)
Diarrhoea	0	2 (0.8)	1 (0.5)	3 (0.7)	14 (2.1)
Haemoptysis	3 (2.3)	0	2 (1.0)	2 (0.4)	1 (0.2)
Nausea	1 (0.8)	0	1 (0.5)	1 (0.2)	18 (2.7)

Preferred terms are included if the incidence was 2% or higher in any Safety Set or treatment arm. Percentages are based on the number of subjects in the relevant Safety Set or treatment arm. Preferred terms are sorted based on the incidence in the All DTC Lenvatinib Safety Set. In the event of a tie, they are sorted alphabetically.
DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.

Deaths

As of the safety cut-off date of 15 March 2014, 82 (31.4%) and 53 (40.5%) subjects in the lenvatinib and placebo arms of Study 303, respectively, had died. Deaths associated with a fatal AE or an unknown reason occurred in 20 subjects (7.7%) in the lenvatinib arm and 6 subjects (4.6%) in the placebo arm. Adjusted by treatment duration, the incidence of fatal AEs was similar between treatment arms (0.07 vs 0.10 events/SY for lenvatinib and placebo, respectively). There was no pattern for any of the fatal AEs.

A total of 32 subjects had a fatal AE in the All DTC Lenvatinib Safety Set.

Severe (Grade 3 or 4) and Grade 5 AEs associated with the CSEs are provided in Table 49 by subject incidence. The ranking of AEs when incidences were adjusted for duration remained the same. The same low value for “GI perforation and fistula formation events” was observed in placebo and lenvatinib groups.

Table 49 : Subject Incidence of Overall, Severe (Grade 3 or 4), and Grade 5 Clinically Significant Events – DTC Randomized and All DTC Lenvatinib Safety Sets

	DTC Randomized Safety Set						All DTC Lenvatinib Safety Set		
	Placebo (N=131) n (%)			Lenvatinib (N = 261) n (%)			Lenvatinib (N = 452) n (%)		
SMQ or SGQ Term	All Grades	Grade 3-4[a]	Grade 5	All Grades	Grade 3-4[a]	Grade 5	All Grades	Grade 3-4[a]	Grade 5
Hypertension	21 (16.0)	5 (3.8)	0	191 (73.2)	116 (44.4)	0	324 (71.7)	172 (38.1)	0
Haemorrhage	24 (18.3)	3 (2.3)	1 (0.8)[b]	91 (34.9)	3 (1.1)	2 (0.8)[c]	173 (38.3)	8 (1.8)	3 (0.7)[d]
Proteinuria	4 (3.1)	0	0	88 (33.7)	28 (10.7)	0	167 (36.9)	41 (9.1)	0
PPE	1 (0.8)	0	0	88 (33.7)	9 (3.4)	0	153 (33.8)	13 (2.9)	0
Liver events	5 (3.8)	1 (0.8)	0	66 (25.3)	13 (5.0)	1 (0.4)[e]	106 (23.5)	20 (4.4)	1 (0.2)[e]
Renal events	3 (2.3)	1 (0.8)	0	37 (14.2)	7 (2.7)	1 (0.4)[f]	54 (11.9)	9 (2.0)	1 (0.2)[f]
Hypocalcaemia	0	0	0	33 (12.6)	13 (5.0)	0	53 (11.7)	18 (4.0)	0
QTc prolongation	2 (1.5)	0	0	23 (8.8)	4 (1.5)	0	34 (7.5)	7 (1.5)	0
Arterial thromboembolism	3 (2.3)	0	1 (0.8)[g]	14 (5.4)	5 (1.9)	2 (0.8)[h]	26 (5.8)	14 (3.1)	2 (0.4)[h]
Venous thromboembolism	6 (4.6)	2 (1.5)	0	14 (5.4)	8 (3.1)	2 (0.8)[i]	21 (4.6)	14 (3.1)	2 (0.4)[i]
Decreased ejection fraction	1 (0.8)	0	0	14 (5.4)	3 (1.1)	0	20 (4.4)	4 (0.9)	0
GI perforation and fistula formation events	1 (0.8)	0	0	5 (1.9)	2 (0.8)	0	10 (2.2)	7 (1.5)	0
PRES	0	0	0	1 (0.4)	0	0	1 (0.2)	0	0

Note: One subject (in Study 303) with Grade 5 hemorrhagic stroke is included in the analysis for both the CSEs of hemorrhagic events and arterial thromboembolic events.

Treatment-emergent AEs are sorted by descending frequency in the All Grade column for the All DTC Lenvatinib Safety Set.

AE = adverse event, CSE = clinically significant event, DTC = differentiated thyroid cancer, GI = gastrointestinal, MedDRA = Medical Dictionary for Regulatory Activities, PPE = Palmer-Plantar erythrodyesthesia syndrome, PRES = Posterior Reversible Encephalopathy Syndrome, SGQ = sponsor-generated query, SMQ = standard MedDRA query.

a: The number of Grade 3-4 episodes was calculated by subtracting the number of Grade 5 episodes from the number of Grades ≥3 episodes in the SAS tables.

b: Grade 5 hemorrhagic event includes 1 subject with hemothorax.

c: Grade 5 hemorrhagic events include 1 subject each with hemorrhagic stroke or intracranial tumor hemorrhage.

d: Grade 5 hemorrhagic events include 1 subject each with haemorrhagic stroke, arterial haemorrhage, or intracranial tumour haemorrhage.

e: Grade 5 hepatic event includes 1 subject with hepatic failure.

f: Grade 5 renal event includes 1 subject with renal failure acute.

g: Grade 5 arterial thromboembolic event includes 1 subject with myocardial infarction.

h: Grade 5 arterial thromboembolic events include 1 subject each with myocardial infarction or hemorrhagic stroke.

i: Grade 5 venous thromboembolic events include 2 subjects with pulmonary embolism.

Table 50 : Incidence of Fatal Adverse Events – All Safety Sets

MedDRA Preferred Term	Safety Sets				
	DTC Randomized		DTC Non-randomized	All DTC Lenvatinib	Non-DTC Monotherapy
	Placebo	Lenvatinib	Lenvatinib	Lenvatinib	Lenvatinib
	(N=131)	(N=261)	(N=191)	(N=452)	(N=656)
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 fatal AEa	6 (4.6)	20 (7.7)	12 (6.3)	32 (7.1)	54 (8.2)
Death[b]	1 (0.8)	2 (0.8)	2 (1.0)	4 (0.9)	0
General physical health deterioration	0	3 (1.1)	0	3 (0.7)	10 (1.5)
Acute respiratory failure	0	1 (0.4)	1 (0.5)	2 (0.4)	0
Cardio-respiratory arrest	0	2 (0.8)	0	2 (0.4)	0
Malignant neoplasm progression	0	1 (0.4)	1 (0.5)	2 (0.4)	2 (0.3)
Pulmonary embolism	0	2 (0.8)	0	2 (0.4)	2 (0.3)
Arterial haemorrhage	0	0	1 (0.5)	1 (0.2)	0
Cardiac arrest	0	0	1 (0.5)	1 (0.2)	0
Chronic obstructive pulmonary disease	0	0	1 (0.5)	1 (0.2)	0
Dyspnoea	2 (1.5)	0	1 (0.5)	1 (0.2)	1 (0.2)
Haemorrhagic stroke	0	1 (0.4)	0	1 (0.2)	0
Hepatic failure	0	1 (0.4)	0	1 (0.2)	2 (0.3)
Intracranial tumour haemorrhage	0	1 (0.4)	0	1 (0.2)	0
Lung infection	0	1 (0.4)	0	1 (0.2)	0
Lymph gland infection	0	0	1 (0.5)	1 (0.2)	0
Multi-organ failure	0	1 (0.4)	0	1 (0.2)	1 (0.2)
Myocardial infarction	1 (0.8)	1 (0.4)	0	1 (0.2)	1 (0.2)
Osmotic demyelination syndrome	0	0	1 (0.5)	1 (0.2)	0
Pneumonia	0	1 (0.4)	0	1 (0.2)	0
Renal failure acute	0	1 (0.4)	0	1 (0.2)	2 (0.3)
Respiratory distress	0	0	1 (0.5)	1 (0.2)	0
Respiratory failure	0	0	1 (0.5)	1 (0.2)	1 (0.2)
Sepsis	1 (0.8)	1 (0.4)	0	1 (0.2)	3 (0.5)
Septic shock	0	0	1 (0.5)	1 (0.2)	1 (0.2)
Sudden death	1 (0.8)	1 (0.4)	0	1 (0.2)	0
Cardiopulmonary failure	0	0	0	0	3 (0.5)
Cerebrovascular accident	0	0	0	0	2 (0.3)
Disease progression	0	0	0	0	7 (1.1)
Haemothorax	1 (0.8)	0	0	0	0
Renal failure	0	0	0	0	3 (0.5)

Percentages are based on the number of subjects in the relevant Safety Set or treatment arm. Preferred terms are sorted based on the incidence in the All DTC Lenvatinib Safety Set. In the event of a tie, they are sorted alphabetically.
AE = adverse event, DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, NOS = not otherwise specified.
a: Fatal AEs include any AE leading to death during treatment or within 30 days after last dose.
b: Verbatim terms for the fatal AE of Death were "death NOS," "unspecified death," "death (cause unknown)," and "death cause unknown" in the lenvatinib-treated subjects; and "unknown cause of death, due to progression of disease" in the placebo-treated subject.
Asthenia, Cardiac failure, Cardiac failure congestive, *Clostridium difficile* colitis, Decreased appetite, Diarrhoea, Dysphonia, Haematemesis, Haemoptysis, Hepatorenal syndrome, Melaena, Metastases to peritoneum, Nausea, Oncologic complication, Paraneoplastic syndrome, Pleural effusion, Renal failure, Respiratory arrest, Stomatitis, Tachycardia, Tumour haemorrhage, Tumour lysis syndrome, Vomiting, Wound infection accounted each for one subject with fatal AE in the Non-DTC Monotheapy set.

Table 51 : Adverse Events Leading to Death That Were Reported by the Investigator as Treatment Related – All Safety Sets

MedDRA Preferred Term	Safety Sets			
	DTC	DTC Non-	All DTC	Non-DTC

	Randomized		randomized	Lenvatinib	Monotherapy
	Placebo (N=131) n (%)	Lenvatinib (N=261) n (%)	Lenvatinib (N=191) n (%)	Lenvatinib (N=452) n (%)	Lenvatinib (N=656) n (%)
Subjects with at least 1 treatment-related[a] fatal AE[b]	0	6 (2.3)	4 (2.1)	10 (2.2)	13 (2.0)
Death	0	2 (0.8)	1 (0.5)	3 (0.7)	0
Dyspnoea	0	0	1 (0.5)	1 (0.2)	0
General physical health deterioration	0	1 (0.4)	0	1 (0.2)	2 (0.3)
Haemorrhagic stroke	0	1 (0.4)	0	1 (0.2)	0
Pulmonary embolism	0	1 (0.4)	0	1 (0.2)	2 (0.3)
Respiratory distress	0	0	1 (0.5)	1 (0.2)	0
Respiratory failure	0	0	1 (0.5)	1 (0.2)	1 (0.2)
Sudden death	0	1 (0.4)	0	1 (0.2)	0

Percentages are based on the number of subjects in the relevant Safety Set or treatment arm. Preferred terms are included if the incidence was 1% or higher in any Safety Set or treatment arm. Preferred terms are sorted based on the AE rate in the All DTC Lenvatinib Safety Set. In the event of a tie, they are sorted alphabetically.
AE = adverse event, DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.
a: Treatment-related TEAEs includes those reported by the investigator to be possibly or probably related to study drug or for which causality was missing.
b: Fatal AEs include any AE leading to death during treatment or within 30 days after last dose.
Asthenia, Cerebrovascular accident, Diarrhoea, Haematemesis, Hepatic failure, Melaena, Renal failure, Sepsis, Tachycardia, Tumour haemorrhage accounted each for one subject in the Non-DTC Monotherapy safety set.

Laboratory findings

Lenvatinib treatment was primarily associated with reductions in platelet counts, decreases in albumin and calcium levels, and increases in alanine aminotransferase, aspartate aminotransferase, bilirubin, amylase, and lipase concentrations.The incidence of Grade 3-4 abnormalities during treatment with lenvatinib was low.

Haematology

The comparison between treatment arms for the DTC Randomized Safety Set focused on the first 12 cycles of treatment because the number of subjects in the placebo arm was small after that.

Haemoglobin

In the DTC Randomized Safety Set, the median haemoglobin concentration increased during the first cycle in the lenvatinib arm and remained elevated through Cycle 12, whereas the median haemoglobin concentration did not change from Baseline in the placebo arm. The results for subjects in other Safety Sets were similar to those for lenvatinib-treated subjects in the DTC Randomized Safety Set.

Platelets

In the DTC Randomized Safety Set, median platelet counts decreased from Baseline and remained decreased throughout treatment, though stayed within the normal range, in the lenvatinib arm but remained near the baseline level over time in the placebo arm. The results for subjects in the other Safety Sets were similar to those for lenvatinib-treated subjects in the DTC Randomized Safety Set.

White blood cells

In the DTC Randomized Safety Set, the pattern of change over time in median values for leukocytes and neutrophils was similar in the 2 treatment arms. In the other analysis sets, there were no consistent upward or downward trends over time.

Lymphopenia has been seen in 6.5% of patients treated with lenvatinib. The numbers of patients with lymphopenia was small but a third of these had concomitant infection at the time of lymphopenia.

Table 52 : Number and Percentage of Subjects With Worst Post-baseline Value of CTCAE Grade 3 or 4 for Hematologic Parameters - All Safety Sets

	Safety Sets									
	DTC Randomized				DTC Nonrandomized		All DTC Lenvatinib		Non-DTC Monotherapy	
	Placebo (N=131)		Lenvatinib (N=261)		Lenvatinib (N=191)		Lenvatinib (N=452)		Lenvatinib (N=656)	
Parameter (CTCAE Term)	**Grade 3 n (%)**	**Grade 4 n(%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n(%)**	**Grade 3 n(%)**	**Grade 4 n(%)**	**Grade 3 n (%)**	**Grade 4 n(%)**
Haemoglobin low (Anaemia)	1/129 (0.8)	0	3/258 (1.2)	0	1/183 (0.5)	0	4/441 (0.9)	0	10/639 (1.6)	0
Haemoglobin high (Haemoglobin increased)	0	0	0	0	0	0	0	0	2/639 (0.3)	0
Leukocytes low (WBC decreased)	0	0	4/258 (1.6)	0	1/183 (0.5)	1/183 (0.5)	5/441 (1.1)	1/441 (0.2)	4/638 (0.6)	0
Neutrophils low (Neutrophil count decreased)	0	0	4/257 (1.6)	0	3/168 (1.8)	0	7/425 (1.6)	0	4/595 (0.7)	4/595 (0.7)
Platelets low (Platelet count decreased)	0	0	6/257 (2.3)	0	5/183 (2.7)	0	11/440 (2.5)	0	9/635 (1.4)	4/635 (0.6)

The data in this table were manually derived from the source tables.
CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, WBC = white blood cell.
Source: table 2.7.4-65 of SCS

Liver and Renal Tests

The comparison between treatment arms for the DTC Randomized Safety Set focused on the first 12 cycles of treatment.

ALT and AST

In the DTC Randomized Safety Set, there were small increases from Baseline in median values for both ALT and AST in the lenvatinib arm during Cycle 1, and the median values remained higher than the baseline level through Cycle 12. For placebo, the median values remained close to Baseline level through Cycle 12. The results for subjects in the other Safety Sets were similar to those for lenvatinib-treated subjects in the DTC Randomized Safety Set.

Alkaline phosphatase

In the DTC Randomized Safety Set, there was a transient increase from Baseline in median value for alkaline phosphatase early in treatment with lenvatinib, which then decreased and remained at or below the baseline level through Cycle 12. For placebo, median values were similar at Baseline through Cycle 12. The results for subjects in the other Safety Sets were similar to those for lenvatinib-treated subjects in the DTC Randomized Safety Set.

Bilirubin and creatinine

There were no consistent patterns of change over time in either treatment arm in the DTC Randomized Safety Set, or in any of the other Safety Sets.

Other Blood Chemistries

Hypocalcaemia was identified as a clinically significant event (see section on CSE). Majority of the subjects with hypocalcaemia had a history of hypothyroidism, hypoparathyroidism, hypomagnesaemia, or hypocalcaemia, and more than 50% of subjects had thyroid carcinoma.

The comparison between treatment arms for the DTC Randomized Safety Set focused on the first 12 cycles of treatment. In the DTC Randomized Safety Set, median values for calcium were similar in the lenvatinib and placebo arms throughout the study. There was no consistent upward or downward trend over time in either group. There were no consistent upward or downward trends over time in any of the other Safety Sets.

Table 53 : Number and percentage of subjects with worst Post-baseline Value of Grade 3 or 4 for Selected Non-hematologic Laboratory Parameters All Safety Sets

	Safety Sets									
	DTC Randomized				**DTC Nonrandomized**		**All DTC Lenvatinib**		**Non-DTC Monotherapy**	
	Placebo (N=131)		**Lenvatinib (N=261)**		**Lenvatinib (N=191)**		**Lenvatinib (N=452)**		**Lenvatinib (N=656)**	
Parameter (CTCAE Term)	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
ALT (ALT Increased)	0	0	10/258 (3.9)	1/258 (0.4)	4/185 (2.2)	0	14/443 (3.2)	1/443 (0.2)	16/637 (2.5)	3/637 (0.5)
Alkaline Phosphatase (Alkaline Phosphatase Increased)	1/130 (0.8)	0	5/258 (1.9)	0	1/185 (0.5)	0	6/443 (1.4)	0	19/642 (3.0)	0
AST (AST Increased)	0	0	12/258 (4.7)	0	2/185 (1.1)	0	14/443 (3.2)	0	11/643 (1.7)	3/643 (0.5)
Bilirubin (Blood Bilirubin Increased)	0	0	2/241 (0.8)	1/241 (0.4)	0	0	2/415 (0.5)	1/415 (0.2)	11/638 (1.7)	1/638 (0.2)
Creatinine (Creatinine Increased)	0	0	7/258 (2.7)	0	1/185 (0.5)	0	8/443 (1.8)	0	9/643 (1.4)	0
Calcium (Hypercalcemia)	0	1/130 (0.8)	1/258 (0.4)	1/258 (0.4)	0	2/185 (1.1)	1/443 (0.2)	3/443 (0.7)	1/639 (0.2)	0
Calcium (Hypocalcaemia)	2/130 (1.5)	0	13/258 (5.0)	10/258 (3.9)	7/185 (3.8)	2/185 (1.1)	20/443 (4.5)	12/443 (2.7)	8/639 (1.3)	4/639 (0.6)

The data in this table were manually derived from the source tables.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer. Source: table 2.7.4-66 of SCS

Safety in special populations

The safety of lenvatinib was explored for a number of intrinsic and extrinsic factors, including age, sex, race, baseline hepatic or renal impairment, and baseline status of hypertension, proteinuria and diabetes, among others.

Clinically significant events and severe TEAEs in the All DTC Lenvatinib Safety Set are summarised below. The numbers of subjects in many of the subgroups were small and therefore caution is required in the interpretation of results.

Age

Table 54: Adverse Event Profile in Elderly Patients - All DTC Lenvatinib and Non-DTC Monotherapy Safety Sets

	All DTC Lenvatinib Safety Set				Non-DTC Monotherapy Safety Set			
MedDRA Terms	Age <65 N = 259 n (%)	Age 65-74 N = 158 n (%)	Age 75-84 N = 33 n (%)	Age 85+ N = 2 n (%)	Age <65 N = 457 n (%)	Age 65-74 N = 147 n (%)	Age 75-84 N = 51 n (%)	Age 85+ N = 1 n (%)
Total AEs (Subjects with at least one TEAE) with maximum Grade of[a]	259 (100.0)	158 (100.0)	32 (97.0)	2 (100.0)	449 (98.2)	146 (99.3)	51 (100.0)	1 (100.0)
1	4 (1.5)	0	0	0	17 (3.7)	5 (3.4)	3 (5.9)	0
2	51 (19.7)	16 (10.1)	2 (6.1)	0	112 (24.5)	25 (17.0)	10 (19.6)	0
3	174 (67.2)	110 (69.6)	20 (60.6)	2 (100.0)	255 (55.8)	83 (56.5)	28 (54.9)	1 (100.0)
4	17 (6.6)	19 (12.0)	4 (12.1)	0	32 (7.0)	20 (13.6)	4 (7.8)	0
5	13 (5.0)	13 (8.2)	6 (18.2)	0	33 (7.2)	13 (8.8)	6 (11.8)	0
Serious TEAEs – Total[b]	127 (49.0)	87 (55.1)	22 (66.7)	1 (50.0)	210 (46.0)	77 (52.4)	26 (51.0)	1 (100.0)
Fatal	13 (5.0)	13 (8.2)	6 (18.2)	0	35 (7.7)	12 (8.2)	6 (11.8)	0
Disability/incapacity	7 (2.7)	3 (1.9)	2 (6.1)	0	3 (0.7)	1 (0.7)	0	0
Hospitalization/ prolongs existing hospitalization	116 (44.8)	79 (50.0)	22 (66.7)	1 (50.0)	176 (38.5)	68 (46.3)	23 (45.1)	1 (100.0)
Life-threatening	11 (4.2)	11 (7.0)	2 (6.1)	0	13 (2.8)	5 (3.4)	4 (7.8)	0
Other (medically significant)	14 (5.4)	13 (8.2)	2 (6.1)	0	21 (4.6)	7 (4.8)	3 (5.9)	0
TEAE leading to drop-out	40 (15.4)	36 (22.8)	11 (33.3)	1 (50.0)	112 (24.5)	43 (29.3)	13 (25.5)	0
Number of Subjects with TEAEs leading to study drug modification[c]	216 (83.4)	142 (89.9)	29 (87.9)	2 (100.0)	262 (57.3)	101 (68.7)	40 (78.4)	1 (100.0)
Interruption	185 (71.4)	129 (81.6)	29 (87.9)	2 (100.0)	239 (52.3)	87 (59.2)	37 (72.5)	1 (100.0)
Reduction	152 (58.7)	111 (70.3)	20 (60.6)	2 (100.0)	117 (25.6)	52 (35.4)	17 (33.3)	0
Psychiatric disorders SOC[d]	16 (26.6)	46 (29.1)	6 (18.2)	0	98 (21.4)	32 (21.8)	14 (27.5)	1 (100.0)
Nervous system disorders SOC[d]	154 (59.5)	94 (59.5)	15 (45.5)	1 (50.0)	277 (60.6)	72 (49.0)	28 (54.9)	0
Cardiac disorders SOC[d]	50 (19.3)	38 (24.1)	5 (15.2)	0	64 (14.0)	25 (17.0)	7 (13.7)	0
Vascular disorders SOC[d]	187 (72.2)	122 (77.2)	20 (60.6)	2 (100.0)	272 (59.5)	92 (62.6)	26 (51.0)	1 (100.0)
Infections and infestations SOC[d]	154 (59.5)	93 (58.9)	13 (39.4)	2 (100.0)	212 (46.4)	57 (38.8)	23 (45.1)	1 (100.0)
Accidents and injuries SMQ[d]	32 (12.4)	27 (17.1)	5 (15.2)	0	46 (10.1)	17 (11.6)	6 (11.8)	0
Cerebrovascular disorders SMQ[d]	11 (4.2)	9 (5.7)	2 (6.1)	0	25 (5.5)	11 (7.5)	2 (3.9)	0
Anticholinergic syndrome SMQ[d]	1 (0.4)	3 (1.9)	2 (6.1)	0	6 (1.3)	4 (2.7)	0	0
Sum of postural hypotension, falls, black outs,	50 (19.3)	38 (24.1)	6 (18.2)	1 (50.0)	86 (18.8)	32 (21.8)	9 (17.6)	0

syncope, dizziness, ataxia, fractures [d]								
Other AEs appearing more frequently in older patients: [e, f]								
Hypertension	172 (66.4)	116 (73.4)	20 (60.6)	2 (100.0)	244 (53.4)	80 (54.4)	22 (43.1)	1 (100.0)
Proteinuria	91 (35.1)	59 (37.3)	16 (48.5)	1 (50.0)	129 (28.2)	50 (34.0)	17 (33.3)	1 (100.0)
Decreased appetite	121 (46.7)	95 (60.1)	16 (48.5)	1 (50.0)	142 (31.1)	71 (48.3)	25 (49.0)	0
Dehydration	23 (8.9)	13 (8.2)	4 (12.1)	0	31 (6.8)	26 (17.7)	8 (15.7)	1 (100.0)

CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.

a: If a subject had more than one TEAE, the subject is only counted once at the maximum grade. Percentages are based on total number of subjects in the subgroups.

b: A subject may be counted in multiple categories.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

d: Subjects with at least one AE in the category of the Preferred Terms.

e: Although not evident from the all grade events, Grade 3 and 4 hypertension, proteinuria, decreased appetite, and dehydration occurred more frequently in older age groups.

f: For each row category, a subject with two or more adverse events in that category is counted only once. Percentages are based on total number of subjects in the subgroups.

The overall incidence of TEAEs or Grade 3-4 TEAEs were similar in the elderly subjects (≥65 years) and the <65 years age group. However, subjects 75 years or older had a higher incidence of fatal AEs. Compared with subjects younger than 65, subjects who were 75 years or older were also more likely to experience (in descending order of frequency) Grade 3-4 hypertension, proteinuria, decreased appetite, and dehydration.

Sex

The incidence of Grade 3-4 hypertension, fatigue and weight decreased was higher in females. Female subjects had a higher incidence of hypertension (including Grade 3 or 4 hypertension), proteinuria, and PPE (analyses per SGQ or SMQ), while males had a higher incidence of decreased EF and GI perforation and fistula formation per SGQ.

Race

Compared with white subjects, the overall AE profile for Asian subjects was not worse than that for white subjects. However, Asian subjects had a higher incidence of oedema peripheral and VEGF-related events such as hypertension, fatigue, PPE, proteinuria, thrombocytopenia, and blood TSH increased. These data were driven primarily by results in Japanese subjects, who comprised approximately 66% of the Asian subgroup, except for thrombocytopenia, whose occurrence was completely accounted for by Japanese subjects. Japanese subjects had a higher incidence (in descending order of frequency) of Grade 3-4 hypertension, decreased appetite, fatigue, and thrombocytopenia compared with non-Japanese subjects. Japanese subjects also had a higher incidence of liver events per SGQ. Arterial and venous thromboembolic events per SGQ occurred at very low rates in Japanese subjects, and GI perforation and fistula formation per SGQ did not occur at all in Japanese subjects. Such low rates for these events in Japanese subjects have not been reported in the literature. The basis for these findings is unclear and these results should be interpreted with caution, given the smaller number of Asian and Japanese subjects enrolled in the lenvatinib clinical trials.

The population PK/PD model showed that Japanese subjects had a higher probability of experiencing hypertension, proteinuria, and fatigue; however, the occurrence of these events did not appear to be correlated with PK parameters (see section on clinical pharmacokinetic).

Baseline body weight

Subjects in the <60 kg weight group had a higher incidence of fatal AEs compared with subjects in the ≥60 kg weight group. Patients with low body weight (<60 kg) had a higher incidence of PPE, proteinuria, of grade 3-4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of grade 3-4 decreased appetite.

Prior VEGF/VEGFR-targeted therapy

Lenvatinib-treated subjects in the DTC Randomized Safety Set who had received a prior VEGF/VEGFR-targeted therapy had a slightly higher incidence of SAEs compared with VEGF-treatment-naïve subjects. This pattern was not observed in the placebo arm. With regard to CSEs, subjects in the All DTC Lenvatinib Safety Set who had received a prior VEGF/VEGFR-targeted therapy had a higher incidence of renal events per SMQ and a trend towards a higher incidence of liver events per SGQ compared with VEGF-naïve subjects.

Baseline renal impairment

The numbers of subjects with renal impairment in the lenvatinib clinical studies was small; all had either mild or moderate impairment. In the DTC Randomized Safety Set, subjects with renal impairment at Baseline had a higher overall incidence of Grade 3-4 TEAEs and Grade 5 (fatal) AEs. Patients with baseline renal impairment had a higher incidence of Grade 3 to 4 hypertension, proteinuria, fatigue, stomatitis, oedema peripheral, thrombocytopenia, dehydration, prolonged electrocardiogram QT, hypothyroidism, hyponatraemia, blood thyroid stimulating hormone increased, pneumonia compared with subjects with normal renal function. These patients also had a higher incidence of renal reactions and a trend towards a higher incidence of liver reactions. These observations were consistent with results of the population PK/PD analysis (see clinical pharmacology).

Baseline hepatic impairment

Grade 3 or 4 hypertension, asthenia, fatigue, and hypocalcaemia were reported more frequently in subjects with baseline hepatic function impairment. With regard to CSEs, subjects with baseline hepatic impairment had a higher incidence of hypertension per SMQ and PPE per SGQ.

Baseline hypertension

Subjects with hypertension at Baseline had a higher incidence of Grade 3-4 TEAEs and SAEs. In particular, subjects with baseline hypertension had a higher incidence of Grade 3-4 hypertension, proteinuria, diarrhoea, and dehydration during treatment than did subjects with normal blood pressure at Baseline. The following SAEs were also reported more frequently among subjects with baseline hypertension (in descending order of frequency): dehydration, hypotension, pulmonary embolism, malignant pleural effusion, atrial fibrillation, and GI symptoms (abdominal pain, diarrhoea, vomiting). With regard to CSEs, subjects with baseline hypertension had a higher incidence of proteinuria, renal events and arterial thromboembolic events per SMQ or SGQ.

Baseline diabetes

Subjects with baseline diabetes had a higher incidence of Grade 3-4 proteinuria, decreased appetite, hypotension and stomatitis, and a trend towards a higher incidence of asthenia and dehydration. With regard to CSEs, subjects with baseline diabetes had a higher incidence of haemorrhage per SMQ and proteinuria per SGQ.

Baseline ECOG Performance status > 0

No analysis was provided in these patients on the ground that the number of patients of PS > 1 was too low. A short analysis of the patients with a baseline ECOG PS =0 vs PS >0 has shown that ECOG PS >0 patients stands less well any treatment, including placebo, than ECOG = 0 patients. Of note ECOG PS > 0 patients treated with lenvatinib showed lower incidences of AEs than ECOG = 0 patients, but for proteinuria.

Safety related to drug-drug interactions and other interactions

Based on a review of data for SAEs, premature discontinuations, and deaths, there did not appear to be any interactions between lenvatinib and the concomitant treatments administered in the monotherapy studies.

Doses reductions, Doses interruption and Discontinuation due to AEs

Dose reductions and interruptions

In phase 2 studies 201 and 208, TEAEs led to dose reduction in 65.5% and in 100% of patients, respectively, and to dose interruption in 74.1% and 36.4% of patients, respectively. The numbers of patients with AEs leading to dose reduction or interruption of study drug in the phase 3 Study 303 are presented in Table 44. One or more dose reductions occurred in 78.5% of subjects taking lenvatinib versus 8.4% of subjects taking placebo.

In the All DTC Lenvatinib Safety Set, a higher percentage of Japanese subjects vs. non-Japanese subjects had dose reductions (95.2% vs. 57.9%) while a lower percentage had dose interruptions (66.1% vs. 77.9%)

Most of dose reductions and interruptions were due to AEs following the dose adjustment algorithm mandated in the protocol. The reasons for dose interruptions or reductions were not collected on the Drug Administration CRF page. Hypertension and proteinuria were events that appeared to be the most frequent causes for dose reductions, but infrequently led to permanent treatment discontinuation (in 3 subjects and 2 subjects, respectively) (see section on adverse events).

As off data cutoff of 15 Nov 2013, the median time-to-first dose reduction (24 to 20 mg/day) or discontinuation was 12 weeks (CI: 8.3 -12, 223 patients), the median time from first to second dose reduction or discontinuation was 8.3 weeks (CI: 7.1 – 11; 166 subjects) and the median time from the second to the third dose reduction / discontinuation was 8.3 weeks (CI: 6.4 – 10; 85 subjects).

Kaplan-Meier plots of time-to-first dose reduction stratified by lenvatinib AUC based on the starting dose of 24 mg showed that a higher lenvatinib AUC resulted in an earlier dose reduction. The median time to first dose reduction for 1st, 2nd, 3rd, and 4th quartiles of exposure were 24.3 weeks (90% CI: 18.3 - 36.3), 16.1 weeks (90% CI: 12.1 - 20.1), 11.4 weeks (90% CI: 7.29 - 12.7), and 4.86 weeks (90 % CI: 4.14 - 9) respectively.

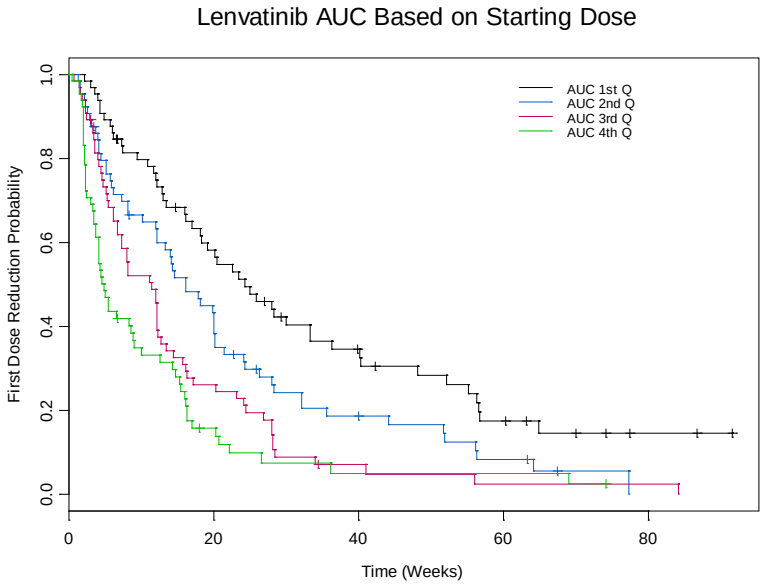


Figure 10: Kaplan-Meier Plots of Time to First Dose Reduction Stratified by Lenvatinib AUC Based on Starting Dose of 24 mg

Discontinuation

Table 55 : Summary of subject disposition and Reasons for Discontinuation (4 safety analysis sets)

	Safety Sets				
	DTC Randomized		DTC Non-Lenvatinib	All DTC Monotherapy	Non-DTC
	Placebo (N=131) n (%)	Lenvatinib (N=261) n (%)	Lenvatinib (N=191) n (%)	Lenvatinib (N=452) n (%)	Lenvatinib (N=656) n (%)
All Treated Subjects	131 (100.0)	261 (100.0)	191 (100.0)	452 (100.0)	656 (100.0)
Treatment Ongoing[a]	6 (4.6)	109 (41.8)	77 (40.3)	186 (41.2)	26 (4.0)
Completed Treatment – Disease Progression[b]	121 (92.4)	105 (40.2)	60 (31.4)	165 (36.5)	392 (59.8)
Discontinued Prematurely	4 (3.1)	47 (18.0)	54 (28.3)	101 (22.3)	238 (36.3)
Primary Reason for Premature Discontinuation of Treatment					
Adverse event	3 (2.3)	39 (14.9)	34 (17.8)	73 (16.2)	149 (22.7)
Subject choice[c]	0	4 (1.5)	7 (3.7)	11 (2.4)	0
Lost to follow-up	0	0	1 (0.5)	1 (0.2)	2 (0.3)
Administrative/Other					
Withdrawal of Consent[c]	0	4 (1.5)	3 (1.6)	7 (1.5)	12 (1.8)
Pregnancy	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0
Other[d]	1 (0.8)	0	9 (4.7)	9 (2.0)	75 (11.4)

CRF = case report form, DTC = differentiated thyroid cancer.
a: Ongoing at ISS data cutoff date.
b: Disease progression is considered as completion of study treatment, as defined per protocol.
c: Subject choice indicates the subject elected to stop the treatment with the investigational drug, but agreed to further data collection, including follow-up data. Withdrawal of consent indicates that the subject did not agree to having any additional data collected.
d: Other was a category on the CRF; no further information is available.

A substantial part of the premature discontinuations (11.4%) in the non-DTC set and 4.7% of patients in non-DTC set had 'other' as reasons for discontinuation, which were satisfactorily explained.

In the OOL part study 303, when adjusted by exposure, the rate of discontinuation for AEs was higher in the 24 mg (0.45 per SY) than in the 20 mg regimen (0.22 per SY).

TEAEs leading to permanent treatment discontinuation that led to discontinuation of treatment in 1% or more of subjects are presented below.

Table 56: Treatment-Emergent Adverse Events That Led to Discontinuation of Treatment in 1% or More of Subjects – All Safety Sets

MedDRA Preferred Term	Safety Sets				
	DTC Randomized		DTC Non-randomized	All DTC Lenvatinib	Non-DTC Monotherapy
	Placebo (N=131) n (%)	Lenvatinib (N=261) n (%)	Lenvatinib (N=191) n (%)	Lenvatinib (N=452) n (%)	Lenvatinib (N=656) n (%)
Subjects with at least 1 TEAE that led to treatment discontinuation	6 (4.6)	46 (17.6)	42 (22.0)	88 (19.5)	168 (25.6)
Proteinuria	0	2 (0.8)	4 (2.1)	6 (1.3)	7 (1.1)
Asthenia	0	3 (1.1)	2 (1.0)	5 (1.1)	7 (1.1)
Death	1 (0.8)	2 (0.8)	2 (1.0)	4 (0.9)	0
General physical health deterioration	0	2 (0.8)	2 (1.0)	4 (0.9)	5 (0.8)
Hypertension	0	3 (1.1)	1 (0.5)	4 (0.9)	12 (1.8)
Cerebrovascular accident	0	1 (0.4)	2 (1.0)	3 (0.7)	2 (0.3)
Diarrhoea	0	0	3 (1.6)	3 (0.7)	4 (0.6)
Malignant pleural effusion	0	1 (0.4)	2 (1.0)	3 (0.7)	0
Pulmonary embolism	0	1 (0.4)	2 (1.0)	3 (0.7)	6 (0.9)
Deep vein thrombosis	0	0	2 (1.0)	2 (0.4)	2 (0.3)
Fatigue	0	1 (0.4)	0	1 (0.2)	22 (3.4)

Preferred terms are included if the incidence was 1% or higher in any Safety Set or treatment arm. Percentages are based on the number of subjects in the relevant Safety Set or treatment arm. For each row category, a subject with two or more TEAEs in that category is counted only once. Sorted in descending order by MedDRA preferred term according to the incidence rate in the All DTC Lenvatinib Safety Set. In the case of a tie, the preferred terms are sorted alphabetically.

DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment- emergent adverse event.

Source: SCS table 2.7.4-32

2.6.1. Discussion on clinical safety

Discussion on starting dose

Although the results from the study 303 at present provide support for the starting dose of 24 mg QD for RR-DTC patients, overall, 89.7% of lenvatinib-treated patients had dose modifications (dose reduction and/or interruption). Lenvatinib exposure based on starting dose was a significant predictor for the occurrence of any grade proteinuria, nausea, and vomiting, and for Grade 3 or higher hypertension. Increased lenvatinib exposure based on dose intensity was a statistically significant predictor for any grade hypertension, proteinuria, nausea, and vomiting, and for Grade 3 or higher proteinuria. As such there was a link between the daily dose of the drug and the incidence of TEAEs of grade 3 or 4 and thus the number of interruptions. This is expected as the relationship between the dose of lenvatinib and the emergence and severity of AEs is a cornerstone of the algorithm of posology and dose reduction. However all quartiles of exposure to drug ("AUC dose intensity") had similar PFS even the last one once corrected for early drop-outs, suggesting that lower doses, with better safety profile might result in similar efficacy (see clinical pharmacodynamic).

In the OOL phase, efficacy between the starting doses of 24 mg and 20 mg was compared. Similar results in terms of PFS and ORR were observed for the starting doses of 24 mg and 20 mg. However, the findings may be confounded by a number of factors: 1) the much shorter time that the 20 mg dose was used compared with the 24 mg dose, 2) a much shorter follow-up period (median 8.3 months for the 20-mg dose vs. 17.0 months for the 24 mg dose), 3) the nonrandomized design and open-label nature of that phase, 4) the fact that enrolled subjects were further along in the course of their disease upon entry, and 5) the observation that the majority of subjects who received the 20 mg starting dose had a better ECOG PS (score of 0) at the start of the OOL Period than did those who received the 24-mg dose (PS score of 1).

Taking dose reductions into account, 24 mg was the dose most frequently given (42.5%), and the number of subject-years of exposure to 24 mg (89.7 SY) was greater than for any lower dose. 70.4% (119 out of 169) of subjects with an objective response (CR/PR) to lenvatinib developed that response during or within 30 days of receiving the 24 mg dose (i.e., before or shortly after first dose reduction). The median time to response (2 months) coincided with the first tumour assessment and was shorter than the median time to dose reduction (3 months). The applicant also argued that since tumour shrinkage occurs for a prolonged period, any response at the 20 mg dose could be due to a carry-over effect of the 24-mg dose, confounding the results. Furthermore, treatment-emergent hypertension occurred more frequently at the 24-mg dose in Study 303 and there was a correlation between increasing number of responses and increasing dose, up to 24 mg in dose-escalation studies. Therefore, at present it is not possible to dissociate the 24 mg starting dose from the observed efficacy of lenvatinib in this study. In addition, available data with the 20 mg dose are limited, as is the duration of follow-up to draw meaningful conclusions.

Overall, the current body of evidence is largely with the starting dose of 24 mg and it is currently not known whether a lower dose may be as effective with an improved safety profile. There is a need to further study an optimal starting dose for the overall target population, to better inform a choice of starting dose in subpopulations of patients and ultimaly to guide treatment in individual patients. Data on safety and activity of lower starting doses will be provided through a randomised dose-finding trial E7080-G000-211 (Study 211) looking at safety and activity of three starting doses (24 mg, 20 mg and 14 mg once daily) (see RMP). Primary endpoints will pertain to safety (rate of TEAE with CTCAE grades of 3 or higher within 6 months after randomization), but also to efficacy (Objective response rate (ORR) at 6 months (ORR_{6M}) as assessed by the investigator according to RECIST 1.1). An assessment of efficacy (including PFS, PFS2 and OS data) will inform whether lower starting doses result in similar efficacy. One of the study objectives will be to evaluate the pharmacokinetic/pharmacodynamic relationship between exposure and efficacy/safety. Further characterisation and use of appropriate biomarkers and PK/PD models is also expected (see discussion on clinical pharmacology and RMP). No interim analysis is planned for this randomized study in which study subjects, investigator site personnel and the sponsor will be blinded to treatment assignment. Interim analyses for safety by Independent Monitoring Committee are advised to closer monitor patients and to obtain additional data in the course of the study.

The final results of the study 303 will also be submitted as reflected in the RMP in order to provide further information on the safety profile at long term for the 20-mg dose versus the 24 mg. Similarly, final results of the ongoing study 201 in patients with thyroid cancer will be submitted to better inform on long-term safety profile of lenvatinib with the starting dose of 24 mg (see RMP).

In the context of relatively long-term treatment of patients, the lack of quality of life data is of particular concern. Quality of life data were not collected in the randomized part of the study but will be assessed in 30 patients from the open-label part of the study. Study of association between quality of life and safety profile will be informative and provide an insight from patient perspective. Studying of adherence at long treatment for an oral anti-cancer drug is of particular importance for long-term outcomes and disease control. These initial data in relatively small number of patients will be supportive and allow an optimized assessment in planned clinical trials. The MAH is also recommended to provide quality of life data from the Real World Observational QoL Study in 30 patients. QoL data will also be collected as part of study 211 in approximately 210 subjects.

Safety profile

Hypertension and proteinuria were the most common dose-limiting toxicities observed with lenvatinib in clinical studies. Hypertension was also associated with the rare occurrence of posterior reversible encephalopathy syndrome (PRES).

Hypertension and proteinuria tend to occur early during lenvatinib treatment (see section 4.8 Description of selected adverse reactions).

It was recognized that the early detection and effective management of hypertension are important to minimise the need for lenvatinib dose interruptions and reductions, which could potentially impact the efficacy of lenvatinib. Blood pressure should be well controlled prior to treatment with lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib. Antihypertensive agents should be started as soon as elevated BP is confirmed. Blood pressure should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter. The choice of antihypertensive treatment should be individualized to the patient's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when elevated BP is observed. For those patients already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. For patients with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred.

Safety results for Study 303 suggest that the precautions taken, as well as appropriate dose modifications, were reasonably successful in managing hypertensive events when they occurred. When necesary, hypertension should be managed as recommended below.

Table 57: Recommended management of hypertension

Blood Pressure (BP) level	Recommended action
Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose (see SmPC section 4.2)

Blood Pressure (BP) level	Recommended action
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

The development of proteinuria can also be managed by the dose/toxicity management plan. The close monitoring of proteinuria, in combination with the dose/toxicity management plan, resulted in a treatment discontinuation rate of only 1.3% in the All DTC Safety Set. Therefore, urine protein should be monitored regularly. If urine dipstick proteinuria ≥ 2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary. Lenvima should be discontinued in the event of nephrotic syndrome (see SmPC section 4.4).

Proteinuria typically occurred early in treatment while other renal events occurred at varying times. Moreover, proteinuria was reported at a substantially higher rate than other renal events. If some association does exist between proteinuria and renal events, proteinuria does not appear to be an indicator for the occurrence of acute kidney injury.

Other common AEs, occurring in 30% or more of subjects in the lenvatinib arm of Study 303, were diarrhoea, decreased appetite, weight decreased, fatigue, nausea, stomatitis, vomiting, dysphonia, headache, and palmar-plantar erythrodysaesthesia syndrome (PPE). The majority of Grade 3 to 4 adverse reactions occurred during the first 6 months of treatment except for diarrhoea, which occurred throughout treatment, and weight loss, which tended to be cumulative over time.

These major effects of lenvatinib appear to be consistent with its pharmacologic activity based on published reports of other VEGF/VEGFR-targeted therapies *(Chen and Cleck, 2009)*. These data were consistent with the events reported in the Phase 2 studies, and all were reported more frequently with lenvatinib than with placebo. The large majority of such AEs were reversible upon treatment modification or discontinuation. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of lenvatinib until resolution or improvement of the reaction, after which treatment should be resumed at a reduced dose as suggested in section 4.2 of the SmPC. Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormality judged to be non-life-threatening, in which case they should be managed as severe reaction (e.g., Grade 3).

Adverse reactions that most commonly led to dose reductions (in ≥ 5% of patients) were hypertension, proteinuria, diarrhoea, fatigue, PPE, weight decreased, and decreased appetite. Adverse reactions that most commonly led to discontinuation of lenvatinib were proteinuria, asthenia, hypertension, cerebrovascular accident, diarrhoea, and pulmonary embolism (see SmPC section 4.8).

Optimal medical management for nausea, vomiting, and diarrhoea should be initiated prior to any interruption or dose reduction of lenvatinib.

Across all safety sets, the most frequently reported non-fatal SAEs were pneumonia, dehydration, hypertension, hypotension, and pulmonary embolism.

Based on the available safety data, the most important serious adverse reactions are renal failure and impairment, cardiac failure, intracranial tumor haemorrhage, PRES / RPLS, hepatic failure, and arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction (see SmPC section 4.8).

The majority of renal events were mild to moderate, with Grade 3-4 events occurring at a very low rate, most renal events were reversible and resolved with hydration and did not lead to premature discontinuation. The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary (see SmPC sections 4.2 and 4.4). If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib. Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see SmPC sections 4.2 and 4.4).

Posterior reversible encephalopathy syndrome (PRES, also known as RPLS), has been reported in patients treated with lenvatinib (<1%; see section 4.8). PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure (see SmPC section 4.4 Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see sections 4.2 and 4.4).

Most hepatic events were related to liver enzyme elevations or hypoalbuminemia, and were Grade 1 or 2. Grade 3-4 hepatic events occurred in 5% or fewer of lenvatinib-treated DTC subjects. No true Hy's Law's case was found. Hepatic events were controlled with dose modification and 1 DTC subject discontinued lenvatinib. There was 1 death among DTC patients. Overall, liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (<1%) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2). If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Although the risk of bleeding has been linked with VEGF/VEGFR-targeted therapies, the incidence of mucocutaneous bleeding was similar in the two arms of study 303 and 1.3% of subjects discontinued on this ground. Serious cases of haemorrhage have been reported in patients treated with lenvatinib (see SmPC section 4.8). Cases of fatal intracranial haemorrhage have been reported in some patients with brain metastases. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be necessary (see SmPC sections 4.2 and 4.4).

Arterial thromboembolism events reported included cerebrovascular accident, transient ischaemic attack, and myocardial infarction (see section 4.8). Lenvatinib has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. Lenvima should be discontinued following an arterial thrombotic event (see SmPC section 4.4).

It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives (see SmPC 4.4).

With regards to gastrointestinal perforation or fistulae, in most cases, these events occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary (see SmPC section 4.2).

Although a thorough QT study (Study 002) concluded that lenvatinib did not have a significant effect on the QT interval, in DTC patients, there appears to be a numerically higher incidence of QTc-prolongation events with lenvatinib. There were no reports of ventricular tachycardia or torsades de pointes. Based on the available data it is considered that electrocardiograms should be monitored in all patients with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics (see SmPC section 4.4). In addition, the association of hypokalemia with QTc prolongation has been shown. Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation, therefore electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment (see SmPC section 4.4). Considering that electrolyte imbalances will be duly monitored (and corrected) before and after the treatment, it is accepted that the use of thiazide diuretics do not need to be restricted in patients treated with lenvatinib.

As serious hypocalcaemia may induce musculoskeletal issues, but also major cardiac issues, it has been included in the RMP as an important identified risk.

Post-treatment changes in serum thyroid stimulating hormone (TSH) levels are of interest in patients already at risk of biochemical hypothyroidism. Considering that lenvatinib impairs exogenous thyroid suppression (see SmPC section 4.8), thyroid Stimulating Hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target (see SmPC section 4.4).

Considering that no ILD-like events have been reported in the placebo group and that the ILD-like events reported with lenvatinib included one grade 3 event, ILD-like events was included as an important potential risk in the RMP.

One class effect (Wound healing) was reported with low frequency (7 out of 452 patients) and low severity grade (grade 1 or 2; 1 event was grade 3). However, since patients with major surgery within 3 to 4 weeks prior to study entry were excluded from clinical trials, the risk of impaired wound healing in clinical trials may not be representative of the risk in clinical practice. Impaired wound healing is included as an important potential risk in the RMP.

Overall, the methodology used to characterize an AE as related to lenvatinib, and included it in section 4.8 of the SmPC was clarified and is considered acceptable. It should be noted that the lenvatinib arm of the pivotal study had a median duration of exposure about 4 times that of the placebo arm and that this was taken into account for the assessment of causality of adverse reactions. Time-adjusted event rates were compared between lenvatinib arm and placebo arm. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Special population

A relatively short duration of exposure in some patient subpopulations is of concern and has been addressed in the RMP.

Patients of age $\geq$ 75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or renal impairment), or body weight below 60 kg appear to have reduced tolerability to lenvatinib. All patients other than those with severe hepatic or renal impairment should initiate treatment at the recommended 24 mg dose, following which the dose should be further adjusted on the basis of individual tolerability.

Dose adjustements are recommended for patients with severe renal impairment and patients with severe (Child-Pugh C) hepatic impairment (see Clinical pharmacokinetics). Further dose adjustments may be necessary on the basis of individual tolerability. This approach will be studied in the future in the elderly aged more than 75 years old as reflected in the RMP.

AEs in Japanese subjects were well managed with the use of concomitant medications and the planned dose modification schema, and premature discontinuations due to AEs were low. Numbers of non-Japanese Asian patients in the pivotal study were small. The Study 208 is still ongoing and relatively short follow-up did not allow adequate assessment of long-term safety profile in this patients. Therefore, final results of the study 208 will be submitted when available (see RMP). Pharmacokinetic data showed that patients weighing less than 60 kg had a 36% higher exposure than subjects weighing 60 kg or more, but that this had no effect on efficacy. However, this cannot be extrapolated to safety and further collection of data in subjects with lower body weight in study 211 could inform whether a lower starting dose is more appropriate (see RMP).

Overall, the results for the subgroup analyses did not indicate any new safety concern for any of the tested populations of subjects. Although higher rates of some TEAEs were observed for subjects who had certain baseline risk factors than for those without the comorbidities, the specific events observed were not unexpected in the disease population. Subjects should be monitored and AEs should be managed on an individual basis, following the algorithm for management of toxicity using early detection, the use of concomitant medication for TEAEs, and dose interruptions or dose reductions, if needed. Since limited data are available for patients of ethnic origin other than Caucasian or Asian, and in patients aged $\geq$ 75 years, lenvatinib should be used with caution in such patients, given the reduced tolerability of lenvatinib in Asian and elderly patients (see SmPC section 4.4 and RMP).

Clinical data are not yet available in the paediatric population (see SmPC sections 4.2 and 4.4).

It is not known whether lenvatinib is excreted in human milk. A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding (see SmPC sections 4.3 and RMP).

There are no data on the use of lenvatinib in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits (see section non-clinical aspects and SmPC sections 4.6 and 5.3). Lenvatinib should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus. Abnormal pregnancy outcome is covered in the RMP.

There are no data on the use of lenvatinib immediately following sorafenib or other anticancer treatments and there may be a potential risk for additive toxicities unless there is an adequate washout period between treatments. The minimal washout period in clinical trials was of 4 weeks (see SmPC section 4.4).

Hypersensitivity to the active substance or to any of the excipients is a contraindication (see SmPC section 4.3).

Lenvatinib has a minor influence on the ability to drive and use machines, due to undesirable effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of lenvatinib was consistent across studies in patients with thyroid cancer and is in line with safety profile of other multiple kinase inhibitors targeting VEGFRs and other receptor tyrosine kinases. The toxicity was considered acceptable and manageable with the starting dose of daily

24 mg and prospectively studied algorithm of dose reductions/interruptions and discontinuation of the drug depending on grade of observed toxicity. This supported long duration of exposure to lenvatinib, in comparison to placebo.

Dose reductions/interruptions were needed in the majority of patients and about one fifth of patients discontinued treatment due to toxicity across the studies. Therefore, there is a need to further study an optimal starting dose for the overall target population. Data on safety and activity of lower starting doses will be provided through a randomised dose-finding trial E7080-G000-211 (see RMP). Overall safety profile and tolerability of the three starting doses will be studied in trial and concomitant collection of quality of life data will further inform on an optimal starting dose in intended population of patients with progressive RR-DTC.

The adverse event profile of the drug has been fairly well documented. Further analyses of long-term safety profile of lenvatinib from currently ongoing studies 201 and 303 will make part of pharmacovigilance activities. Considering the pattern of toxicity in Japanese patients, its evaluation based on the final results of the ongoing study 208 will be provided (see RMP). Further collection of data in other subgroups of patients (such as patients aged ≥ 75 years or patients with lower body weight) will be ensured by the planned study 211.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 6.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Hypertension Proteinuria Renal failure or impairment Hypokalaemia Cardiac failure Posterior reversible encephalopathy syndrome (PRES) Hepatotoxicity Hemorrhagic events Arterial thromboembolic events (ATEs) QTc prolongation

Summary of safety concerns	
	Hypocalcemia
Important potential risks	Gastrointestinal perforation and fistula formation Venous thromboembolic events (VTEs) Abnormal pregnancy outcome, excretion of lenvatinib in milk Male and female fertility Pancreatitis Bone and teeth abnormalities in the pediatric population Impaired wound healing Interstitial Lung Disease (ILD)-like conditions Potential of lenvatinib for induction/inhibition of CYP-3A4 mediated drug metabolism
Missing information	Use in the pediatric population Use in severe hepatic impairment Use in severe renal impairment Use in patients from ethnic origins other than Caucasian or Asian Use in patients aged ≥ 75 years

Pharmacovigilance plan

Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Study 201 (Interventional Clinical Study: Category 3)	To evaluate the long-term safety of lenvatinib in Medullary and Iodine-131 Refractory, Unresectable DTC, Stratified by Histology	Hypertension Proteinuria Renal failure or impairment Cardiac failure Hepatotoxicity Hemorrhagic events Arterial thrombotic events QTc prolongation Hypocalcemia Gastrointestinal perforation and fistula formation Venous thrombolic events Pancreatitis Impaired wound healing	Completed*	Feb 2014 Future safety updates from patients still being followed (for survival) will be reported in future PSURs

		ILD-like conditions		
Study 207 (Interventional Clinical Study: Category 3)	To evaluate PK, PD, tolerability, and safety of lenvatinib in children from 2 to less than 18 years of age with a relapsed or refractory solid malignant tumor (including RAI-refractory DTC) and in patients with osteosarcoma, an extension phase to evaluate lenvatinib in combination with two chemotherapy agents.	Use in pediatric population aged 2 to <18 years	Start date: 29 Dec 2014, first dose of lenvatinib 15 Jan 2015 2 subjects enrolled in cohort 1	30 Jun 2018
Study 208 (Interventional Clinical Study: Category 3)	To determine the long-term safety profile of lenvatinib in Japanese patients with advanced thyroid cancer.	Hypertension Proteinuria Renal failure or impairment Cardiac failure Hepatotoxicity Hemorrhagic events Arterial thrombotic events QTc prolongation Hypocalcemia Gastrointestinal perforation and fistula formation Venous thrombolic events Pancreatitis Impaired wound healing ILD-like conditions	Completed*	Final CSR: 2016
Study 303 (Interventional Clinical Study: Category 3)	To evaluate long-term safety of lenvatinib in patients with RR-DTC in a	Hypertension Proteinuria Renal failure or impairment	Completed*	Ongoing Future safety updates from patients still being

	randomized, double-blind, placebo-controlled Phase 3 study.	Cardiac failure Hepatotoxicity Hemorrhagic events Arterial thrombotic events QTc prolongation Hypocalcemia Gastrointestinal perforation and fistula formation Venous thrombolic events Pancreatitis Impaired wound healing ILD-like conditions		followed (for survival) will be reported in future PSURs
Study 211 (Interventional Clinical Study: Category 3)	Primary objective: To determine whether a starting dose of lenvatinib 20 mg or 14 mg QD will provide comparable efficacy (based on Objective Response Rate at 6 months [ORR6M]) with an improved safety profile to 24 mg QD (based on TEAE Grade 3 or higher in the first 6 months after randomization) Secondary objectives: To evaluate PFS in subjects treated with doses of 24 mg, 20 mg, and 14 mg lenvatinib QD; to evaluate safety and tolerability of doses of 24 mg, 20 mg, and 14 mg QD of lenvatinib; to evaluate PK/PD	Hypertension Proteinuria Renal failure or impairment Cardiac failure Hepatotoxicity Hemorrhagic events Arterial thrombotic events QTc prolongation Hypocalcemia Gastrointestinal perforation and fistula formation Venous thrombolic events Pancreatitis Impaired wound healing ILD-like conditions	Planned	31 Aug 2020

	relationship between exposure and efficacy/safety			
Study number TBC (Interventional Clinical Study: Category 3)	A drug-drug interaction (DDI) study to investigate the potential of lenvatinib for CYP3A4 inhibition/induction	To investigate correctly the potential of lenvatinib for CYP3A4 inhibition/induction, an in vivo study with midazolam as a probe substrate for CYP3A4.	Planned	Mar 2018

* Completed for primary efficacy analysis and CSR submitted.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Hypertension	Section 4.2 of the SmPC states that for patients with baseline hypertension, BP should be well controlled prior to treatment and regularly monitored. Section 4.4 requires that BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter. If a patient develops SBP ≥140 mmHg or DBP ≥90 mmHg, active management is indicated. Advice on action to take in the event of hypertension above these levels is also provided. Hypertension is discussed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Proteinuria	Section 4.4 of the SmPC warns that proteinuria usually occurs early in the course of treatment, and that urine protein should be monitored regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary. Proteinuria is discussed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Renal failure or impairment	Section 4.2 of the SmPC alerts the reader that GI toxicity should be actively managed and refers the reader to the warning in Section 4.4. Section 4.4 warns that the primary risk factor for renal failure or impairment is dehydration and/or hypovolemia due to GI toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary. Renal failure is listed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hypokalaemia	Hypokalaemia is listed in Section 4.8 of the SmPC as a very common (≥1/10) adverse reaction	None planned
Cardiac failure	Section 4.4 of the SmPC warns that patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary. Cardiac failure is listed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Posterior reversible encephalopathy syndrome (PRES)	Section 4.4 of the SmPC warns that BP is a risk factor for PRES and should be controlled. In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary. PRES is listed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hepatotoxicity	Section 4.4 of the SmPC warns that hepatic failure events were generally reported in subjects with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary. Hepatotoxicity is discussed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hemorrhagic events	Section 4.4 of the SmPC warns that fatal intracranial hemorrhagic events have been reported in some patients with brain metastases. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be necessary. Hemorrhage is discussed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Arterial thromboembolic events (ATEs)	Section 4.4 of the SmPC warns that ATEs (cerebrovascular accident, transient ischemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib. Lenvatinib has not been studied in patients who have had an ATE within the previous 6 months, therefore use with caution in such patients. ATEs are listed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
QTc prolongation	Section 4.4 warns that QT/QTc interval prolongation has been reported at a higher rate in patients treated with lenvatinib. Electrocardiograms should be monitored in patients with congenital long QT syndrome, congestive heart failure, or bradyarrhythmias, as well as those receiving medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Electrolyte abnormalities should be monitored and corrected in all patients. QT interval prolongation is discussed in Section 4.8.	None planned
Hypocalcemia	Section 4.4 of the SmPC warns that electrolyte disturbances such as hypocalcaemia increase the risk of QT prolongation, therefore electrolyte abnormalities should be monitored and corrected in all patients. Secton 4.8 of the SmPC characterizes the adverse reactions reported in the placebo-controlled trial and refers back to section 4.4.	None planned.
Gastrointestinal perforation and fistula formation	Section 4.4 of the SmPC warns that, in in most cases, gastrointestinal perforation and fistulae occurred in subjects with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary. Anal fistula is listed in Section 4.8. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned.
Venous thromboembolic events (VTEs)	Pulmonary embolism is listed in Section 4.8.	None planned.

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Abnormal pregnancy outcome, excretion in breast milk	Section 4.6 of the SmPC warns that women of child-bearing potential should avoid becoming pregnant and use effective contraception during treatment with lenvatinib and for at least one month after finishing treatment. Lenvatinib should not be administered to pregnant women, unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus. It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk. A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breastfeeding. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Male and female fertility	No risk minimization measures are considered necessary based on the available nonclinical evidence. Section 4.6 of the SmPC warns that effect on human fertility is unknown. Detail regarding the testicular and ovarian toxicity observed in rats, dogs, and monkeys, which was reversible at the end of a 4-week recover period is provided in section 5.3. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Pancreatitis	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Bone and teeth abnormalities in the pediatric population	Section 4.2 of the SmPC warns that lenvatinib must not be used in children younger than 2 years of age because of safety concerns and that the safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established. Section 5.3 provides information on lesions attributable to pharmacologic effects (incisors, femur [epiphyseal growth plate]) observed in juvenile rat studies. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Impaired Wound Healing	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data.	None planned

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Interstitial Lung Disease (ILD)-like conditions	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine.	None planned
Potential of lenvatinib for induction/ inhibition of CYP-3A4 Mediated Drug Metabolism	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine.	None planned
Use in the pediatric population	Section 4.2 of the SmPC warns that lenvatinib must not be used in children younger than 2 years of age because of safety concerns and that the safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in severe hepatic impairment	Section 4.2 of the SmPC advises that the recommended starting dose is 14 mg taken once daily, and that further dose adjustments may be necessary. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in severe renal impairment	Section 4.2 of the SmPC advises that the recommended starting dose is 14 mg taken once daily, and that further dose adjustments may be necessary. Patients with end stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in patients from ethnic origins other than Caucasian or Asian	Section 4.2 of the SmPC warns that limited data are available on use in patients from ethnic origins other than Caucasian or Asian. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in patients aged ≥75 years	Section 4.2 of the SmPC warns that limited data are available on use in patients aged ≥75 years. Section 4.8 notes that patients of age ≥75 years were more likely to experience Grade 3 to 4 hypertension, proteinuria, decreased appetite, and dehydration. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request of translation exemption of the labelling of the outer carton as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons:

The justification was not considered strong enough and, on the other hand, the product was meant to be handled directly by patients. Multilingual packs could be an option provided readability is not compromised.

A request of translation exemption of the labelling of the blister as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group was in agreement to have an English only blister that includes the pharmaceutical form.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

3. Benefit-Risk Balance

Benefit

The pivotal Phase 3 Study 303 showed a significant improvement of 14.7 months (HR 0.21 (99% CI: 0.14, 0.31), p<0.0001) in progression free survival in RR-DTC patients treated with lenvatinib compared to those patients treated with placebo.

The PFS results were shown to be robust, using multiple sensitivity and based on the secondary efficacy analyses, all of which were highly significant (P<0.0001) in favour of lenvatinib.

An effect on PFS of this magnitude is considered to be clinically relevant and should be associated with a delay in onset or worsening of symptoms.

The PFS results were supported by a high response rate (64.8% ORR with lenvatinib compared to 1.5% with placebo). 4 subjects attained a complete response. Responses were durable and the median duration of response was not reached, but the lower bound of the confidence interval exceeded 16 months and 75% of the responses lasted longer than 9 months.

Tumour shrinkage was initially rapid and continued throughout the treatment period. The observed nadir in tumour size continued to decrease over time and additional partial responses were detected even after

6 months of lenvatinib treatment. In particular, for the subset of subjects treated for at least 1 year, continued tumour shrinkage was observed throughout the treatment period.

Response and PFS data from Phase 2 Study 201 were consistent with, and fully support, the results of the Phase 3 study.

Lenvatinib showed efficacy in all subgroups tested, including subjects who had received prior VEGF/VEGFR-targeted therapy. The majority of these subjects had received prior sorafenib, suggesting that lenvatinib can induce responses in subjects who have failed sorafenib treatment.

Uncertainty in the knowledge about the beneficial effects

The results from the Study 303 are based mainly on, and provide support for, the starting dose of 24 mg QD for RR-DTC. However, in the DTC Randomized Safety Set of Study 303, 83.1% and 68.2% of lenvatinib-treated subjects had dose interruptions or reductions, respectively. Results for 30 subjects in the optional open labelled phase of the Study 303, that received lenvatinib at a starting dose of 20 mg, showed efficacy results similar to that obtained with a starting dose of 24 mg, though there are possible confounding factors which may affect the results favourably in the subjects who received the lower starting dose. Considering the small number of patients, and possible confounding factors, firm conclusions could not be reached. Data on lower doses (20 mg and 14 mg) will be provided from study 211 in order to optimise the benefit/ risk profile of the product.

Another uncertainty is whether lenvatinib significantly improves overall survival. Median OS for lenvatinib in Study 303 was not reached as of the cutoff date for the primary analysis of PFS. Furthermore, the OS analysis in Study 303 is confounded by the crossover design and the use of subsequent anticancer therapy post study. As of the most recent cutoff date of 15 June 2014, with a median follow-up period of 23.6 months in the lenvatinib arm the median OS was still not reached while in the placebo arm with a median follow-up time of 24.1 months, the median OS was 19.1 months (95% CI: 14.3, NE). The analysis of OS, although not statistically significant, showed a numerical superiority for lenvatinib with an HR of 0.80 (95% CI: 0.57, 1.12; P=0.1993). Analyses of OS to correct for cross-over did not reveal any concerns in terms of a possible detriment in terms of OS.

Quality of life data from Study 303 (30 subjects in the Study 303 OOL treatment phase) may provide further understanding about the benefits (and risks) of lenvatinib (see RMP). In addition, PROs and symptomology in relation to adherence, safety and efficacy outcomes in patients that will receive different starting doses in the planned Study 211 will contribute to benefit/risk assessment of different starting doses (see RMP).

Risks

Unfavourable effects

The safety of single-agent lenvatinib has been examined in 1108 cancer patients including 452 subjects with RR-DTC in Phase 2 and 3 studies (423 of whom received the recommended dose of 24 mg) and 656 subjects with other cancer types, including MTC and ATC. Almost all subjects had at least 1 TEAE.

The most common AEs are hypertension (69%), diarrhoea (67%), decreased appetite (54%), weight decrease (51%) among which hypertension, proteinuria, liver events and hypocalcaemia were the most frequent grade 3 and grade 4 clinically significant adverse effects, and haemorrhages, arterial

thromboembolisms (including myocardial infarction), liver and renal events were possible causes of deaths.

Hypertension and proteinuria were the most common dose-limiting toxicities observed with lenvatinib in clinical studies.

Risks of hypertension, proteinuria and thromboembolic events commonly associated with VEGFi treatment were higher in lenvatinib-treated patients. About 2/3 of the patients had a worsening of their blood pressure, 56% reached grade 3 or 4 and about 3.4% discontinued. Hypertension has also likely an influence on other AEs such as hemorrhages, proteinuria, pulmonary embolism, together linked to the discontinuation of about 4% of the patients and at least 1/10th of the fatal events. Hypertension was also associated with the rare occurrence of posterior reversible encephalopathy syndrome (PRES).

Based on the expected adverse effects, early detection and effective management of hypertension are important to minimize the need for dose interruptions and reductions. Effective management includes use of antihypertensive treatment individualized to the subject's clinical circumstances and following standard medical practice. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred. Safety results for Study 303 show that these precautions, as well as appropriate dose modifications, were successful in managing hypertensive events when they occurred.

The development of proteinuria can also be managed by the dose/toxicity management plan as reflected in the SmPC. In the Phase 3 clinical study, the risk of developing proteinuria was routinely monitored via dipstick testing. The close monitoring of proteinuria, in combination with the dose/toxicity management plan, resulted in a treatment discontinuation rate of only 1.3% in the All DTC Safety Set.

Other common AEs, occurring in 30% or more of subjects in the lenvatinib arm of Study 303, were weight decrease, GI symptoms, fatigue, headache, PPE, and dysphonia. The large majority of such AEs were reversible upon treatment modification or discontinuation. Across all safety sets, the most frequently reported nonfatal serious adverse events were pneumonia, dehydration, hypertension, hypotension, and pulmonary embolism.

The GI track is the most frequently affected. Diarrhoea has a similar incidence than hypertension and even exceeds it when the duration of the AEs is taken into account. Nausea, stomatitis, vomiting, all are concerns for more than 1/3 of the patients and constipation for more than ¼. All together about 20% of the patients suffered from AEs grade 3 or 4.

Hypocalcaemia was observed during clinical development at a higher rate with lenvatinib than with placebo and 23 cases of grade 3/4 hypocalcaemia have been reported with lenvatinib vs 2 with placebo. Electrolyte abnormalities should be monitored as reflected in the SmPC.

Overall, adverse events were well managed using the dose reduction and interruption schemes used in the studies.

Uncertainty in the knowledge about the unfavourable effects

The chosen dose of 24 mg is associated with frequent and important levels of dose reductions and interruptions. Lower starting doses, at least in some patients, might result in similar efficacy and provide more favourable safety profile. However, currently available data are inadequate to support recommendations for a starting dose lower than 24 mg QD. In view of important toxicities of lenvatinib and frequently asymptomatic course of disease in patients, a choice of an adequate dose with the aim of optimizing benefit/risk balance is of importance, in particular considering the relatively long survival of

patients with DTC. Study 211 will provide relevant data to compare the 24 mg starting dose with lower starting doses.

Safety profiles in patients aged ≥ 75 years old, patients from ethnic origins other than Caucasian or Asian are poorly characterised. Therefore these populations are covered in the Risk Management Plan.

The higher incidence of adverse events in Japanese subjects and subjects less than 60 kg body weight is noted, with earlier dose reduction. The Applicant will evaluate the suitability of a lower starting dose in all patients with particular attention to these populations in study 211 (see RMP).

There are no data on the use of lenvatinib in paediatric population. Lenvatinib must not be used in children younger than 2 years of age because of safety concerns identified in animal studies. Lenvatinib has been shown to be teratogenic and embryotoxic in rats and rabbits at doses below the recommended human dose (based on body surface area). Bone and teeth abnormalities in the paediatric population are adequately addressed in the Risk Management Plan.

There are no studies in pregnant women, and the effects of lenvatinib on human foetal development or in breastfeeding infants are unknown. Lenvatinib should not be used during pregnancy (see SmPC).

In addition, it is not known if lenvatinib is excreted in milk. A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding.

Balance

Importance of favourable and unfavourable effects

RR-DTC patients may be asymptomatic at the time of progression and symptoms generally appear in more advanced stages of the disease when tumour burden is important and prognosis is very poor. In this context, an important objective of treatment is to delay progression and delay symptomatic disease.

The clinical benefit of lenvatinib has been demonstrated in the pivotal, randomized, placebo-controlled, randomized Phase 3 trial, Study 303. The results of this study provide clear evidence of a clinically meaningful improvement in PFS in subjects with RR-DTC.

The magnitude of PFS improvement is of clear clinical relevance and is consistently associated with an ORR of about 50%. The median PFS gain of about 14.7 months is undoubtedly beneficial.

Another important objective of treatment is to prolong survival. Although no detriment in overall survival has been observed, differences in duration of overall survival between treatment groups are difficult to observe in the context of the pivotal trial because of the cross-over design. Exploratory analyses adjusting for cross-over showed a significant difference in overall survival between the treatment groups at the data cutoff for the primary efficacy analysis. However, such analyses are exploratory and the methods used rely on assumptions that cannot be easily verified. Thus, whether lenvatinib is associated with a significant effect on overall survival remains to be established.

Hypertension and proteinuria were the most clinically relevant dose-limiting toxicities observed with lenvatinib in clinical studies. About 2/3 of the patients had a worsening of their blood pressure, 56% reached grade 3 or 4 and about 3.4% discontinued. Hypertension has also likely an incidence on other AEs such as hemorrhages, proteinuria, pulmonary embolism, together linked to the discontinuation of about 4% of the patients and at least 1/10th of the fatal events). Hypertension was also associated with the rare occurrence of posterior reversible encephalopathy syndrome (PRES). Liver and renal events were possible causes of deaths.

Despite the high incidence of TEAEs and SAEs observed, safety analyses showed that lenvatinib had predominantly a predictable and manageable safety profile. Although lenvatinib 24 mg QD was associated with significant toxicity, in general, the toxicities were expected, consistent with those associated with VEGF/VEGFR-targeted agents, and could be managed with the planned dose/toxicity management plan.

Effect	Short Description	Unit	Placebo	Lenvatinib	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression or death	Months	3.6 (2.2, 3.7)	18.3 (15.1, NE)	Consistent and significant effect on PFS with a HR of 0.21 (0.14, 0.31)	See 'clinical efficacy' section
OS	Median time from randomization to death of any cause	Months	NE (14.3, NE)	NE (22.0, NE)	The OS data are confounded by crossover with a HR of 0.80 (0.57, 1.12)	
Unfavourable Effects						
Hypertension	Incidence of grade 3 or 4 events	%	3.8	42.9	The association with these risks is further supported by the analysis in the extended safety population The chosen dose of 24 mg is associated with important levels of dose reductions and interruptions	Numbers presented were taken from the DTC Randomized Safety Set (see 'clinical safety' section)
Proteinuria	Incidence of grade 3 or 4 events	%	0	10.7		
Liver events	Incidence of grade3 or 4 events	%	1	10.7		
Hypocalcaemia	Incidence of grade 3 and 4 events	%	0	4.9		
Diarrhoea	Incidence of grade 3 and 4 events	%	0	9.2		
Fatal AE	Incidence of treatment-related fatal AE	%	0	2.3	Uncertainties linked to low numbers	

Abbreviations: AE: adverse event; HR: hazard ratio; NE: not estimable; OS: overall survival; PFS: progression-free survival
data cut-off dates : efficacy - PFS: 15 November 2013, OS:15 June 2014 ;safety: 25 March 2014.

Benefit-risk balance

The benefit-risk balance of lenvatinib in the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) is considered positive.

Discussion on the benefit-risk assessment

The pivotal Study 303 met its primary endpoint and demonstrated a robust and statistically significant improvement in median PFS associated to treatment with lenvatinib comparing to placebo. The observed

PFS gain of 14.7 months is of clinical relevance in patients with progressive locally advanced and metastatic disease. There is a positive initial signal in terms of OS improvement but more mature data is needed.

Overall, available evidence-based data are associated with a dose of 24 mg used in the pivotal Phase 3 study and data on lower starting doses are limited precluding current recommendation to an alternative dose or schedule. Nevertheless lower doses will be evaluated post-marketing in Study E7080-G000-211. Study E7080-G000-211 is conducted with primary objective to determine whether a starting dose of lenvatinib 20 mg or 14 mg QD will provide comparable efficacy (based on ORR at 6 months) with an improved safety profile to 24 mg QD (based on TEAE Grade 3 or higher in the first 6 months after randomization). The results of exposure-biomarkers-clinical endpoint relationship analyses will be informative for efficacy and safety of different dose levels.

Based on indirect comparison, lenvatinib is associated with a similar overall safety profile to sorafenib, although lenvatinib seems to be associated with higher rates of hypertension, proteinuria and GI events such as nausea and vomiting while sorafenib is associated with higher rates of PPE, rash, alopecia, and blood TSH increased. Despite the higher proportion of lenvatinib-treated subjects having SAEs, the dose reduction and the discontinuation rates due to AEs in the active treatment arms (lenvatinib and sorafenib) were similar, indicating that the majority of TEAEs experienced with lenvatinib can be adequately managed to avoid premature discontinuations. With regard to efficacy, in Study 303 and DECISION, the active treatments (lenvatinib and sorafenib respectively) highly significantly improved PFS ($p<0.0001$) compared with placebo. The difference in median PFS between the active treatment and placebo arms was 14.7 months with lenvatinib in Study 303 and 5.0 months with sorafenib in the DECISION study. The differences in populations might have contributed to the differences observed between the placebo arms of the two studies (median PFS of 3.6 months with placebo in the study 303 vs median PFS of 5.8 months with placebo in the DECISION study).

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Lenvima is not similar to Nexavar within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lenvima in the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that lenvatinib mesilate is qualified as a new active substance.