Assessment report

Kisplyx

International non-proprietary name: lenvatinib

Procedure No. EMEA/H/C/004224/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

Table of contents

List of abbreviations

AE adverse event

ALT alanine aminotransferase

AST aspartate aminotransferase

ATC anaplastic thyroid cancer

AUC area under the concentration-time curve

AUC0-24 area under the concentration-time curve from time zero to 24 hours

BID *bis in die*, twice daily

BOR best overall response

CHMP Committee for Medicinal Products for Human Use

CI confidence interval

Cmax maximum observed plasma concentration

CNS central nervous system

CPMP Committee for Proprietary Medicinal Products

CR complete response

CRF case report form

CSE clinically significant event

CSR Clinical Study Report

CTCAE Common Terminology Criteria for Adverse Events

CVA cerebrovascular accident

dc discontinuation

decr decreased

DTC differentiated thyroid cancer

ECOG PS Eastern Cooperative Oncology Group Performance Status

EMA European Medicines Agency

EF ejection fraction

ESMO European Society for Medical Oncology

EU European Union

EVER Everolimus

FAMHP Federal Agency for Medicines and Health Products

FDA Food and Drug Administration

FGF fibroblast growth factor

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)

genl phys general physical

GI gastrointestinal

Hgb hemoglobin

HR hazard ratio

HUVEC human umbilical vein endothelial cell

IBD International Birth Date

IC50 half maximal inhibitory concentration

ICH International Conference on Harmonisation

ICR Independent Central Review

IFN-α interferon-α

IIR independent imaging review

IL-2 interleukin-2

ILD interstitial lung disease

incr increased

IPCW inverse probability of censoring weighted (analysis)

ISS Integrated Summary of Safety

ITT intent-to-treat

KDR kinase insert domain receptor (VEGFR2)

KIT a stem cell factor receptor

LENV lenvatinib

MAA marketing authorisation application

MAPK mitogen activated kinase

MedDRA Medical Dictionary for Regulatory Activities

MHRA Medicines and Healthcare Regulatory Agency

MTC medullary thyroid cancer

MI myocardial infarction

mRCC metastatic renal cell carcinoma

MSKCC Memorial Sloan-Kettering Cancer Center

MTD maximum tolerated dose

mTOR mammalian target of rapamycin

NAv not available

NCCN National Comprehensive Cancer Network

NE not estimable

OOL optional open-label (extension to lenvatinib treatment phase for subjects who received placebo in the double-blind Randomization Phase in Study 303)

ORR objective response rate

OS overall survival

PD progressive disease or disease progression

PDGF platelet-derived growth factor

PDGFR platelet-derived growth factor receptor

PFS progression-free survival

PK pharmacokinetic(s)

PopPK population pharmacokinetics

PPE palmar-plantar erythrodysesthesia (syndrome)

PR partial response

PRAC Pharmacovigilance Risk Assessment Committee

PRES posterior reversible encephalopathy syndrome

QD *quaque die*, once daily

RCC renal cell carcinoma

RECIST Response Evaluation Criteria in Solid Tumors

resp respiratory

RET "rearranged during transfection" protein receptor

RP2 recommended Phase 2 (dose)

RR radioiodine-refractory or rate ratio, depending on context

RTK receptor tyrosine kinase

SAE serious adverse event

SD stable disease or standard deviation, depending on context

SGQ sponsor-generated query

SmPC Summary of Product Characteristics

SMQ standard MedDRA query

SY subject-year

TC thyroid cancer

TEAE treatment-emergent adverse event

TKI tyrosine kinase inhibitor

TSH thyroid-stimulating hormone

US United States

VEGF vascular endothelial growth factor

VEGFR vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eisai Europe Ltd. submitted on 11 January 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Kisplyx, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 May 2015. The acceptability of an accelerated review was agreed upon by the EMA/CHMP on 19 November 2015.

The applicant applied for the following indication: Kisplyx is indicated in combination with everolimus for the treatment of adult patients with unresectable advanced or metastatic renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

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.

This application is submitted as a multiple of Lenvima authorised on 28 May 2015 in accordance with Article 82(1) of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

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

Scientific Advice

The applicant did not seek scientific advice at the CHMP for the pivotal study in this indication..

Licensing status

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

1.2. 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 11 January 2016.

- Accelerated Assessment procedure was agreed upon by CHMP on 19 November 2015

- The procedure started on 28 January 2016.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 April 2016. 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.

- During the meeting on 13 May 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.

- During the meeting on 26 May 2016, 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 30 May 2016.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 June 2016.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 08 July 2016.

- During the meeting on 21 July 2016, 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 Kisplyx.

- The CHMP adopted the similarity report on 21 July 2016.

2. Scientific discussion

2.1. Problem statement

Lenvatinib is an oral multiple kinase inhibitor. It was approved as an orphan medicine in the EU under the tradename of Lenvima in the treatment of adult patients with differentiated thyroid cancer (DTC) on 28 May 2015.

2.1.1. Disease or condition

Renal cell carcinomas are kidney tumours which represent approximately 90% of cases of kidney cancer in adults (Wahal and Mardi, 2014). These tumours arise from the cells of the proximal renal tubular epithelium.

The applicant applied for the following indication:

Kisplyx is indicated in combination with everolimus for the treatment of adultpatients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

According to the American Joint Committee on Cancer, both metastatic (M1 – distant metastasis present) and locally unresectable (T4 – tumor invades beyond Gerota's fascia; N - any; M0) RCC are classified as Stage IV (Edge, et al., 2010). The terms "unresectable advanced RCC" and "metastatic RCC" are used interchangeably, and since both represent Stage IV RCC, the treatment of adult patients with advanced RCC is stated in the approved indications for second-line agents.

2.1.2. Epidemiology, clinical presentation, diagnosis and stage/prognosis

Kidney cancer represents approximately 3% of all cancers worldwide (Cohen, et al., 2005, Garcia and Rini, 2007). The incidence of RCC has been rising steadily and the 5-year prevalence of RCC in the EU-28 (plus Iceland and Norway) in 2015 was estimated to be 229,465 cases (adapted from Globocan 2012). Despite substantial progress in the understanding and treatment of mRCC in recent years, its incidence is increasing, and the disease is still considered incurable. Smoking and obesity are established risk factors for RCC development. RCC also appears to be more common in patients with end-stage renal failure, acquired renal cystic disease and tuberous sclerosis. Approximately 2%–3% of RCC are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being Von Hippel Lindau (VHL) disease. In recent years, many new genes associated with RCC have been reported (such as PBRM1, SETD2, BAP1) (ESMO guidelines, 2014; NCCN guidelines 2016).

2.1.3. Biologic features and pathogenesis

Clear cell RCC is the most frequent pathological subtype of sporadic RCC in adults (70%–85%), with loss of 3p and the classical clear aspect of the cells due to glycogen and lipids in their cytoplasm. Other subtypes historically called non clear RCC include papillary RCC (7%–15%) shows distribution of malignant cells around capillary cores (papillae), chromophobe RCC (5%–10%) is made up of typical polygonal cells with a clear delimitation of the cytoplasmic membrane and reticular cytoplasm, renal medullary carcinoma, etc (Escudier et al, 2014). Due to a better understanding of the correlation between chromosomal alterations,

histological subtypes and molecular pathway abnormalities, new morphological variants of RCC are now recognised according to the Vancouver classification (Escudier et al, 2014). Each of the most frequent morphological genetic RCC subtypes correlates with a specific molecular pathway. Examples include the hypoxia-inducible pathway (clear-cell, papillary type II through the FH gene), the mTOR signalling pathway (clear-cell and papillary type II), the c Met-RAF-MEK-ERK pathway (papillary type I and translocation RCC).

Inactivation of the von Hippel–Lindau (VHL) tumour suppressor protein is a characteristic of clear cell tumours, resulting in the deregulation of the VEGF signalling pathway. VEGFRs are typical receptor tyrosine kinases with an extracellular domain for ligand binding, a transmembrane domain and a cytoplasmic domain, including a tyrosine kinase domain. Activation of VEGF signalling pathways promotes the growth of tumour blood cells. The major pro-angiogenic signal is generated from the ligand-activated VEGFR-2.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

More than 50% of RCCs are currently detected incidentally. However, some patients with RCC still present with clinical symptoms, such as flank pain, gross haematuria and palpable abdominal mass (the classical triad); metastatic symptoms like bone pain or lung nodules; or paraneoplastic syndromes, such as hypercalcaemia, unexplained fever, erythrocytosis or wasting syndromes (Escudier et al, 2014). About 30% of patients with RCC have metastatic disease at the time of diagnosis, and a significant proportion of patients with localized disease treated with curative nephrectomy relapse subsequently with metastatic disease. Metastatic RCC is associated with a high quality-of-life burden, based on physical, psychological, and social criteria, and drastically reduced survival; only about 8% to 22.5% of mRCC patients survive for five years or more as compared to 90% of patients with localized renal cancer. The extent of tumour burden and site of metastasis contribute to local symptoms. The most frequent locations of metastases are the lungs, mediastinum, bone, liver, and brain. Among solid cancer types, RCC has the second highest incidence of brain metastases.

Risks assessment models have been developed to provide prognostic information for patients and to inform on eligibility and risk stratification factors for clinical trials. The Memorial Sloan-Kettering Cancer Centre (MSKCC) stratifies patients by favourable, intermediate and poor risk according to 6 prognostic risk factors; Karnofsky performance status (KPS), haemoglobin level, corrected serum calcium, time from diagnosis to treatment, platelets and neutrophil levels. Subsequently established and validated in first-line and second-line setting International mRCC Database Consortium (IMDC) model includes 3 prognostic factors (haemoglobin level, corrected serum calcium and performance status) to stratify patients to risk groups.

2.1.5. Management

Management of local disease includes partial or radical nephrectomy. The role of neo-adjuvant or adjuvant therapy is not yet established. In the advanced disease setting systemic therapy is used. Until the development of agents that target tumour angiogenesis and other signaling pathways, systemic therapy with the cytokines interleukin 2 (IL-2) or interferon (IFN)-α was the main treatment for advanced RCC. However, the use of both agents has declined substantially since the introduction of molecular targeted therapies.

Current approved treatments for metastatic RCC in the first-line setting comprise targeted therapies, either tyrosine kinase inhibitors (TKI: sunitinib and pazopanib) or mammalian target of rapamycin (mTOR) inhibitors (temsirolimus) administered as single agents, bevacizumab + interferon (IFN), or high-dose interleukin-2 (IL-2) (ESMO guidelines, 2014; NCCN guidelines, 2016).

Approved second-line agents include TKIs: sorafenib, sunitinib, axitinib, and pazopanib; the mTOR inhibitor everolimus.

A novel immunotherapeutic agent, Opdivo (nivolumab), belonging to a class of immune checkpoint inhibitors (PD-1/PD-L1), has been recently granted approval by EC on 19/06/2015 for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy. The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Relapsed RCC is an aggressive tumor and the optimal sequencing of therapies, or combination of therapies which would lead to durable responses and minimize relapse remains a challenge. Current strategies have focused on the development of new therapeutic agents, optimal sequencing, and combinations of these agents to maximize their impact on clinical outcomes. To date, however, results of combination-therapy studies (ie, temsirolimus plus bevacizumab, temsirolimus plus sunitinib, erlotinib plus bevacizumab, everolimus plus bevacizumab) have shown no advantage in PFS over monotherapy with approved single agents and, in some cases, an unacceptably high degree of toxicity (Bukowski et al., 2007; Dorff, et al., 2014; Feldman, et al., 2009; Graves, et al., 2013; Hainsworth, et al., 2010; Kanesvaran, et al., 2015; Negrier, et al., 2011; Powles, et al., 2014; Ravaud, et al., 2013). Therefore, there remains a significant unmet medical need for more effective treatment options, including possible combination therapies, with a manageable safety profile in patients with advanced RCC.

Table 1 Approved indications of Second line therapies in advanced RCC:

INN	Date Authorized	Indication
Sorafenib	Jul 2006	Treatment of patients with advanced RCC who have failed prior interferon-alpha- or interleukin 2-based therapy or are considered unsuitable for such therapy
Everolimus	Aug 2009	Treatment of patients with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy
Pazopanib	Jun 2010	In adults for the first-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease
Axitinib	Sep 2012	Treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine
Nivolumab	Apr 2016	Treatment of advanced RCC after prior therapy in adults

About the product

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. The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

In the scope of this application, everolimus (Afinitor) is intended to be used in combination with lenvatinib.

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 applicant applied for the following indication:

"Lenvatinib is indicated in combination with everolimus for the treatment of patients with unresectable advanced or metastatic renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy".

The approved indication further to the CHMP review is:

"Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one vascular endothelial growth factor (VEGF)-targeted prior therapy".

The proposed recommended daily dose of lenvatinib is 18 mg (one 10 mg capsule and two 4 mg capsules) once daily in combination with 5 mg of everolimus once daily. The daily doses of lenvatinib and, if necessary, everolimus are to be modified as needed according to the dose/toxicity management plan.

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 there is clinical benefit or until unacceptable toxicity occurs.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

- The benefit-risk balance is expected to be positive.

- The applicant has provided comprehensive data.

- Unmet medical needs will be addressed, as there is a need to develop strategies that may increase the degree of the antitumor effects and impedes the onset of/ or eliminates refractory disease. Combinations of targeted agents may be one method to achieve these goals. Hence the proposed combination of lenvatinib and everolimus in the 2nd line setting could be seen as addressing an area of unmet medical need. The results of the Phase 2 part of the conducted pivotal Study E7080-G000-205 suggest that the proposed combination of lenvatinib with everolimus is a successful combination therapy in the treatment of metastatic renal cancer which could have an impact on medical practice. The presented data appear to support a therapeutic advantage for efficacy in favor of the proposed lenvatinib-everolimus combination over existing monotherapies.

- The intended drug combination is of major interest from the point of view of public health with regards to the number of patients that would benefit from improved treatment strategies for metastatic renal cancer.

2.2. Quality aspects

2.2.1. Introduction

The proposed product is identical from a quality point of view to the Lenvima (EU/1/15/1002) approved on 28 May 2015 via Centralised procedure. An updated Module 3 has been submitted to support this application, as this considered a stand-alone application due to different indications and another trade name.

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:
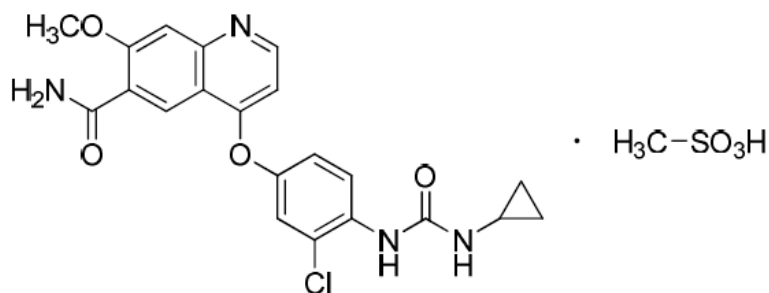
The active substance is a white, non-hygroscopic, crystalline powder, slightly soluble in water and practically insoluble in ethanol. The structure of lenvatinib mesilatewas elucidated by using elemental analysis, ultraviolet-visible (UV-Vis) spectroscopy, infrared spectroscopy, ^{1}H and ^{13}C nuclear 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 held 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. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. 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.

Lenvatinib mesilate is packed inside linear low-density polyethylene (LLDPE) film on the inside and a nylon film on the outside and secured with a cable.

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. Satisfactory information regarding the reference standards used for impurities testing has been presented.

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 °C ± 3 °C and for up to 6 months under accelerated conditions at 25 °C ± 2 °C /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 were observed.

Stress testing on the active substance in the solid state was performed under conditions of heat (60 °C), light exposure (ICH photostability conditions) and high humidity (30 °C/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 is a tyrosine kinase inhibitor which works as an anticancer drug. The aim was to develop and oral immediate release form which allows patients 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. During development, it was decided to have multiple strengths to enable dose reduction during treatment and to minimize occurrence of side effects and exposure to genotoxic process impurities.

The excipients for Kisplyx 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.

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 finished product is manufactured in two manufacturing sites.

The manufacturing process of the finished product 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.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Proven acceptable ranges have been defined for the following steps of the medicinal product: drying, encapsulation, weight sorting and blister packaging. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

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 3 commercial scale batches for each strength 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 °C / 60% RH and for up to 6 months under accelerated conditions at 40 °C / 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. 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 proposed shelf-life of 36 months and the following storage condition "do not store above 25°C" as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

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 finished product and their manufacturing process. However, no design space was claimed for the manufacturing process of the active substance and finished product. 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. Recommendation(s) 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.

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 pharmacodynamic 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, and in vitro cell-based assays evaluating the effects of lenvatinib on VEGF- and FGF-driven cellular activities in endothelial cells as well as the direct antitumor activity of lenvatinib.

The following new studies were conducted in addtioion to non-clinical data provided during the Lenvima MAA (EMEA/H/C/3727) procedure:

In vitro studies

- Inhibition of FGF-driven cellular functions of endothelial cells
- Inhibition of VEGF- and FGF-driven cellular functions of endothelial cells when combined with everolimus
- Direct antiproliferative effects on H460 and Colo205 cancer cells

In vivo studies:

- Inhibitory activity in an in vivo angiogenesis model
- Evidence for FGFR inhibition in vivo
- Antitumor effects in human tumor xenograft models in combination with other anticancer agents

In vitro studies

Kinase Inhibition Profiling Studies

Studies 1 and 2 (Studies W-2012086 and W-20120814)

Two kinase inhibition profiling studies (W-20120816 & W-20120814) targeting 66 purified recombinant protein kinases demonstrated that lenvatinib is a potent multiple kinase inhibitor. IC_{50} values were determined by measuring the cell-free kinase activities with lenvatinib (0.3 - 10,000 nmol/L) by enzyme-linked immunosorbent assay (ELISA) or mobility shift assay under optimized condition for each kinase. The profile for sorafenib, another multikinase inhibitor in clinical use, was also studied under the same condition as a reference (see table 4).

Table 2. Kinase inhibition profile of lenvatinib and sorafenib against 66 kinases

Kinase	IC$_{50}$ (nmol/L)		Kinase	IC$_{50}$ (nmol/L)	
	Lenvatinib	Sorafenib		Lenvatinib	Sorafenib
KIT^{V560G}	0.74	4.6	KIT^{V654A}	520	920
VEGFR3 (FLT4)	2.3	16	MET	520	>10,000
VEGFR2 (KDR)	3.0	21	EGFR	620	>10,000
VEGFR1 (FLT1)	4.7	21	PDGFRα^{T674I}	630	86
RET	6.4	15	ABL	660	1050
RET^{M918T}	12	33	EPHB2	660	710
PDGFRα^{V561D}	25	5.4	FGR	910	1200
FGFR2	27	150	AurA	1100	2500
PDGFRα	29	1.6	RAF1	1600	46
FGFR4	43	3400	TIE2	2500	1700
FGFR3	52	340	CSK	2600	5300
FGFR1	61	340	FLT3	4100	57
KIT	85	140	EPHB4	4600	660
FGFR3^{K650E}	110	100	EPHA1	5100	1200
LCK	130	960	SRC	5700	4500
FRK	160	370	BRAF	8700	310
PDGFRβ	160	27	SYK	8700	>10,000
HER4	170	>10,000	MUSK	>10,000	68
BRK	180	8300	BRAF^{V600E}	>10,000	380
FGFR3^{K650M}	250	110	P70S6K	>10,000	460
HGK	400	3300	KIT^{D816V}	>10,000	1400
KIT^{T670I}	410	60	JAK2	>10,000	4400

Other kinases with IC$_{50}$ values above 10,000 nmol/L for lenvatinib and sorafenib include: AKT1, CDK2/CycE1, CDK4, CDK6, CHK1, COT, EPHB3, FAK, GSK3b, HER2, IGF1R, IKKb, INSR, IRAK4, MLK1, MEK2, PIM1, PKACa, PLK1, PRKX, SGK3, WEE1.
Kinases listed are in order of low to high based on the IC$_{50}$ values for lenvatinib. Kinases with superscripts are known mutants with single amino acid substitutions. IC$_{50}$ = half-maximal inhibitory concentration.
Source: Study Nos. W-20120816 and W-20120814.

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

A study was also conducted to determine inhibition constants (Ki) for selected kinases (W-20120815). 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 (see table 3).

Table 3. Kinase inhibition profile of lenvatinib against 10 kinases

Kinase		K_i (nmol/L)
VEGF receptor	VEGFR1 (FLT1)	1.3
	VEGFR2 (KDR)	0.74
	VEGFR3 (FLT4)	0.71
FGF receptor	FGFR1	22
	FGFR2	8.2
	FGFR3	15
	FGFR3^{K650E}	28
	FGFR3^{K650M}	62
RET		1.5
KIT		11

FGF = fibroblast growth factor, K_i = inhibition constant, VEGF = vascular endothelial growth factor.
Source: Study No. W-20120815.

Results:

Lenvatinib selectively inhibited tyrosine kinase activities of VEGF receptors (VEGFR1-3) and RET with half-maximal inhibitory concentration (IC_{50}) values below 10 nmol/L (table 4) and inhibition constant (Ki) values of approximately 1 nmol/L.

Secondly, lenvatinib also inhibited other proangiogenic and oncogenic pathway-related RTKs including FGFR1-4, PDGFRα, and KIT with IC_{50} values between 10 and 100 nmol/L. The Ki values were higher: respectively 22, 8.2, 15 and 11 nmol/L for FGFR1, 2 and 3, and KIT. The inhibition mode against these kinases was found to be competitive. Ki values for FGFR-4 and PDGFRα were not determined.

Against VEGFR1 – 3 and FGFR1 – 3, IC_{50} values for lenvatinib were several-fold lower than those of sorafenib. In particular, the IC_{50} of lenvatinib against FGFR4 was approximately 80-fold lower than that of sorafenib. In contrast, the IC_{50} 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.

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.

Effect of Lenvatinib on FGF-Driven Tube Formation of Endothelial Cells (Study No. M14012)

This study examined the inhibitory activity of lenvatinib against FGF-driven tube formation of HUVECs. The activity of sorafenib was also evaluated.

Effect of lenvatinib in combination with everolimus on VEGF- or FGF-driven cellular functions of endothelial cells (Study No. BIOMT-2015-009, Study No. BIOMT-2015-010, Study No. M15015, Study No. M15016)

Four studies were conducted to evaluate the effects of lenvatinib in combination with everolimus on VEGF- or FGF-driven cellular activities in HUVECs.

In the first study (Study No. BIOMT-2015-009), the effects of lenvatinib and everolimus on VEGF-activated intracellular signaling in HUVECs were examined, specifically the phosphorylation of Erk1/2 (p44/42 MAPK), S6K (p70 S6 kinase), and S6 (S6 ribosomal protein). Erk1/2 is a signaling molecule involved in the MAPK pathway (RAS-RAF-MEK-Erk1/2 pathway) and S6K and S6 are signaling molecules involved in the mTOR-S6K-S6 pathway. Both pathways are downstream of RTKs including VEGFR and FGFR.

Combination of lenvatinib and everolimus inhibited the phosphorylation of Erk1/2(Thr202/Tyr204), S6K(Thr389), S6K(Thr421/Ser424), and S6(Ser235/Ser236). Specifically in mTOR-S6K-S6 pathway, the combination showed greater inhibition than each single agent for the phosphorylation of S6K(Thr421/Ser424) and S6(Ser235/Ser236). S6K(Thr389) directly downstream of the mTOR complex was already maximally inhibited by everolimus

In the second study (Study No. BIOMT-2015-010), the effects of lenvatinib and everolimus on FGF-activated intracellular signaling in HUVECs were examined; specifically the phosphorylation of Erk1/2, S6K, and S6 were evaluated.

The combination of lenvatinib and everolimus also inhibited the phosphorylation of Erk1/2(Thr202/Tyr204), S6K(Thr389), S6K(Thr421/Ser424), and S6(Ser235/Ser236). The combination showed greater inhibition than each single agent for the phosphorylation of S6K(Thr421/Ser424) and S6(Ser235/Ser236), similar to what was observed with VEGFstimulated phosphorylation.

In the third study (Study No. M15015), the effects of lenvatinib in combination with everolimus on VEGF-driven proliferation of HUVECs were examined. Dilutions of lenvatinib mesilate alone, everolimus alone, and their mixtures (molar ratios of 2.5:1, 5:1, 10:1, and 20:1 (lenvatinib: everolimus)), were added to HUVECs on tissue culture plates.

The combination of lenvatinib and everolimus at the different molar ratios resulted in combination indexes of 0.80, 1.11, 1.12, and 1.17, respectively, indicating moderate synergistic or additive effects.

In the fourth study (Study No. M15016), the effects of lenvatinib in combination with everolimus on FGF-driven tube formation of HUVECs were evaluated. Dilutions of lenvatinib alone, everolimus alone, and their mixtures with molar ratios of 1:4, 1:8, 1:12, and 1:16 (lenvatinib : everolimus) were added to HUVECs.

The combination of lenvatinib and everolimus resulted in combination indexes of 0.47, 0.56, 0.61, and 0.74, respectively, indicating synergistic or moderate synergistic effects.

Direct Anti-proliferative Activities against Cancer Cells

Two studies were conducted to evaluate the effects of lenvatinib on in vitro proliferation of human cancer cell lines. Lenvatinib exhibited weak, direct anti-proliferative activity in vitro against the H460 human non-small cell lung cancer (NSCLC) and Colo205 human colorectal cancer cell lines, with IC50 values of 14.000 and 26.000 nmol/L (~ 7321 ng/ml and 13597 ng/ml), respectively (Study No. M03007).

In a second study, lenvatinib exhibited a weak anti-proliferative activity against the A-498 human RCC cell line with an IC_{50} value above 10,000 nmol/L, while everolimus inhibited the growth of A-498 cells with an IC_{50} value of 4.6 nmol/L (95% CI: 2.4 – 8.7) (Study No. M15005).

In vivo studies

The inhibitory activity of lenvatinib was evaluated in an *in vivo* angiogenesis model and the antitumor activity of lenvatinib as monotherapy or in combination with other anticancer agents was evaluated in various human tumor xenograft models in athymic mice.

Antiangiogenesis activity of lenvatinib in VEGF- and FGF-induced angiogenesis model in mice (DAS Model)

This study examined the inhibitory activity of lenvatinib against VEGF- or FGF-induced angiogenesis in a murine DAS model (Yamamoto, et al., 2014). The activity of sorafenib was also evaluated. Recombinant KP-1 human pancreatic cancer cells expressing human VEGF or murine FGF (KP-1/VEGF cells or KP-1/FGF cells) were packed in Millipore chambers with collagen gels, and the chambers were embedded in dorsal air sacs of C57BL/6 mice (Day 1) in order to induce angiogenesis in the skin attached to the chamber membrane (Funahashi, et al., 1999). Then, vehicle for lenvatinib (distilled water), lenvatinib mesilate (3, 10, and 30 mg/kg) or sorafenib tosylate (100 and 300 mg/kg) was orally administered to the mice (3 – 5/group) once daily for 4 days (Day 1 – 4). Angiogenesis was evaluated on Day 5 by measuring the pre-radiolabelled red blood cell content in the skin attached to the chamber membrane, and treatment/ control (T/C) (%) was calculated.

Angiogenesis was markedly induced in the skin of mice bearing the Millipore chamber with KP-1/VEGF or KP-1/FGF cells compared to those bearing the Millipore chamber with KP-1 mock cells (mock-transfected cells) or collagen only, demonstrating that in vivo angiogenesis was induced by VEGF or FGF secreted from the tumor cells. In this model, lenvatinib at doses of 10 and 30 mg/kg significantly inhibited both VEGF- and FGF-induced in vivo angiogenesis. Sorafenib (100 and 300 mg/kg) also significantly inhibited the VEGFinduced angiogenesis, but did not inhibit the FGF-induced angiogenesis.

Effects of Lenvatinib on Plasma FGF23 Levels in Mice

FGF23, a protein hormone regulating mineral metabolism, is a potential pharmacodynamics marker for FGFR inhibition in vivo, since its plasma level is elevated as a compensatory response when intracellular FGFR signaling is blocked (Wöhrle, et al., 2011; Kim, et al., 2011). This study examined the effect of lenvatinib on plasma FGF23 levels in mice in order to obtain evidence for FGFR inhibition in vivo (Study No. W-20140842). Sorafenib was also evaluated. Seven-week-old female non-tumor-bearing BALB/c mice (8/group) were administered a single oral dose of the vehicle for lenvatinib (distilled water), lenvatinib mesilate (3 and 10 mg/kg), or sorafenib tosylate (9 and 30 mg/kg). Twenty-four hours after dosing, blood was collected from the abdominal aorta and the concentration of FGF23 in the plasma fraction was measured by ELISA.

The plasma FGF23 concentration increased dose-dependently in mice treated with lenvatinib, with a significant increase confirmed at a dose of 10 mg/kg compared to the vehicle-control group; no significant increase in FGF23 concentration associated with treatment with sorafenib was observed. The result provides evidence that lenvatinib is able to inhibit the FGFR signaling pathway in mice, whereas sorafenib does not show such activity.

Combination therapy with everolimus

Antitumor Effects of Lenvatinib in Combination With Everolimus in the A-498 Human RCC Xenograft Model in Athymic Mice

The antitumor effects of lenvatinib, everolimus, and lenvatinib in combination with everolimus, were evaluated in the A-498 human RCC xenograft model in athymic mice (Study No. M14026).

A-498 cells were inoculated subcutaneously into 8-week-old female mice. At 21 days after inoculation, vehicle, lenvatinib mesilate (10 mg/kg), everolimus (30 mg/kg), or lenvatinib mesilate in combination with everolimus were orally administered to the mice (10/group) once daily for 14 days (Day 1 – 14). The TV and body weight were measured twice a week.

Lenvatinib monotherapy, everolimus monotherapy, and the combination of the 2 agents showed significant inhibition of tumor growth compared to vehicle control with T/C values of 26%, 0%, and −20% on Day 15, respectively. The combination resulted in growth inhibition with tumor shrinkage, which was significantly greater than that for each monotherapy.

Antitumor Effects of Lenvatinib in Combination With Everolimus in the Caki-1 Human RCC Xenograft Model in Athymic Mice

The antitumor effects of lenvatinib, everolimus, and lenvatinib in combination with everolimus, were evaluated in the Caki-1 human RCC xenograft model in athymic mice (Study No. W-20110629).

Caki-1 cells were inoculated subcutaneously into 7-week-old female mice. At 48 days after inoculation (Day 1), vehicle, lenvatinib mesilate (10 mg/kg), everolimus (30 mg/kg), or lenvatinib mesilate in combination with everolimus were orally administered to the mice (5/group) once daily for 14 days (Day 1 – 14).

The TV and body weight were measured twice a week. The TV was calculated according to the formula: length × width2 × ½, and described as the RTV compared with that on Day 1.

Lenvatinib monotherapy, everolimus monotherapy, and the combination of the 2 agents showed significant inhibition of tumor growth compared to vehicle control with T/C values of 2%, −23%, and −86%, respectively, on Day 15. The combination resulted in tumor shrinkage, and the antitumor activity was significantly greater than that for lenvatinib monotherapy. It was also numerically greater than that for everolimus monotherapy, but the difference was not significant (P=0.0683).

Antitumor Effects of Lenvatinib in Combination With Everolimus in the KP-1/VEGF Xenograft Model in Athymic Mice

The antitumor effects of lenvatinib, everolimus, and lenvatinib in combination with everolimus, were evaluated in the KP-1/VEGF xenograft model in athymic mice (Study No. M15012), where VEGF-induced tumor angiogenesis and resulting tumor growth were expected to be enhanced due to the excess VEGF secreted from the recombinant KP-1/VEGF cells (Yamamoto, et al., 2014). KP-1/VEGF cells were inoculated subcutaneously into 6-week-old female mice. At 14 days after inoculation, vehicle, lenvatinib mesilate (7.5 and 10 mg/kg), everolimus (15 and 30 mg/kg), or lenvatinib mesilate (7.5 mg/kg) in combination with everolimus (15 mg/kg) were orally administered to the mice (5/group) once daily for 14 days. The TV and body weight were measured twice a week.

Lenvatinib monotherapy, everolimus monotherapy, and their combination showed significant inhibition of tumor growth compared to vehicle control on Day 15. The combination of lenvatinib mesilate (7.5 mg/kg) and everolimus (15 mg/kg) showed significantly greater antitumor effect than either monotherapy. The antitumor effect of the combination was also significantly greater than with the higher dose of either lenvatinib mesilate (10 mg/kg) or everolimus (30 mg/kg) monotherapy.

Combination therapy with other compounds
- Combination of lenvatinib with:
  - temozolomide (TMZ) (Study No K08038) or eribulin (Study No JW1012) in the A375 melanoma xenograft model,

- o cisplatin or carboplatin in the A549 NSCLC xenograft model (Study No K06053),
- o paclitaxel in the MKN-74 gastric cancer xenograft model (Study No K06008), and
- o golvatinib in the SEKI melanoma, KP-4 pancreatic cancer, IM95m gastric cancer, and A2780 ovarian cancer (Study No W-20100607)
- o human xenograft models in athymic mice showed greater antitumor effects as compared with each monotherapy.

- **Tumor regression** has occurred for the combination of lenvatinib with eribulin, ciplatin/carboplatin and golvatinib:

- The combination of lenvatinib with eribulin (3.0 mg/kg, Q7D×2) showed greater antitumor effects than the monotherapy, which resulted in tumor regression.

- The antitumor effects of the combinations of lenvatinib with carboplatin were of similar magnitude to the combination with cisplatin. The effects were greater than each monotherapy, although not statistically significantly different from the lenvatinib monotherapy. Tumor regression was observed in the combinations of lenvatinib (10 and 30 mg/kg) with cisplatin and lenvatinib (10 mg/kg) with carboplatin.

- Golvatinib (an investigational multiple kinase inhibitor) is a potent inhibitor of MET, while lenvatinib showed little inhibitory activity against MET. The combination of lenvatinib and golvatinib showed significant and greater inhibition of tumor growth as compared to each monotherapy. Regression of IM95m tumors was observed in mice treated with the combination.

- **Body weight loss**

- Lenvatinib (10, 30 mg/kg) weakly enhanced the transient BWL caused by TMZ (80 mg/kg).

- When given in combination with 3.0 mg/kg eribulin (QD×7), lenvatinib weakly enhanced the BWL caused by eribulin.

- Lenvatinib (10 and 30 mg/kg) enhanced the transient BWL caused by carboplatin. The combination of lenvatinib (30 mg/kg) with carboplatin (100 mg/kg) was lethal in this model.

- Lenvatinib at each dose weakly enhanced the transient BWL caused by paclitaxel.

- In the SEKI and A2780 xenograft models for golvatinib where BWL was observed in the vehicle group (attributed to tumor burden), lenvatinib had no effect on, or weakly enhanced, this BWL.

Secondary pharmacodynamic studies

To evaluate the potential secondary pharmacodynamic effects of lenvatinib, the binding of lenvatinib (1 and 10 µmol/L) to a panel of 50 non-kinase receptors (ExpresSProfile) known to play significant biological roles was determined. 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), no significant binding (greater than 50% inhibition) of lenvatinib to any of the 50 receptors was observed at the tested concentrations. These are not considered relevant at human therapeutic dose levels.

Safety pharmacology programme

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

Table 4: 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

Effects of lenvatinib on general physical condition and behavior were evaluated in SD rats after a single oral administration of lenvatinib mesilate at 10, 30, and 100 mg/kg using Irwin's method (Study No. B030401). Lenvatinib, up to 100 mg/kg, showed no effect on general physical condition and behavior in rats.

The effects of a single oral dose of lenvatinib mesilate (6 and 30 mg/kg) on body temperature were assessed in beagle dogs (Study No. B030402). Lenvatinib did not cause body temperature changes at any dose in dogs.

Cardiovascular system

Two in vitro electrophysiology studies were conducted to assess the effect of lenvatinib on hERG tail current or action potential parameters (Study Nos. DJNR1029 and B030403). No significant adverse effects were observed in these studies except for a weak inhibitory effect on hERG potassium current (IC50 = 11.89 µmol/L). The effects of a single oral dose of lenvatinib mesilate (6 and 30 mg/kg) on heart rate, mean blood pressure, and ECG (PR interval, QRS duration, and QT interval) were assessed in beagle dogs (Study No. B030402). Lenvatinib at doses up to 30 mg/kg had no significant effect on heart rate, mean blood pressure, or ECG (including QT) except for a minimal increase in mean blood pressure within the normal biologic range.

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 SD rats were evaluated using unrestrained whole body plethysmography (Study No. S03019). Lenvatinib at doses up to 100 mg/kg showed no effects on respiratory rate, tidal volume, or minute volume in rats.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted. *In vivo* xenograft studies of lenvatinib in combination with other anticancer agents that evaluate pharmacodynamic interactions were conducted (please see *in vivo* pharmacology studies above).

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 ([14C] lenvatinib mesilate and [14C]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 5: 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/k g)	$t_{1/2}$ (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	7.054 2[b]	NA	NA
	PO	3	5.596	NA	NA	2.09	1.965 1	0.5	64.4
	PO	10	27.720	NA	NA	1.74	10.51 00	0.5	NC
	PO	30	118.198	NA	NA	1.85	31.25 65	1	NC
Rat/SD/Male	IV	3	30.107	100.2	391.5	3.65	14.05 67[b]	NA	NA
	PO	3	20.697	NA	NA	3.61	6.167 1	0.5	68.7
	PO	10	78.321	NA	NA	5.27	16.64 50	0.5	NC
	PO	30	145.580	NA	NA	4.95	23.20 15	1	NC
Dog/Beagle/ Male	IV	3	8.417	368.3	1610.0	5.27	2.288 9[b]	NA	NA
	PO	3	5.481	NA	NA	4.76	1.271 7	2	70.4
Monkey/ Cynomolgus/ Male	IV	3	12.900	237.7	793.7	4.28	4.642 7[b]	NA	NA
	PO	3	10.272	NA	NA	4.07	2.501 3	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 time or lower than that in the plasma. Elimination half-life was 3.70 days.

Protein Binding and Distribution in Blood Cells

To clarify the nature of covalently-bound lenvatinib-related material with human plasma proteins and to evaluate its reversibility, the effect of the nucleophiles GSH and cysteine was examined. Covalent binding of lenvatinib to human plasma protein occurred in vitro, and GSH and cysteine successfully released lenvatinib-related components bound to plasma protein as conjugates in the same manner as the 2-ME conjugates in previous studies (E7080 E044 104 and AE-6748-G). Since abundant amounts of GSH and cysteine exist in humans, the covalent binding observed in human plasma is expected to be reversible in vivo.

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 14C-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 14C-lenvatinib was observed, and ranked from highest to lowest as follows: dog > monkey = mouse $\geq$ rat > human. The Rb values in animals declined with increasing concentration; however, in human, the Rb was constant between 0.1 and 10 μ g/mL.

The in vitro transfer ratios of 14C-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 14C-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 14C-lenvatinib mesilate in dog blood may be distributed to blood cells more than unchanged 14C-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

The applivant demonstrated that no glutathione metabolites with the quinolone form were identified in the monkey or human studies and that exposure is likely to be very low in humans. In addition, the levels of the aniline metabolite are low and probably similar to those seen for other tyrosine kinase inhibitors. This was raised during the review of Lenvima.

In vitro and *in vivo* studies using lenvatinib, [14C] lenvatinib, or [14C]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 [14C]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 [14C]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 14C-labeled lenvatinib radio-labeled on the chlorobenzene moiety. After a single oral dose of 14C-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.

Study DMPKT2013-017

Pharmacokinetic parameters of total radioactivity, extracted radioactivity, radioactive peaks including lenvatinib, and unextracted radioactivity in monkey plasma obtained in Study Nos. AE-6748-G, AE-6917-G, and AE-6918-G were calculated. Lenvatinib was the main fraction of total radioactivity in plasma after administration of both $[^{14}C]$lenvatinib mesilate (C_{max}: 89.9%, $AUC_{(0-inf)}$: 69.7%) and $[^{14}C]$CB-lenvatinib mesilate (C_{max}: 78.4%, $AUC_{(0-inf)}$: 60.4%). After administration of $[^{14}C]$lenvatinib mesilate, C_{max} and $AUC_{(0-inf)}$ of all radioactive metabolite peaks did not exceed 1.9% of the total radioactivity values. After administration of $[^{14}C]$CB-lenvatinib mesilate, mCB9a was the major radioactive metabolite, with C_{max} and $AUC_{(0-inf)}$ values that were 12.1% and 17.0% of the total radioactivity values, respectively. mCB9a is equivalent to me50 (i.e. glucuronide of me92). With the exception of mCB9a, C_{max} and $AUC_{(0-inf)}$ of all radioactive metabolite peaks detected after administration of $[^{14}C]$CB-lenvatinib mesilate did not exceed 4.7% of total radioactivity. C_{max} and $AUC_{(0-inf)}$ of unextracted radioactivity after administration of $[^{14}C]$CB-lenvatinib mesilate were 0.5% and 2.6% of the total radioactivity, respectively, and were lower than those after administration of $[^{14}C]$lenvatinib mesilate (C_{max}: 7.3%, $AUC_{(0-inf)}$: 22.6%).

Study W-20140601

In the monkey study, methanol was unable to extract the entire radioactivity in plasma protein. This was likely due to covalent binding of $[^{14}C]$lenvatinib. Treatment with nucleophilic 2-mercaptoethanol (2-ME) recovered additional radioactivity from the modified plasma protein which likely included conjugates between 2-ME and the quinoline moiety of lenvatinib. In the human mass balance study, incorporation of radioactivity originating from $[^{14}C]$lenvatinib to plasma protein, possibly due to covalent binding was also observed. To clarify the nature of covalently-bound lenvatinib-related material with human plasma proteins and to evaluate its reversibility, the effect of the nucleophiles GSH and cysteine was examined. Covalent binding of lenvatinib to human plasma protein occurred in vitro, and GSH and cysteine successfully released lenvatinib-related components bound to plasma protein as conjugates in the same manner as the 2-ME conjugates in previous studies (E7080-E044-104 and AE-6748-G). Since abundant amounts of GSH and cysteine exist in humans, the covalent binding observed in human plasma is expected to be reversible in vivo.

Excretion

After oral administration of [14C] lenvatinib mesilate to rats and cynomolgus monkeys or [14C]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 6: 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 [14C]Lenvatinib mesilate/3	12.2	87.2	99.4
Study No. AE-4151-G	Monkey/Cynomolgus [14C]Lenvatinib mesilate/3	17.2	72.8	90.0
Study No. AE-6917-G	Monkey/Cynomolgus [14C]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 [14C]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

Protein binding of lenvatinib in human liver microsomes solution was evaluated using an equilibrium dialysis method. The percentages of protein binding of lenvatinib in the human liver microsomes sample (1 mg protein/mL) at 0.3, 1, 3, 10, and 30 µg/mL lenvatinib mesilate were 29.24±0.91%, 26.93±1.26%, 25.49±0.21%, 24.53±0.52%, and 23.85±1.06%, respectively. The mean unbound fraction in the study at 1 mg/mL microsomal protein was 0.74, and DDI simulation using Simcyp was re-evaluated using this value.

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 IC50 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 IC50 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 IC50 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 (IC50 > 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 IC50 values of 7.36, 4.11, 10.8, and 7.29 µmol/L, respectively, and minimal or no inhibitory effect on OATP1B3 (IC50 >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 IC50 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.

The applicant provided the same as for the Lenvima MAA.

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 7: 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 8: 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, **0.4**, 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 9: 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 10: 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, **0.3**, 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, **0.1**, 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, **0.1**, 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 11: Overview of genotoxicity studies with lenvatinib mesilate

Type of test/study ID/GLP	Test system	Concentrations/ Metabolising system	Results
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 12: 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

Species Number/Group Study ID	Duration	Route Dose (mg/kg)	Major findings
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 ossification split of vertebral centrum)

Table 13: 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 14: 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	D1 : 2893.37 D14 :2270.39	22007.37 12441.32

	Histology: changes limited to the incisors, adrenals, and bone		
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 ↑ 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).	D1 :15712.41 D14 :5678.36	128762.71 60448.51

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 15: 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 16: Comparative overview of AUC values at steady state in rats, dogs, monkeys and humans

Species	Steady State AUC (µg·h/mL)						
	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 17: Comparative overview of Cmax values at steady state in rats, dogs, monkeys and humans

Species	Steady State C_{max} (µg/mL)						
	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

An environmental risk assessment has already been performed to evaluate the potential environmental risk resulting from the use of lenvatinib hard capsules in the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC).

Using a worst-case refined Fpen value of 0.00001 for RR-DTC, the PECSURFACEWATER for lenvatinib has been calculated to be 0.00012 µg/L. This value is ~100 times lower than the action limit of 0.01 µg/L.

A new environmental risk assessment has now been performed to evaluate the additional potential environmental risk resulting from the use of lenvatinib hard capsules in the treatment of patients with advanced and/or metastatic renal cell carcinoma (RCC) with lenvatinib hard capsules in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

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 Lenvatinib and this was used to refine Fpen. Using the refined Fpen, a PECsw was calculated that was below the action limit. Therefore lenvatinib is not expected to pose a risk to the environment.

Table 18: 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)	0.00408	µg/L	< 0.01 threshold

2.3.6. Discussion on non-clinical aspects

With regard to pharmacology, the applicant has conducted additional *in vitro* studies in cell-based assays (7 in total) and *in vivo* studies in xenograft models with the combination of lenvatinib and everolimus (4 in total), to support the original data submitted under the previous MAA for lenvatinib mesilate (EMEA/H/C/3727). The additional *in vitro* studies showed that lenvatinib inhibited both the MAPK and mTOR-S6K-S6 pathways and that inhibition of the latter pathway was enhanced by the combination with everolimus in both VEGF- and FGF-stimulated HUVECs. Both lenvatinib and everolimus inhibited VEGF-driven proliferation in HUVECs *in vitro*, with the combination of lenvatinib and everolimus having mostly additive effects for inhibition of VEGF-driven proliferation and mostly synergistic effects for inhibition of FGF-driven tube formation of HUVECs. The human tumour xenograft in vivo studies suggested that lenvatinib may be an effective anticancer therapy for the treatment of advanced and/or metastatic renal cell carcinoma, in combination with everolimus, following failure of treatment with 1 prior therapy. Results of the nonclinical 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 (IC50 = 11.89 µmol/L or 6,2 µg/ml) at a concentration approximately 20-fold higher than the total maximum observed concentration (Cmax) at the clinical dose of 18 mg (in Study E7080-G000-205) and 1378-fold higher than the free Cmax 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.

According to the ICH S9 guideline, conduct of standalone safety pharmacology studies is not required for advanced cancer indications; however, the core battery of stand-alone safety pharmacology studies was nonetheless conducted.

Results from additional pharmacokinetic studies performed by the applicant showed that lenvatinib was the main fraction of total radioactivity in plasma after oral administration of both [^{14}C]lenvatinib mesilate and [^{14}C]CB-lenvatinib mesilate. Metabolite peaks did not exceed 1.9% of the total radioactivity values after administration of [^{14}C]lenvatinib mesilate. No non-clinical combination pharmacokinetic studies with lenvatinib and everolimus have been conducted. Further exploration on the potential interaction between lenvatinib and everolimus is needed and will be addressed in a post marketing study (Study 109, please see RMP section 2.8). This drug-drug interaction study will investigate the potential of Lenavtinib for CYP3A4 inhibition/induction.

No new toxicology studies with lenvatinib alone or in combination with everolimus have been conducted, which may be acceptable according to ICHS9. This means that all observed toxicities and corresponding exposures in animals have been compared with clinical exposures at a dose of 24 mg/day, which was the recommended dose for the DTC MAA. For the current MAA, the proposed dose is 18 mg/day (in combination with everolimus, 5 mg/day). It is not considered that this would lead to different overall conclusions, therefore this can be accepted. However, since the clinical anticipated exposure to lenvatinib is thus lower with the dosing regimen as proposed in the current MAA, all safety margins should in principle be somewhat higher. The administration route of *in vivo* studies was oral, which is the intended route for clinical use.

In accordance with the recommendations of the ICH S9 guideline, carcinogenicity studies, fertility studies, and pre-and postnatal toxicity studies were not conducted with lenvatinib to support marketing approval in the proposed advanced cancer indication.

Clinical experience with the combination is limited. Non-clinical combination PD studies in vivo for 15 days give some reassurance on the absence of acute synergistic toxicities. Based on the toxicity profile of each drug in nonclinical studies, the kidney, GI tract, and reproductive organs are the target organs in which additive or synergistic toxicity might be expected. The available data overall suggest a low potential for additive or synergistic toxicities with the combination, apart from increased toxicities at the level of the GI tract with potential deterioration of general condition.

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

The non-clinical data are considered adequate to support a marketing authorisation for Kisplyx. However, further exploration of the potential interaction between lenvatinib and everolimus is needed and will be addressed in a post marketing study (Study 109). This drug-drug interaction study will investigate the potential of Lenvatinib for CYP3A4 inhibition/induction (please see RMP in section 2.8).

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.

- **Tabular overview of clinical studies**

Table 19: 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

Table 20: Main clinical efficacy and safety studies in the lenvatinib development program

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-G000-205	Unresectable or mRCC following 1 prior VEGFtargeted treatment	37 sites: Czech Republic, Poland, Spain, UK, and USAb	12 Aug 2010/ 13 Jun 2014	Phase 1/2b, Open-Label, Multicenter with Treatment and Extension Phases. **Phase 1b**: dose escalation in sequential cohorts to determine MTD and RP2 dose **Phase 2**: randomized (1:1:1)	**Phase 1b**: LENV 12 mg, 18 mg, or 24 mg + EVER 5 mg **Phase 2**: *Combination Arm*: LENV 18 mg + EVER 5 mg, oral, QD *Monotherapy arms*: LENV 24 mg, oral QD; EVER 10 mg, oral, QD Continuous, 28-day cycles	**Phase 1b**: 20/0 **Phase 2**: 153/23

EVER = everolimus, mRCC = metastatic renal cell carcinoma, MTD = maximum tolerated dose; LENV = lenvatinib, QD = once daily, RP2 dose =
recommended Phase 2 dose; VEGF = vascular endothelial growth factor.
a: Clinical start date is date of the first subject's signed informed consent.
b: All 4 sites that participated in the Phase 1b portion also participated in the Phase 2 portion of Study E7080-G000-205.

The primary evidence of efficacy of combination treatment with lenvatinib and everolimus in the unresectable advanced of metastatic RCC indication following one prior VEGF-targeted treatment comes from a single, open-label, Phase 1b/2 study, which is randomised in Phase 2 only (Study E7080-G000-205 [Study 205]).

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 used in the studies 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:

- o 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,

- o 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),

- o a Phase 2 trial in subjects with advanced or recurrent thyroid cancer (Study E7080-J081-208),

- o a Phase 2 trial in subjects with medullary and ^{131}I refractory, unresectable differentiated thyroid cancers (Study E7080-G000-201), and

- o 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 $\geq$ 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 $AUC_{(0-inf)}$ (ratio%, 90% CI: 106.3, 95.66 to 118.09) and $AUC_{(0-t)}$ 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_{0-24} 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_{0-24}) 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.

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.

In vitro studies indicate that lenvatinib is a substrate for multidrug resistance protein 1 (MDR1), P-gp, and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or the BSEP.

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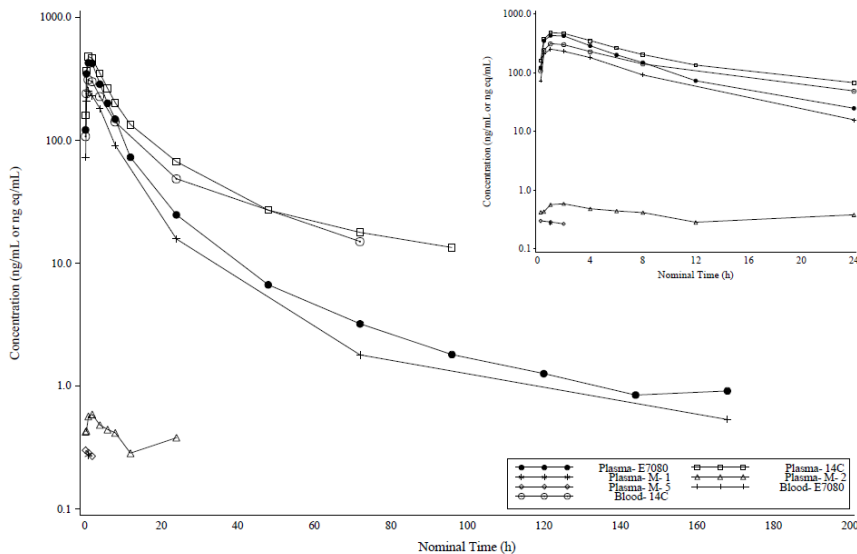
Figure 1: Semi-Log plot of mean total radioactivity, E7080 and key metabolites in plasma and blood, study phase, pharmacokinetic analysis set

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.
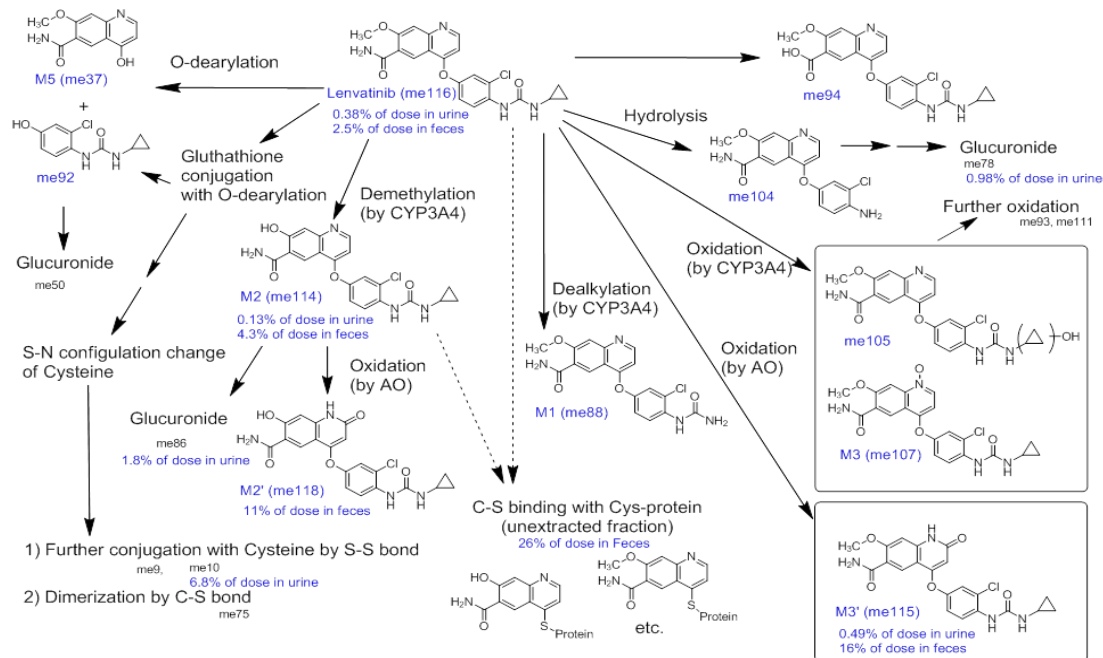
Figure 2: Overview of metabolic pathways for lenvatinib in humans

In total, the contribution to lenvatinib clearance in human is summarized in the table 22 below. The ratio of aldehyde oxidase (AO): CYP3A: non-enzymatic process is approximately 3:4:3 in humans.

Table 21: 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.		

There is a substantial body of literature confirming that it is possible to observe clinically relevant drug-drug interactions mediated by inhibition of AO. The article by Obach et al.,2004 showed that there is a wide variety of drugs on the market which are able to inhibit aldehyde oxidase activity and so have the potential to affect exposure of co-administered drugs which are metabolised via this enzyme. However, the proportion of the dose of lenvatinib which is metabolised through AO is quite low (approx. 17%), with the remainder being cleared via other metabolic routes with just a small amount of parent drug excreted unchanged. Conversely, this means that a large proportion of the dose is eliminated via non-AO mediated mechanisms. There are multiple alternative clearance pathways available for lenvatinib in addition to AO metabolism which are likely to buffer any minor influence of inhibition of the enzyme. Hence, there is no expectation that inhibition of this pathway will lead to clinically significant effects on lenvatinib exposure.

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 22: 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.

- **Children**

The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established.

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.

- Everolimus

In study E7080-G000-205, based on the dose-normalized Cmax and (AUC(0-24)), the mean lenvatinib Cmax was similar between the combination and the lenvatinib arms while the mean systemic exposure as measured by AUC(0-24) was approximately 20% lower in the combination arm compared to the lenvatinib arm. These results should be viewed with caution given the small number of subjects in each treatment arm. In the population PK analysis, a log-likelihood ratio test at a P value of 0.01 showed that everolimus did not significantly affect lenvatinib clearance. Based on these results, the sponsor concluded that concomitant everolimus did not have a statistically significant effect on lenvatinib PK

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.

However, the in vitro data on the potential induction were judged as not sufficient and an *in vivo* study with midazolam as a probe substrate for CYP3A4 was required as a PAM (category 3) in the DTC MAA to investigate adequately the potential of lenvatinib for CYP3A4 induction. In the RMP for RCC, the study is listed in the pharmacovigilance studies/activities and planned in March 2018.

- Repaglinide as CYP2C8 substrate

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.

- Everolimus

In study E7080-G000-205, based on the dose-normalized Cmax and AUC(0-24), the mean everolimus Cmax was approximately 30% greater in the combination arm compared with the everolimus monotherapy arm. The mean AUC(0-24) of everolimus was approximately 50% higher in the combination arm compared with the everolimus arm. Several methodological flaws were noted that prevent to draw a clear conclusion with regards to the possible PK interaction between everolimus and lenvatinib (small number of subjects who contributed to PK data in study 205, the only intergroup comparison, the fact that everolimus is a narrow therapeutic index drug with highly variable PK). Further exploration on the potential interaction between lenvatinib and everolimus is still needed and comprehensive data collected in a manner permitting adequate characterization of PK drug-drug interactions between lenvatinib and everolimus will be provided at the time of submission of results of pop PK analysis of post marketing studies (218 and 307) data. The company is requested to ensure that data will be. Studies 218 and 307 are included in the RMP.

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. The most sensitive kinases for lenvatinib include 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).

Rationale for Development of Combination Lenvatinib/Everolimus for Unresectable, Advanced or Metastatic Renal Cell Carcinoma

The scientific rationale for combining lenvatinib (an RTK inhibitor) and everolimus (an mTOR inhibitor) was to target angiogenesis and tumour cell survival, as well as to escape resistance mechanisms to antiangiogenic therapy. The dual targeting of the mitogen activated kinase (MAPK) and mTOR-S6K-S6 pathways by lenvatinib and everolimus may contribute towards the increased anti-tumour activity of the combination compared to each agent alone.

Angiogenesis has been identified as a key factor in the development of RCC. VEGF is a crucial regulator of both physiologic and pathologic angiogenesis, and increased expression of VEGF is associated with a poor prognosis in many human tumour types, including RCC. Accumulated evidence suggests that fibroblast growth factor (FGF) and its receptor tyrosine kinase, FGFR, also play a role in angiogenesis and contribute to the aggressiveness of RCC. Recently, FGF-induced angiogenesis has also been reported to be involved in resistance against anti-VEGF/VEGFR therapy; therefore, inhibition of FGF has been postulated to decrease the rate of drug resistance to VEGF/VEGFR-targeting agents, but clinical data are limited to date.

An alternative pathway for angiogenesis is mediated by mTOR, which is downstream of phosphoinositide 3-kinase and protein kinase B and is regulated by the phosphatase and tensin homolog tumour suppressor gene. Inhibition of the mTOR pathway can inhibit both angiogenesis and tumour cell proliferation.
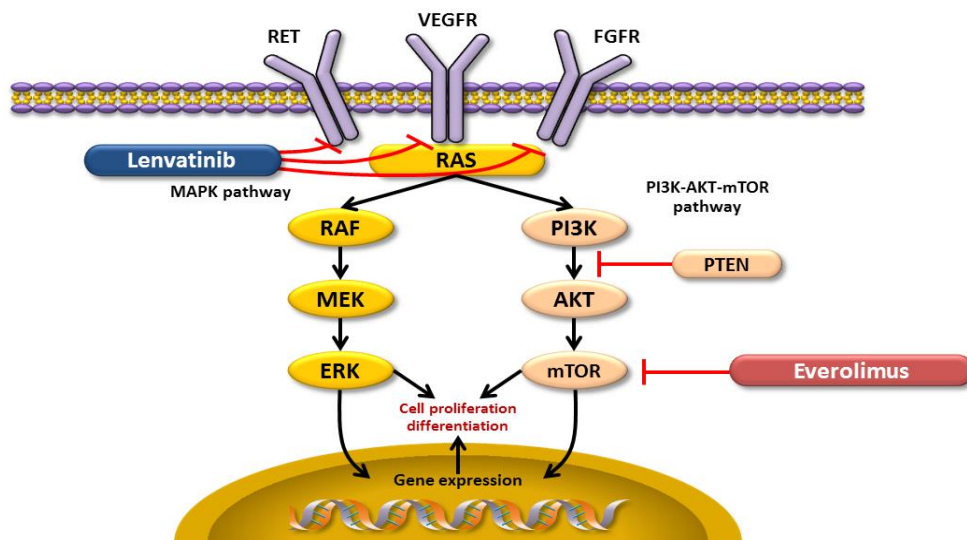
Figure 3: Inhibition of Receptor Tyrosine Kinase and mTOR Pathways by Lenvatinib and Everolimus: Proposed Mechanism of Action

Several studies indicate the lack of absolute cross-resistance between TKIs and that sequential VEGF/VEGR TKIs use or sequential use of VEGF/VEGFR TKIs and mTOR inhibitors can provide clinical benefit in mRCC, for instance sorafenib-sunitinib sequential trial in patients with mRCC (Sablin, et al., 2009), the use of sunitinib after bevacizumab (Rini, et al., 2006) or of axitinib after sorafenib (Rini, et al., 2007). In a Phase 2 study comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with mRCC, similar efficacy outcomes were observed, favouring however sequential sunitinib followed by everolimus use (Motzer, et al., 2014).

Several trials have previously evaluated combinations of a VEGF TKI with an mTOR inhibitor. For clear cell RCC, combinations of TKIs and mTOR inhibitors generally led to earlier onset and more severe toxicity. The most of studies for VEGFRi-mTORi combinations reported high unacceptable toxicity precluding further development. The majority of studies did not comprehensively evaluate the potential PD and/or PK interactions (Patel et al, 2009; Patnaik et al, 2007; Rosenberg et al, 2008; Molina et al, 2012; Poweles et al, 2014).

Although not studied directly, the MOA for the worsening of diarrhea with the combination is postulated to be mediated by the impairment of intestinal function related to the MOAs for the individual agents – VEGF/VEGFR and c-KIT inhibition by lenvatinib coupled with mTOR/NHE3 inhibition by everolimus. (see SmPC section 5.1) Mechanisms for other potential worsening of AEs (e.g. renal events, electrolyte abnormalities, constitutional symptoms) are suggested (Launay-Vacher et al. 2015).

The PD interactions have not been studied in the pivotal study 205. The underlying mechanisms of observed toxicity of the lenvatinib-everolimus combination may at least in part be due to PD interactions and enhanced inhibition of downstream targets of signaling pathways (e.g. mTOR pathway). As observed in non-clinical studies, lenvatinib inhibited the VEGF- and FGF-driven angiogenic signaling by the MAPK and mTOR-S6K- S6 pathways. The inhibition of the mTOR pathway was enhanced by the combination with everolimus, indicating potential for worsening of adverse reactions associated with everolimus (see non-clinical part).

Primary pharmacology

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.

In human umbilical vein endothelial cell (HUVEC) models, lenvatinib inhibited 2 important intracellular signal pathways for angiogenesis: mitogen activated kinase (MAPK) and the PI3K/AKT/mTOR-S6K-S6 signal transduction pathway (hereafter referred to as mTOR-S6K-S6) (see figure 2 above). These 2 pathways are triggered by activated VEGFR and FGFR. Since cross-talk between the VEGF-signalling pathway and the FGF-signalling pathway possibly accelerates angiogenesis in the tumour, this mode of dual inhibition by lenvatinib may more effectively inhibit tumour angiogenesis. The anti-tumour activity of lenvatinib may also stem from a direct inhibitory effect on cellular growth of some tumours.

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase involved in integrating growth factor-activated and nutrient-sensing signals that regulate diverse cellular processes, including growth, survival, differentiation, autophagy, and metabolism. The mTOR kinase exerts its effects through the regulation of protein synthesis. Stimulation of the mTORC1 complex also results in increased VEGF-induced angiogenesis via activation of hypoxia-inducible factor 1α. The deregulation of mTOR signalling has been implicated in a number of cancer types.

Everolimus is an oral rapamycin analogue. Everolimus inhibits mTOR kinase activity downstream of the PI3K/AKT pathway by forming a complex with an intracellular protein, FKBP-12. This results in inhibition of mTORC1 and loss of mTORC1 substrate interactions. In addition, everolimus inhibits the expression of HIF-1 and reduces the expression of VEGF.

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 are expected to be based on its mechanism of action (inhibition of VEGFRs, FGFRs and PDGFRs). 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 and cardiotoxicity.

Genetic differences in PD response

Genotyping was performed in relation to metabolism of lenvatinib. Subject phenotype was determined using data derived from the Affymetrix drug metabolizing enzyme and transporter (DMET Plus®) microarray genotyping platform based on DNA extracted from human whole blood from consenting study subjects (both healthy volunteers and subjects with thyroid tumors; report CPMS-E7080-007pheno).

The enzymes chosen were ones for which a clear phenotype could be assigned to the SNP data, and, had been identified pre-clinically as being involved in the metabolism of lenvatinib (CYP1A2, CYP2A6, CYP3A4, CYP3A5) or of as potential interest (CYP2C19, study E7080-E044-104). Exposure data (steady state AUC normalized to a 24 mg dose) were determined from a previously developed population PK model for lenvatinib (CPMS-E7080-007R). None of the phenotypes of CYP1A2, CYP3A5, CYP2A6 or CYP2C19 have a significant impact on lenvatinib clearance. For the CYP3A4 phenotypes, 450 subjects from a total of 476 were classified as extensive metabolizers and 26 as unknown, therefore no correlative analyses was possible.

Genetic biomarkers (genetic constitutional variants in the VEGF pathway) could guide patient selection for treatment with the anti-VEGFR therapy. Higher responses to angiogenic drugs have been reported in familial VHL (von Hippel-Lindau) syndrome cases (i.e. RCC with germline *VHL* mutations). Given that loss of VHL expression in tumours is the most frequent molecular event in RCC. Choueri et al (2008) found that patients with an alteration of the VHL gene had a better response to anti-VEGF therapy.

Planned assessment in the Phase 2 study 205 included biomarker discovery and/or validation of blood or tumor biomarkers that may be useful to predict subject response to study drug, evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Glen et al (2015) concluded based on the results of the submitted Phase 2 study that elevated levels of VEGF and FGF23 confirmed lenvatinib target inhibition. Further studies on post-treatment changes in FGF23 levels in everolimus and the combination were considered warranted. The OS benefit observed with lenvatinib/everolimus combination in the high-baseline ANG2 subgroup suggested a potentially unique response, overcoming this otherwise poor prognostic characteristic. A complete report with results of these serum biomarker and pharmacogenetic studies will be submitted by the Applicant within 6 moths post-marketing (recommendation).

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 ($\Delta\Delta$QTcF) 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.

In the phase 3 study 303 in DTC patients, 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 for Lenvima). QTc prolongation is currently considered as an important potential risk addressed in the Risk Management plan. Post-marketing data from patients in DTC showed new cases with positive dechallenge. The electrocardiogram data from the Study 205 do show more cases of maximum QT increase from baseline (> 60 msec) and of maximum postbaseline value (> 500 msec) when lenvatinib is combined with everolimus, compared with lenvatinib alone. However, the QTcF values were machine-read. Furthermore, no case of torsades de pointes was reported, and no subject discontinued the drugs because of this event.

Given totality of data collected in patients in different indications and uncertainty regarding the effects of the combination (lenvatinib/everolimus) on QTc due to the limited number of patients exposed to date, the Applicant comitted to collect ECG data in further studies and to perform a concentration-response analysis for QTc in order to have a better understanding of the impact of the combination on QTc.

Relationship between plasma concentration and effect

Relationships between lenvatinib, everolimus and the lenvatinib/everolimus combination and efficacy and safety endpoints in RCC were explored using Population PK/PD analysis.

The following efficacy endpoints were explored: progression free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR), durable stable disease rate, and tumor shrinkage.

The following treatment emergent adverse events (TEAE) were considered: hypertension [during cycle 1], proteinuria, fatigue, decreased appetite, diarrhoea, nausea, vomiting, renal events, hypertriglyceridaemia and hyperglycaemia.

For each of the adverse events in the DTC submission including hypertension, the main analyses were based on data from Phase 3 Study 303, and binary logistic regression analysis was used. In all clinical studies with lenvatinib conducted to date, including DTC and RCC, blood pressure readings showed pronounced diurnal patterns. The time of day of blood pressure measurement is important in fitting indirect response model; however, the time of blood pressure measurement was not recorded in Study 205. Moreover, the effect of concomitant antihypertensive therapy needs to be considered in the complex indirect model using all the available blood pressure data. However, most subjects (78.7%) in the RCC Safety Set took concomitant antihypertensive therapy, which included a wide range of drugs, multiple classes of antihypertensive therapy, and combinations of drugs. Thus, the doses of each drug or class are not directly comparable. Moreover, antihypertensive treatment is highly individualized, with each subject responding differently to the same dose. Hence, the simple binary logistic regression model for hypertension as AE was used. In order to

minimize the bias from concomitant antihypertensive therapy in the exposure-response relationship for lenvatinib-related hypertension, data from the first 28 days (1 cycle) only were selected.

Data were not collected in a manner permitting more adequate modelling for toxicity endpoints such as hypertension, hypertriglyceridemia and hyperglycaemia. Empirical binary regression analysis as performed by the applicant is more suitable for descriptive purpose than for predictive use. They can only be acceptable in case there is no possibility to have more informative data as for fatigue, nausea, decreased appetite, and renal events. The Applicant is therefore strongly advised to collect (systolic and diastolic) blood pressure, triglyceridemia (and cholesterolemia), and glycaemia data in an appropriate manner that will allow developing predictive models with these endpoints modelled as continuous variables within study 218.

The impact of everolimus exposure on the different endpoints will be assessed in a more robust manner in future studies with the combination therapy of lenvatinib and everolimus (Studies 218 and 307).

The data that has been provided does not allow excluding a possible drug-drug interaction between lenvatinib and everolimus. The power analysis using clinical trial simulations tools for example would be a convincing evidence to show that the available data would allow detecting drug-drug interactions when applicable. The applicant is advised to perform power analysis as part of study design for study 218. This study will be designed in a manner permitting appropriate characterization of interactions between lenvatinib and everolimus if present.

PK/PD analyses for efficacy biomarkers and endpoints

In regard to PK/PD analyses for efficacy biomarkers and endpoints, planned assessment in the proposed Phase 2 study 218 will include the analysis the exposure (to everolimus and lenvatinib)-biomarkers-clinical endpoint relationships for drug efficacy and safety using integrative models and mechanism-based approaches supported by the knowledge about the disease pathophysiology and the drug pharmacology in order to provide better insight into doses selection that would allow an optimal benefit-risk ratio.

A binary logistic model for any adverse event leading to drug interruption, reduction or discontinuation as well as an Emax model for tumor growth inhibition model by lenvatinib and everolimus has been developed using data from RCC subjects from Study 205. The developed models were then used to simulate AEs and percentage of reduction in tumor size profiles and, subsequently, overall response rate at 6 months for different doses of lenvatinib in combination with everolimus 5 mg for dose selection in a planned study 218.

2.4.4. Discussion on clinical pharmacology

Pharmacodynamics

There is strong biologic rationale supported by available non-clinical data for combining VEGF receptor blockade by lenvatinib with mTOR inhibition by everolimus in the treatment of patients with metastatic RCC. Downstream signal transduction inhibition of the PTEN/Akt/mTOR pathway by everolimus may complement upstream VEGF receptor inhibition by either simple additive effects when both targets are inhibited or by downstream blockade of pathways if there is partial resistance to receptor inhibition.

PD biomarkers for efficacy and safety and PD interactions between lenvatinib and everolimus will be further investigated in Studies 218 and 307.

Pharmacokinetics

Several methodological flaws prevent to draw a clear conclusion with regards to the possible PK interaction between everolimus and lenvatinib. Further exploration on the potential interaction between lenvatinib and everolimus is needed and comprehensive data should be provided at the time of submission of results of pop PK analysis of post marketing studies (218 and 307) data.

This study 218 will evaluate PK interactions between lenvatinib and everolimus. It will also establish exposure-safety and exposure-efficacy relationships and better inform the choice of the optimal starting dose, the results of the integrated and mechanism-based PK/PD modelling should be submitted at the time of submission of the CSR. Data will be collected in a manner permitting adequate characterization of PK drug-drug interactions between lenvatinib and everolimus (see RMP).

Data from Study 307 will contribute to PK and PD analyses (see RMP).

In addition, as also required for Lenvima, an *in vivo* study (Study 109) with midazolam as a probe substrate for CYP3A4 will assess the lenvatinib potential for CYP3A4 induction/inhibition, including time-dependency inhibition. This is an Open-Label Phase 1 Study to Determine the Effect of Lenvatinib (E7080) on the Pharmacokinetics of Midazolam, a CYP3A4 Substrate, in subjects with Advanced Solid Tumours (see RMP).

In line with the Lenvima MA, no adjustment of starting dose is required in patients with mild or moderate renal impairment and no adjustment of starting dose is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. However in patients with severe hepatic or renal impairment, the recommended starting dose of lenvatinib should be reduced to 10 mg (see section 4.2 of the SmPC).

The following dose recommendation for hepatic impaired patients is provided in section 4.2 of the SmPC: "No data with the combination is available in patients with hepatic impairment. No adjustment of starting dose of the combination is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the everolimus SmPC. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk."

The following statement is provided in section 4.2 of the SmPC: "No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 10 mg of lenvatinib with 5 mg of everolimus 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".

In subjects with hepatic and with renal impairment it is unknown whether there is a change in the plasma protein binding. The correct determination of unbound drug concentrations should be provided to define the appropriate dose-adjustment in patients with severe hepatic and renal impairment

Hence, in order to define correctly the dose-adjustment in patients with severe hepatic and renal impairment, the MAH should conduct and submit the results of Study E7080-A001-010 (entitled "A Multicenter Phase 0 Study In Healthy Subjects As Well As Subjects With Either Hepatic Or Renal Impairment To Obtain Plasma To Assess In Vitro Lenvatinib Protein Binding") as reflected in the RMP (see section 2.7).

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.

Pharmacology

The potential interaction between lenvatinib and everolimus requires further exploration to address uncertainties from the available data. The applicant will therefore submit the results of:

- Study 218 will allow to assess two dosing regimens, PK and PK/PD of the two drugs and related drug-drug interactions between lenvatinib and everolimus. It will also establish exposure-safety and exposure-efficacy relationships and better inform the choice of the optimal starting dose. The protocol and the data analysis plan for PK/PD should be submitted by November 2016. The results of the integrated and mechanism-based PK/PD modelling should be submitted at the time of submission of the CSR. Please section 2.7 of the RMP.

- Study 307 will allow to further characterize PK and PK/PD of the two drugs and related interactions and to contribute to integrated and mechanism-based PK/PD modelling. The protocol and the data analysis plan for PK/PD should be submitted by November 2016. Please see section 2.7 of the RMP.

- Study 109 is requested to assess the lenvatinib potential for CYP3A4 induction/inhibition, including time-dependency inhibition (with midazolam as a probe substrate for CYP3A4). This is an Open-Label Phase 1 Study to Determine the Effect of Lenvatinib (E7080) on the Pharmacokinetics of Midazolam, a CYP3A4 substrate, in subjects with advanced Solid Tumors. Please see section 2.7 of the RMP.

In subjects with severe hepatic and renal impairment it is unknown whether there is a change in the plasma protein binding and what are the potential implications regarding dose-adjustment. The applicant will submit the results of Study 010, a multicenter Phase 0 study in healthy subjects as well as subjects with either hepatic or renal impairment to obtain plasma samples, to assess in vitro Lenvatinib protein binding and to determe unbound drug concentrations in order to define correctly the dose-adjustment in patients with severe hepatic and renal impairment (see RMP).

Pharmacodynamics

The pharmacodynamic biomarkers for efficacy and safety and PD interactions will be further explored in planned studies (studies 307 and 218).

2.5. Clinical efficacy

Four Phase 1 studies (E7080 E044-101, E7080-A001-102, E7080-J081-103, and E7080-J081-105) were conducted to determine the maximum tolerated dose (MTD) of lenvatinib and the optimal frequency of administration. These studies looked at administration of lenvatinib on its own (monotherapy).

The main study supporting the proposed indication, the study E7080-G000-205, had a Phase 1b part and a Phase-2 part. Dose escalation was performed, during the Phase 1b part of the study, to determine the MTD of lenvatinib in combination with everolimus. The Phase 2 part of the study 205 compare the combination of lenvatinib with everolimus against the use of lenvatinib on its own and everolimus on its own in the treatment of unresectable or metastatic renal cell carcinoma.

2.5.1. Dose response studies

Lenvatinib Monotherapy

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 subjects with advanced solid tumours. In this study, the MTD was determined to be 25 mg QD. Proteinuria was the dose limiting toxicity.

Study 102

Study 102 (monotherapy portion) was a dose escalation study with 2 dosing schedules (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 subjects with solid tumours or resistant/refractory lymphomas. The MTD was determined to be 10 mg BID with continuous dosing.

Study 103

Study 103 was a dose escalation study (0.5 to 20 mg BID) in which 27 subjects with advanced solid tumours were treated with lenvatinib BID in a 2 week on/1 week off schedule. In Study 103, the MTD was determined to be 13 mg BID. For lenvatinib monotherapy, the MTD from Study 101 (25 mg QD) correlated with a higher drug exposure (Cmax, AUC) compared with the MTD from Study 102 (10 mg BID) and was chosen for monotherapy to allow maximum anti-tumour activity with a degree of hypertension controllable by administration of antihypertensive therapy. To simplify drug administration, a dosage of 24 mg QD (two 10 mg capsules plus one 4-mg capsule) was selected as the dose for continued development of lenvatinib monotherapy.

Study 105

Study 105 was a study in 9 Japanese patients with solid tumours resistant to standard therapies. No dose-limiting toxicities were reported in either the 20-mg or 24-mg QD group on a once daily dose schedule.

Lenvatinib Combination with Everolimus (Phase 1b of study E7080-G000-205)

The primary objective of Phase 1b part of study 205 was to determine the dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of lenvatinib plus everolimus, and establish the optimal recommended Phase 2 (RP2) dose for the combination.

The dose for initiating combination therapy was a half of the recommended single-agent dose for each compound in RCC indication and in DTC indication; that is respectively, half of 10 mg everolimus dose (5 mg) and half of 24 mg lenvatinib dose (12 mg). Priority in terms of escalating dose was given to lenvatinib based on data from previous Phase 1 studies of lenvatinib in which subjects with metastatic RCC demonstrated a median PFS of approximately 9 months. The majority of these subjects (8 of 9) had already shown disease progression after prior anticancer medication. Of the 9 subjects treated, 5 (55%) achieved a PR and a further single subject (11%) had an unconfirmed PR when treated with lenvatinib.

The dose of lenvatinib was planned to be escalated sequentially (12 mg → 18 mg → 24 mg) in combination with a dose of everolimus of 5 mg or 10 mg (only with 24 mg lenvatinib) in subsequent cohorts.

The dose escalations were planned to proceed as shown in Figure 4 below.
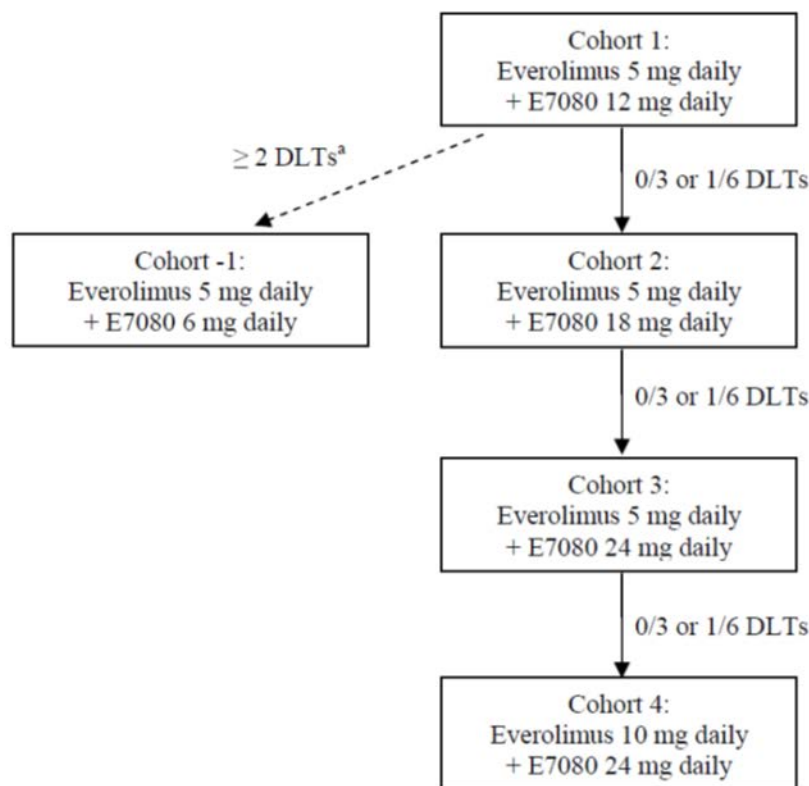
ᵃ where DLTs are considered E7080 related.

Figure 4: Phase 1b dose escalation design

A total of 20 subjects were enrolled across 3 cohorts, no recruitment occurred in Cohort 4.

Overall, four (4) subjects had DLTs as follows:

- Cohort 1: one subject with Grade 3 abdominal pain out of 7 treated subjects (n=1). As of the first 3 subjects enrolled one subject had a DLT, per dose escalation scheme, 3 more subjects were enrolled. There was no further DLT in this cohort. One subject had progressive disease early during Cycle 1 of treatment, was discontinued, and was replaced by another subject.

- Cohort 2: one subject with failure to administer >75% of planned dose, due to intolerable Grade 2 fatigue associated with Grade 1 GI reflux and Grade 1 anorexia out of 11 treated subjects. This occurred during the Cohort 2 expansion to confirm MTD and RP2 (n=1). Of the first 3 subjects enrolled into this cohort, none experienced a DLT allowing enrolment into the next dose level. Subsequent the outcome of Cohort 3, Cohort 2 was expanded to treat 8 more subjects.

- Cohort 3: both of the first 2 enrolled subjects had DLTs; one subject with Grade 3 nausea and vomiting, and one subject with failure to administer >75 % of the planned dose of study medication, due to intolerable Grade 2 stomatitis (n=2). Further enrolment of subjects was stopped in Cohort 3.

Testing the dose level Cohort 4 i.e. everolimus 10 mg in combination with lenvatinib 24 mg was considered not feasible.

The dose received by Cohort 2 subjects, i.e. lenvatinib 18 mg QD + everolimus 5 mg QD, was determined by to be both the MTD and the RP2 dose for the subsequent Phase 2 part of Study 205.

2.5.2. Main study

Phase 2 part of Study E7080-G000-205

The Phase 2 part of Study 205 was designed as an open-label, three-arm, randomized and controlled trial.

Eligible subjects were randomized in a 1:1:1 ratio to receive in either lenvatinib in combination with everolimus combination (Arm A), lenvatinib monotherapy (Arm B), or everolimus monotherapy (Arm C). Description of the study and its design are provided in Table 21 above and Figure 5 below.

Methods

Both the Phase 1b and Phase 2 portions of the study included a Pre-treatment Phase, a Treatment Phase, and an Extension Phase.
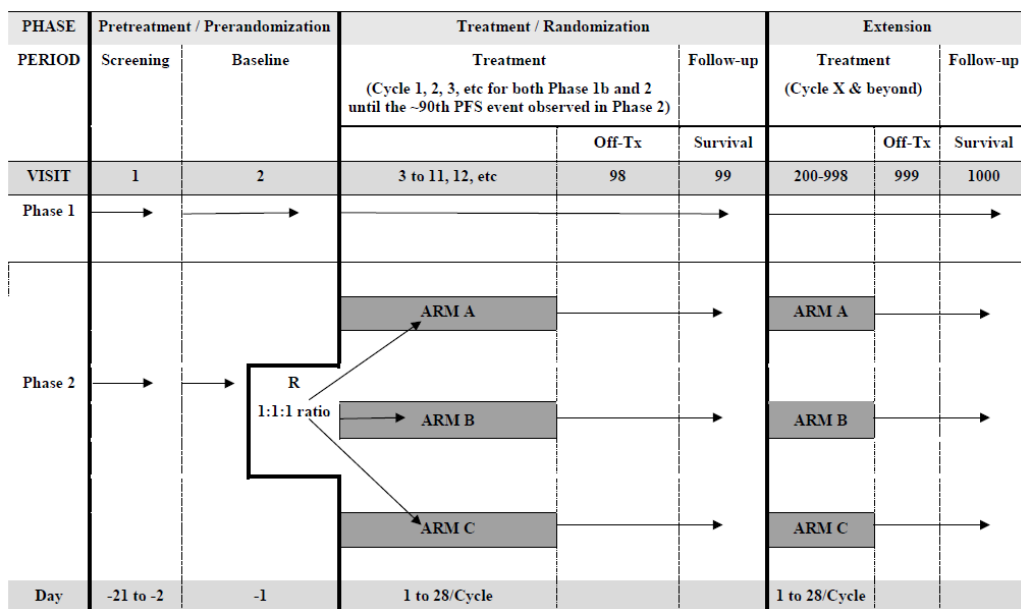
Figure 5: Study design

Tumour assessments using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 were performed during the Pre-randomization Phase and then every 8 weeks (or sooner if there was evidence of progressive disease) during the Treatment Phase, and in the Extension Phase by the Investigator-determined response assessments at each time point and represent the basis for the primary analysis of efficacy. As per agreement with the FDA and EMA, a post-hoc independent, blinded review of radiology assessments was performed to support the primary analysis of the Phase 2 portion of the study. The Treatment Phase ended at the data cut-off date for the primary efficacy analysis (13 Jun 2014). Subjects who were receiving study medication at the time of the data cut-off continued to receive the same treatment during the Extension Phase. Once the subjects were off treatment, they were followed for survival every 8 weeks. Subjects who discontinued study treatment before disease progression continued to undergo tumour assessments every 8 weeks until documentation of disease progression or start of another anticancer therapy. Subjects who were being followed for survival at the time of data cut-off (i.e. at the end of the Randomization Phase) continued to be followed for survival during the Follow-up Period of the Extension Phase.

•   **Study participants**

Eligible subjects had advanced unresectable RCC, histological or cytological confirmation of predominantly clear cell RCC, radiographic evidence of disease progression within 9 months of stopping prior therapy, 1 prior VEGF-targeted therapy, and measurable disease according to RECIST 1.1. Other key eligibility criteria are presented in Table 23 below.

Eligibility criteria

Table 23: Eligibility criteria in Study 205 (Phase 1b and 2)

Inclusion criteria	Exclusion criteria
1. Histologically confirmed diagnosis of renal cell carcinoma.	1. Phase 1b or Phase 2 specific per below:
2. Phase 1: Disease progression after prior vascular endothelial growth factor (VEGF)-targeted treatment.	- Phase 1b only: Subjects with untreated or unstable metastases to the central nervous system (CNS) are excluded. Subjects who have completed local therapy and have discontinued the use of steroids for this indication at least 4 weeks prior to commencing treatment and in whom stability has been proven by at least 2 CT or MRI scans obtained at least 4 weeks apart are eligible for Phase 1b only.
3. Phase 2: Histological or cytological confirmation of predominant clear cell RCC (original tissue diagnosis of RCC is acceptable).	
4. Documented evidence of unresectable advanced or metastatic RCC	- Phase 2 only: subjects with CNS (eg, brain or leptomeningeal) metastases are excluded.
5. Phase 2: Radiographic evidence of disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1), on or within 9 months of stopping prior therapy.	2. Phase 2 only: More than one prior disease progression episode on or after VEGF-targeted treatment for unresectable advanced or metastatic RCC (not including disease progression after VEGF-targeted adjuvant treatment).
6. Phase 2: One prior disease progression episode on or after vascular endothelial growth factor (VEGF)-targeted treatment (for example, but not limited to, sunitinib, sorafenib, pazopanib, bevacizumab, axitinib, vatalanib, AV951/ tivozanib) for unresectable advanced or metastatic RCC (not including disease progression after VEGF-targeted adjuvant treatment).	3. Phase 1b or Phase 2 specific per below: - Phase 1b only: Prior exposure to E7080 -Phase 2 only: Prior exposure to E7080 or mammalian target of rapamycin (mTOR) inhibitor
7. Phase 2: Measurable disease meeting the following criteria:	4. Subjects should not have received any anti-cancer 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 anti-cancer treatment.
a. At least 1 lesion of $\geq$ 1.5 cm in the longest diameter for a non-lymph node or $\geq$ 1.5 cm in the short-axis diameter for a lymph node which is serially measurable according to RECIST 1.1 using computerized tomography /magnetic resonance imaging (CT/MRI) or photography	5. Major surgery within 3 weeks prior to the first dose of study drug
b. Lesions that have had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.	6. Subjects having > 1+ proteinuria on urinalysis will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein $\geq$ 1 g/24-hour will be ineligible.
	7. Uncontrolled diabetes as defined by fasting

8. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

9. Adequately controlled blood pressure with or without antihypertensive medications, defined as blood pressure (BP) $\geq$ 150/90 mmHg at screening and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1.

10. Adequate renal function defined as calculated creatinine clearance $\geq$ 30 mL/min per the Cockcroft and Gault formula.

11. Adequate bone marrow function: absolute neutrophil count (ANC) $\geq$ 1500/mm3 ($\geq$ 1.5 x 103/µL); platelets $\geq$ 100,000/mm3 ($\geq$ 100 x 109/L); hemoglobin $\geq$ 9.0 g/dL.

12. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) $\leq$ 1.5.

13. Adequate liver function: bilirubin $\leq$ 1.5 x the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome; alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) $\leq$ 3 x ULN ($\leq$ 5 x ULN if subject has liver metastases).

14. Males or females age $\geq$ 18 years at the time of informed consent.

15. All females must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [β-hCG]) at the Screening Visit (and/or within 72 hours of the first dose of study drug). Females of child-bearing potential, if not practicing total abstinence or having a vasectomised partner with confirmed azoospermia, must agree to use two highly effective methods of contraception (shortened).

16. Male subjects who are partners of women of childbearing potential must use a condom + spermicide and their female partners if of childbearing potential must use a highly effective

serum glucose > 1.5 x ULN.

8. Fasting total cholesterol > 7.75 mmol/L (> 300 mg/dl).

9. Fasting triglyceride level > 2.5 x ULN.

10. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of E7080 or everolimus.

11. Significant cardiovascular impairment: history of congestive heart failure

greater than New York Heart Association (NYHA) Class II (Appendix 4), unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug; or cardiac arrhythmia requiring medical treatment.

12. Prolongation of QTc interval to > 480 msec.

13. Bleeding disorder or thrombotic disorder requiring anticoagulant therapy, such as warfarin, or similar agents requiring therapeutic international normalized ratio (INR) monitoring (treatment with low molecular weight heparin [LMWH] is allowed).

14. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.

15. Active infection (any infection requiring treatment)

16. Phase 2 only: Active malignancy (except for renal cell carcinoma, melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months.

17. Known intolerance to any of the study drugs (or any of the excipients) and/or known hypersensitivity to rapamycins (eg, sirolimus, everolimus, temsirolimus) or any of the excipients.

18. Phase 1b only: Subjects who discontinued prior tyrosine kinase inhibitor due to toxicity will

method of contraception beginning at least 1 menstrual cycle prior to starting study drug(s), throughout the entire study period, and for 30 days after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile. 17. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.	be ineligible. 19. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial. 20. Females who are pregnant or breastfeeding. 21. Medical need for the continued use of potent inhibitors of CYP3A4

- **Treatments**

The RP2 dose determined in the Phase 1b part of the study was further investigated in the open-label, randomized Phase 2 part, in which eligible subjects were randomized into 3 arms in a 1:1:1 ratio to receive:

1) 18 mg/day lenvatinib + 5 mg/day everolimus (RP2 dose; combination arm A),

2) lenvatinib 24 mg/day (lenvatinib arm B), or

3) everolimus 10 mg/day (everolimus arm C).

In both Phase 1b and Phase 2, lenvatinib capsules and everolimus tablets were self-administered orally by the subjects in continuous 28-day cycles. For subjects receiving combination therapy, the doses of everolimus and lenvatinib were taken at the same time. Dose interruption, dose reduction, or treatment discontinuation were allowed according to the protocol-specified dose management scheme for subjects who experienced lenvatinib toxicity and for subjects in the combination arm who experienced everolimus toxicity. Subjects who experienced everolimus-related toxicity in the everolimus arm had dose adjustments (temporary dose interruptions and no dose reduction below 5 mg) according to prescribing information.

Prior therapy: see 'Baseline data' subsection

Concomitant therapy

All subjects received at least 1 concomitant medication.

Concomitant antihypertensive medications were taken by a higher percentage of subjects in the combination and lenvatinib arms (82.4% and 86.5%, respectively) than the everolimus arm (60.0%). The most frequently reported concomitant antihypertensive medication was amlodipine (49.0% combination arm; 67.3% lenvatinib arm; 28.0% everolimus arm).

Concomitant therapy with the anti-propulsive agent loperamide for diarrhea was highest in the combination arm (58.8%, 30 subjects), followed by the lenvatinib arm (46.2%, 24 subjects), and was lowest in the everolimus arm 12.0% (6 subjects).

Concomitant therapy with thyroid preparations was used most often in the combination and lenvatinib arms, and less often in the everolimus arm. Thyroid Preparations were used in 27 (52.9%), 32 (61.5%) and 10 (20.0%), respectively, and levothyroxine in 27 (52.9%), 32 (61.5%) and 10 (20.0%), respectively.

- **Objectives**

Primary objective

- To compare the progression-free survival (PFS) of 1) lenvatinib in combination with everolimus at the RP2 dose once daily (QD) (Arm A) and 2) single-agent lenvatinib 24 mg QD (Arm B) to single-agent everolimus 10 mg QD (Arm C) in subjects with unresectable advanced or metastatic RCC and disease progression following 1 prior VEGF-targeted treatment.

Secondary objectives

- To determine the tolerability and safety profile of lenvatinib in combination with everolimus and of single-agent lenvatinib.

- To compare PFS of Arm A, lenvatinib/everolimus combination therapy to Arm B, single-agent lenvatinib.

- To assess overall survival (OS).

- To assess objective response rate (ORR) (complete response [CR] +partial response [PR]); disease control rate (DCR: CR + PR + stable disease [SD]); durable SD (SD ⩾23 weeks) and clinical benefit rate (CBR: CR, PR + durable SD rate).

- To assess PK profiles (e.g. AUC, Cmax) of lenvatinib and everolimus during single-agent and combination therapy.

- To assess PK and PD relationship of lenvatinib as single-agent and combination therapy.

- **Outcomes/endpoints**

Primary efficacy endpoint:

PFS defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first). The PFS endpoint was based on investigator assessments using RECIST version 1.1. PFS censoring rules were based on the FDA guidelines. The date of objective disease progression was defined as the earliest date of radiological disease progression, as assessed by the investigator based on radiographic images.

The primary comparisons for PFS were the combination arm versus the everolimus arm and the lenvatinib arm versus the everolimus arm.

Secondary efficacy endpoints:

- OS defined as the time from the date of randomization until date of death from any cause. Subjects who were lost to follow-up or alive at the date of data cut-off (13 Jun 2014 for the collection of the data for

the primary outcome measure, 10 Dec 2014 cut-off for the first OS update, and 31 Jul 2015 cut-off for the second OS update) were censored at the date the subject was last known alive.

- Objective response rate defined as the proportion of subjects who had best overall response of complete response or partial response (CR + PR) (assessed by investigators).

- Disease control rate (DCR: CR + PR + SD; SD had to be ≥7 weeks after randomization).

- Durable SD (SD ≥23 weeks) rate and clinical benefit rate (CBR: CR, PR + durable SD rate).

- **Sample size**

For the Phase 2 part, the primary basis for the sample size determination was a comparison of the progression-free survival based on the following assumptions.

The assumed median PFS for everolimus 10 mg was 5 months based on the historical data. A minimum of a 50% increase in the median PFS (i.e., achieving a median PFS of at least 7.5 months in the investigational Arms A or B) relative to the median PFS of 5 months for everolimus as single agent, would be considered worthy of further investigation. Given that there were no prior clinical data available for the combination of lenvatinib plus everolimus, and limited data for lenvatinib alone in the target population, it was deemed appropriate to consider a hazard ratio (HR) of 0.67 as a clinically meaningful improvement in PFS. The planned sample size for the primary analysis required a total of at least 90 PFS events to be observed across all 3 treatment groups and at least 60 PFS events to be observed for each of the comparisons of the combination versus the everolimus arm, and the lenvatinib versus the everolimus arm. PFS events for each of the comparisons of the combination versus the everolimus arm, and the lenvatinib versus the everolimus arm events were required to detect a HR of 0.67 with 70% power using an (1-sided) alpha of 0.15 for the comparison of the combination arm (and lenvatinib arm) versus the everolimus arm. This trial was not designed and powered to primarily investigate differences in OS.

Sample size rationale for the everolimus/Lenvatinib Phase 2 PK Sub Analysis Set assumed a between-subject CV on logarithmically transformed plasma Lenvatinib clearance of 40%. A sample size of 9 to 12 completing subjects in each study arm will provide 68% to 80% power to detect a 1.5-fold change in exposure between Lenvatinib administered alone and Lenvatinib in combination with everolimus.

- **Randomisation**

Randomization was performed centrally by an Interactive Voice Response System (IVRS) vendor.

The IVRS randomly assigned eligible subjects in a 1:1:1 ratio to receive either lenvatinib 18 mg QD plus everolimus 5 mg QD (N=51; combination arm), lenvatinib 24 mg QD (N=52; lenvatinib arm), or everolimus 10 mg, QD (N=50; everolimus arm).

Randomisation was stratified by baseline haemoglobin (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium levels (≥10 mg/dL vs <10 mg/dL).

- **Blinding (masking)**

This was an open-label study; therefore blinding procedures were not applicable.

- **Statistical methods**

Primary efficacy endpoint: PFS

The primary efficacy variable was PFS, defined as the time from the date of randomisation to the date of first documentation of disease progression or death. The primary PFS was based on investigator review data using RECIST 1.1. As requested by the FDA and EMA, a post-hoc independent, blinded review of radiology assessments was performed to support the primary analysis.

The primary comparisons for PFS were the combination arm versus the everolimus arm and the lenvatinib arm versus the everolimus arm. No multiplicity adjustment was planned at the inception of the study. Each null hypothesis of no difference in PFS was evaluated using the stratified log-rank test, and tested at a (2-sided) α =0.05 stratified by haemoglobin level ($\leqslant$13 g/dL vs >13 g/dL for males and $\leqslant$11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium ($\geqslant$10 mg/dL vs <10 mg/dL).

There was no prespecified ordering in testing these hypotheses and each null hypothesis was tested at a nominal α=0.05. Kaplan-Meier (K-M) estimates were used to estimate the median PFS.

Hazard ratio (HR) between treatment groups and corresponding 95% CI were estimated using stratified Cox regression model with treatment as a factor. The Efron method was used for correction for tied events. Three-month, 6-month, 9-month and 1-year PFS rates were estimated from K-M and corresponding 95% CI were calculated using the Greenwood formula. Originally, a pre-planned sensitivity analysis to the primary analysis was planned adjusting for ECOG PS (0 vs. 1) as a factor in the stratified Cox regression model. As decided after database lock, sensitivity analysis to the primary analysis was performed with ECOG PS (0 vs 1) as an additional stratum in the stratified Cox regression model. For subgroup analyses of PFS, the (unstratified) Cox proportional hazard model was used adjusting for treatment and subgroup as factors and treatment-by-subgroup as an interaction term in the model. The HR was estimated for each treatment comparison along with 95% CI. The interaction test across different levels of the subgroup for each treatment comparison was also performed by setting up an appropriate contrast for the corresponding interaction test.

Secondary endpoints: OS, ORR, DCR, CBR, and durable SD

The secondary efficacy variables were OS, ORR, DCR, CBR, and durable SD (SD $\geqslant$23 weeks). The Median survival time (OS) and the cumulative probability of survival at 12 months, 18 months, and 24 months were calculated using K-M estimates for each treatment arm and presented with 2-sided 95% CIs. K-M survival probabilities for each arm were plotted over time. OS was measured from the date of randomization until date of death from any cause.

Subjects who were lost to follow-up and those who were alive at the date of data cut-off were censored. Planned analyses were performed to test null hypothesis of treatment difference in OS at a nominal significance level of 0.05 (2-sided) using the stratified log-rank test using stratification factors. The stratified Cox proportional hazard model was performed to estimate HR between treatment groups and their corresponding 95% CI.

Objective response rate (ORR), DCR, CBR, and durable SD rate were calculated with exact 95% CIs using the method of Clopper and Pearson Ad-hoc analyses were performed to estimate the crude rate ratio of each treatment comparison and to compute P values using the Fisher's exact (2-sided) test..

Results

- ## Participant flow

Of the 235 subjects who were screened 82 (34.9%) subjects were screen failures (majority failed to meet entry criteria) and 153 (65.1%) subjects were randomly assigned to treatment as follows: 51 subjects with combination, 52 subjects with lenvatinib and 50 with everolimus. (see Figure 6 below)
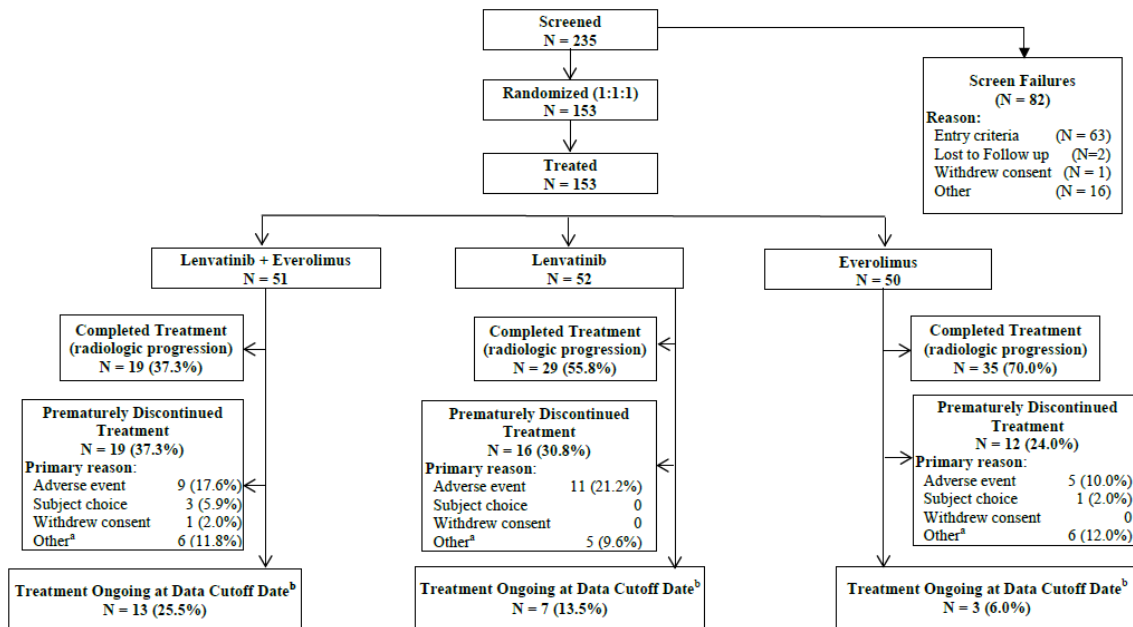
Figure 6: Flowchart of Subject Disposition in Phase 2 part of Study 205

- ## Recruitment

The Phase 2 portion of Study 205 was conducted between 16 March 2012 (when first subject signed informed consent) and 13 June 2014 (data cut-off date for the primary analysis). A total of 37 sites were involved: 24 in Europe (the Czech Republic, Poland, Spain, and the UK) and 13 in the US.

- ## Conduct of the study

The original protocol was dated 19 April 2010. Four protocol amendments were issued until the data cut-off date (13 Jun 2014). Amendment 05 (11 Nov 2014) was implemented after the cut-off date for the primary analysis; therefore subject data included in the study report of Phase 2 part of the study were not affected. The final SAP (dated 20 May 2014) included more technical details regarding the original planned analyses in the protocol.

Overall, 9 major protocol deviations were reported for 9 (5.9%) subjects (2 subjects in the combination arm, 3 subjects in the lenvatinib arm, and 4 subjects in the everolimus arm). One subject in the lenvatinib arm did not have predominant clear cell RCC and 7 subjects (2 in the combination, 2 in the lenvatinib, and 3 in the everolimus arm) did not have any brain scans performed. The remaining deviation was in a subject in the

everolimus arm who took lenvatinib 10 mg QD for 1 cycle as a result of a dispensing error at the site. This major protocol deviation occurred at a site in the UK, and was reported to the Medicines and Healthcare Products Regulatory Agency on 3 May 2013. The Applicant did not perform the Per Protocol analysis to assess the robustness of the primary analysis since the majority of the deviations (7 out of 8 subjects in total) were not considered necessary to be excluded from the Per Protocol Analysis Set.

- **Baseline data**

Table 24: Demographic and Baseline Characteristics – FAS - Phase 2 - Study 205

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)	Total (N=153)
Age (years)				
Mean (SD)	61.7 (8.2)	63.3 (8.6)	58.9 (9.2)	61.3 (8.8)
Median	61.0	64.0	58.5	61.0
Min, Max	44, 79	41, 79	37, 77	37, 79
Age Group (years), n (%)				
≤65	31 (60.8)	29 (55.8)	39 (78.0)	99 (64.7)
>65	20 (39.2)	23 (44.2)	11 (22.0)	54 (35.3)
Sex, n (%)				
Male	35 (68.6)	39 (75.0)	38 (76.0)	112 (73.2)
Female	16 (31.4)	13 (25.0)	12 (24.0)	41 (26.8)
Race, n (%)				
White	50 (98.0)	52 (100.0)	47 (94.0)	149 (97.4)
Asian	1 (2.0)	0	2 (4.0)	3 (2.0)
Chinese	1 (2.0)	0	0	1 (0.7)
Unknown[a]	0	0	1 (2.0)	1 (0.7)
Ethnicity, n (%)				
Hispanic or Latino	5 (9.8)	2 (3.8)	3 (6.0)	10 (6.5)
Not Hispanic or Latino	46 (90.2)	50 (96.2)	46 (92.0)	142 (92.8)
Unknown[a]	0	0	1 (2.0)	1 (0.7)
ECOG Performance Status, n (%)				
0	27 (52.9)	29 (55.8)	28 (56.0)	84 (54.9)
1	24 (47.1)	23 (44.2)	22 (44.0)	69 (45.1)
Weight (kg)				
Mean (SD)	79.4 (13.5)	80.4 (15.6)	82.7 (15.5)	80.8 (14.9)
Median	80.2	76.6	81.1	80.0
Min, Max	55.0, 116.0	53.0, 129.5	50.0, 128.0	50.0, 129.5
Haemoglobin, n (%)				
≤13 g/dL for males or ≤11.5 g/dL for females	33 (64.7)	36 (69.2)	31 (62.0)	100 (65.4)
>13 g/dL for males or >11.5 g/dL for females	18 (35.3)	16 (30.8)	19 (38.0)	53 (34.6)
Corrected serum calcium, n (%)				
≥10 mg/dL	6 (11.8)	8 (15.4)	8 (16.0)	22 (14.4)
<10 mg/dL	45 (88.2)	44 (84.6)	42 (84.0)	131 (85.6)
MSKCC Risk Group				
Favourable (Risk Score = 0)	12 (23.5)	11 (21.2)	12 (24.0)	-
Intermediate (Risk Score = 1)	19 (37.3)	18 (34.6)	19 (38.0)	-
Poor (Risk Score ≥2)	20 (39.2)	23 (44.2)	19 (38.0)	-
Heng's Risk Group				

Table 24:   Demographic and Baseline Characteristics – FAS - Phase 2 - Study 205

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)	Total (N=153)
Favourable (Risk Score = 0)	8 (16.0)	7 (13.5)	9 (18.0)	-
Intermediate (Risk Score = 1 or 2)	32 (64.0)	33 (63.5)	29 (58.0)	-
Poor (Risk Score ≥3)	10 (20.0)	12 (23.1)	12 (24.0)	-

Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.

ECOG = Eastern Cooperative Oncology Group, FAS = full analysis dataset, Max = maximum, Min = minimum, MSKCC = Memorial Sloan Kettering Cancer Centre, NYHA = New York Heart Association, SD = standard deviation.

a: Race and ethnicity was not recorded for 1 subject in the everolimus arm and is reported as unknown.

Table 25: Number and sites of metastases

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg N=52)	Everolimus 10 mg (N=50)	Total (N=153)
Based on independent review assessment				
Number of Metastases, n(%)				
0	1 (2.0)	1 (1.9)	1 (2.0)	3 (2.0)
1	7 (13.7)	3 (5.8)	5 (10.0)	15 (9.8)
2	13 (25.5)	12 (23.1)	7 (14.0)	32 (20.9)
>=3	30 (58.8)	36 (69.2)	37 (74.0)	103 (67.3)
Site of Metastases, n(%)				
Bone	16 (31.4)	23 (44.2)	17 (34.0)	56 (36.6)
Liver	15 (29.4)	17 (32.7)	16 (32.0)	48 (31.4)
Lung	34 (66.7)	35 (67.3)	39 (78.0)	108 (70.6)
Lymph Nodes	29 (56.9)	32 (61.5)	31 (62.0)	92 (60.1)
Visceral Organs	41 (80.4)	49 (94.2)	44 (88.0)	134 (87.6)
Based on Investigator assessment				
Number of Metastases, n(%)				
1	18 (35)	9 (17)	5 (10)	32 (21)
2	15 (29)	15 (29)	15 (30)	45 (30)
>=3	18 (35)	28 (54)	30 (60)	76 (50)
Site of Metastases, n(%)				
Bone	12 (24)	13 (25)	16 (32)	41 (27)
Liver	10 (20)	14 (27)	13 (26)	37 (24)
Lung	27 (53)	35 (67)	35 (70)	97 (63)
Lymph Nodes	25 (49)	31 (60)	33 (66)	89 (58)

Prior therapy

Nephrectomy was reported in the medical history of 135 subjects (88% overall; respectively 86.3%, 82.7% and 96% in the combination, lenvatinib and everolimus arms). The proportion of subjects who received prior radiotherapy was respectively 11.8%, 21.2% and 22.0% in the combination, lenvatinib and everolimus arms.

All patients received 1 previous VEGF-targeted therapy and the most frequent agent being sunitinib (64.7%) and pazopanib (22.9%). Only 5 subjects received prior treatment with checkpoint inhibitors (anti-PD1).

Table 26:   Prior Cancer Therapies – FAS - Phase 2 – Study 205

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)	Total (N=153)
Prior Therapy Regimens, n (%)				
1	44 (86.3)	46 (88.5)	41 (82.0)	131 (85.6)
2	6 (11.8)	4 (7.7)	9 (18.0)	19 (12.4)
3	1 (2.0)	2 (3.8)	0	3 (2.0)
Prior VEGF-Targeted Therapy, n (%)				
Yes	51 (100.0)	52 (100.0)	50 (100.0)	153 (100.0)
1	51 (100.0)	52 (100.0)	50 (100.0)	153 (100.0)
Type of Prior VEGF Targeted Therapy [a], n (%)				
Adjuvant[b]	5 (9.8)	5 (9.6)	1 (2.0)	11 (7.2)
Neo-Adjuvant[b]	0	0	2 (4.0)	2 (1.3)
Therapeutic	40 (78.4)	43 (82.7)	44 (88.0)	127 (83.0)
Maintenance	5 (9.8)	4 (7.7)	3 (6.0)	12 (7.8)
Unknown	1 (2.0)	0	0	1 (0.7)
Prior Biologic Agent[c], n (%)				
Yes	8 (15.7)	7 (13.5)	13 (26.0)	28 (18.3)
1	7 (13.7)	4 (7.7)	12 (24.0)	23 (15.0)
2	1 (2.0)	3 (5.8)	1 (2.0)	5 (3.3)
No	43 (84.3)	45 (86.5)	37 (74.0)	125 (81.7)
Previous VEGF Targeted Therapy [a], n (%)				
• ANTINEOPLASTIC AGENTS	1 (2.0)	0	1 (2.0)	2 (1.3)
• AXITINIB	1 (2.0)	2 (3.8)	0	3 (2.0)
• BEVACIZUMAB	0	1 (1.9)	4 (8.0)	5 (3.3)
• PAZOPANIB	9 (17.6)	13 (25.0)	13 (26.0)	35 (22.9)
• SORAFENIB	1 (2.0)	0	2 (4.0)	3 (2.0)
• SUNITINIB	36 (70.6)	35 (67.3)	28 (56.0)	99 (64.7)
• TIVOZANIB	3 (5.9)	1 (1.9)	2 (4.0)	6 (3.9)
Duration of Most Recent VEGF Targeted Therapy (Months)				
Mean (SD)	17.2 (15.22)	17.6 (14.21)	12.4 (10.94)	15.7 (13.72)
Median	9.8	14.5	8.9	11.5
Q1, Q3	5.6, 25.3	7.6, 25.6	5.3, 15.8	5.6, 21.9
Time from End of Most Recent VEGF Targeted Therapy to Study Entry (Months)				
Mean (SD)	2.3 (2.31)	2.2 (2.52)	3.2 (5.35)	2.6 (3.65)
Median	1.5	1.3	1.4	1.4
Q1, Q3	1.1, 2.3	0.9, 2.2	1.2, 2.9	1.0, 2.3
Best Response for Most Recent VEGF Targeted therapy, n (%)				
Complete Response	1 (2.0)	0	0	1 (0.7)
Partial Response	14 (27.5)	10 (19.2)	10 (20.0)	34 (22.2)
Stable Disease	20 (39.2)	28 (53.8)	21 (42.0)	69 (45.1)
Progressive Disease	7 (13.7)	10 (19.2)	15 (30.0)	32 (20.9)
Not Evaluable	3 (5.9)	1 (1.9)	0	4 (2.6)
Not Applicable	3 (5.9)	2 (3.8)	2 (4.0)	7 (4.6)
Unknown	3 (5.9)	1 (1.9)	2 (4.0)	6 (3.9)

Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group. Previous therapy excludes radiotherapy and surgery. Data cut-off date = 13 Jun 2014. CSR = clinical study report, FAS = full analysis dataset, VEGF = vascular endothelial growth factor.

a: Subjects could have been counted in multiple categories.
b: After database lock it was determined that these subjects received prior therapy for metastatic disease, and not as adjuvant or neoadjuvant treatment.
c: Interferon, interleukin 2, or other experimental biologic agents such as anti-PD1 antibody, anti-angiopoietin peptibody, peptide vaccine, anti-CD20 antibody.

A total of 47 subjects discontinued treatment for a reason other than progressive disease; of these 18 subjects received subsequent anticancer therapy. The type and and time to first subsequent anticancer therapy received are provided in table below.

Table 27: Post-treatment anticancer therapy for subjects who discontinued treatment for a reason other than progressive disease – FAS – Phase 2 – Study 205

	Lenvatinib 18 mg + Everolimus 5 mg	Lenvatinib 24 mg	Everolimus 10 mg
Subjects who discontinued treatment for a reason other than PD, n (%)[a]	19 (37.3%)	16 (30.8%)	12 (24.0%)
Subjects who took anticancer therapy after treatment discontinuation, n (%)[a]	7 (36.8)	6 (37.5)	5 (41.7)
Type of subsequent anticancer treatment received			
mTOR Inhibitor:	4 (21.1)	2 (12.5)	1 (8.3)
Everolimus	4 (21.1)	2 (12.5)	1 (8.3)
VEGF Inhibitor:	2 (10.5)	2 (12.5)	3 (25.0)
Axitinib	2 (10.5)	0	2 (16.7)
Bevacizumab	0	1 (6.3)	0
Cabozantinib	0	1 (6.3)	0
Sunitinib	0	0	1 (8.3)
Monoclonal Antibody[b]	1 (5.3)	2 (12.5)	0
Cytokine:	0	0	1 (8.3)
Interferon	0	0	1 (8.3)
Duration to start of subsequent therapy (days)[c]			
Number of subjects	7	6	5
Mean (SD)	56.1 (58.5)	54.2 (27.4)	68.0 (71.2)
Median	29	47	36
Q1, Q3	22, 91	34, 76	13, 135
Min, Max	16, 176	25, 96	2, 154

AE = adverse event, max = maximum, min = minimum, mTOR = mammalian target of rapamycin, PD = progressive disease, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, VEGF = vascular endothelial growth factor. a: Denominator includes all subjects who discontinued treatment for non-PD reasons.b: Name of monoclonal antibody was not specified.c: Duration from end of treatment = date of first dose of new therapy - date of last dose of study drug + 1.

- **Numbers analysed**

All 153 subjects were treated. Data cut-off occurred as planned on 13 Jun 2014 following the occurrence of 101 PFS events among the 3 treatment arms, 63 PFS events in the combination versus everolimus arm, and 75 PFS events in the lenvatinib versus everolimus arm.

At the time of data cut-off, a higher number of subjects in the combination arm (13; 25.5%) were still on treatment than in the lenvatinib or everolimus arms (7; 13.5% and 3; 6.0%, respectively). Fewer subjects ended treatment due to disease progression in the combination arm (19; 37.3%) and lenvatinib arms (29; 55.8%) than in the everolimus arm (35; 70.0%).

As of the date of data cut-off, 69 (45.0%) subjects (31 in the combination arm, 23 in the lenvatinib arm, and 15 in the everolimus arm) remained in the study, including 23 (15.0%) subjects who were still receiving study treatment.

All 153 subjects who were randomized and treated were included in the FAS and the Safety Analysis Set.

- **Outcomes and estimation**

Primary endpoint

Progression Free Survival
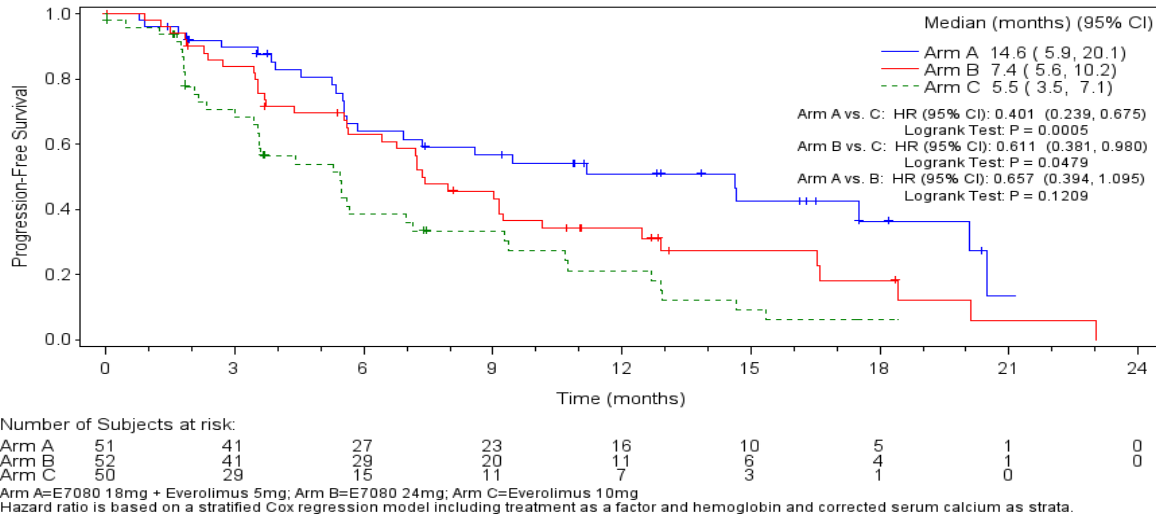
Data cut-off date = 13 Jun 2014.

Hazard ratio is based on a stratified Cox regression model including treatment as a factor and haemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events.

Median PFS is based the Kaplan-Meier method and 95% CI is based on the Greenwood formula using log-log transformation.

Figure 7: Kaplan-Meier Plot of Progression-Free Survival – Full Analysis Set – Study 205 Phase 2 – Investigator Assessment

At the data cutoff of 13 Jun 2014 for the primary analysis, 101 PFS events occurred among the 3 treatment arms. Per arm, the primary endpoint PFS analysis is based on 26 PFS events (51%) in the combination arm vs. 37 events (74%) for everolimus. For lenvatinib arm, 38 events (73%) were observed.

The lenvatinib/everolimus combination significantly prolonged PFS compared with everolimus (median 14.6 months [95% CI: 5.9, 20.1] vs. 5.5 months [95% CI: 3.5, 7.1]; HR=0.40, 95% CI: 0.24, 0.68; p=0.0005).

Secondary endpoints

Overall Survival

At the data cut-off for the final PFS analysis (13 Jun 2014), fewer subjects had died in the combination arm (19; 37.3%) than in the lenvatinib arm (26; 50.0%) and in the everolimus arm (26; 52.0%). At the date of the first OS update (10 Dec 2014), 24 (47.1%) subjects in the combination arm, 31 (59.6%) in the lenvatinib arm and 33 (66.0%) subjects in the everolimus arm had died. At the date of the second OS update (31 July 2015), 32 (62.7%) subjects in the combination arm, 34 (65.4%) in the lenvatinib arm and 37 (74.0%) subjects in the everolimus arm had died.

Table 28: Summary of the results of the Overall Survival Analyses –Full Analysis Set

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)
Primary Analysis			
Median (months) (95% CI)	25.5 (20.8, 25.5)	18.4 (13.3, NE)	17.5 (11.8, NE)
Hazard Ratio (95% CI) vs everolimus	0.55 (0.30, 1.01)	0.74 (0.42, 1.31)	0.74 (0.40, 1.36)
P-value vs everolimus	0.06	0.29	0.30
First Update (10 Dec 2014)			
Median (months) (95% CI)	25.5 (16.4, NE)	19.1 (13.6, 26.2)	15.4 (11.8, 19.6)
Hazard Ratio (95% CI) vs everolimus	0.51 (0.30, 0.88)	0.68 (0.41, 1.14)	0.75 (0.43, 1.30
P-value vs everolimus	0.02	0.12	0.32
Second Update (31 Jul 2015)			
Median (months) (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
Hazard Ratio (95% CI) vs everolimus	0.59 (0.36, 0.96)	0.75 (0.47, 1.20)	0.79 (0.48, 1.30)
P-value vs everolimus	0.06	0.13	0.31

A - Overall Survival at the planned time point (13 Jun 2014)
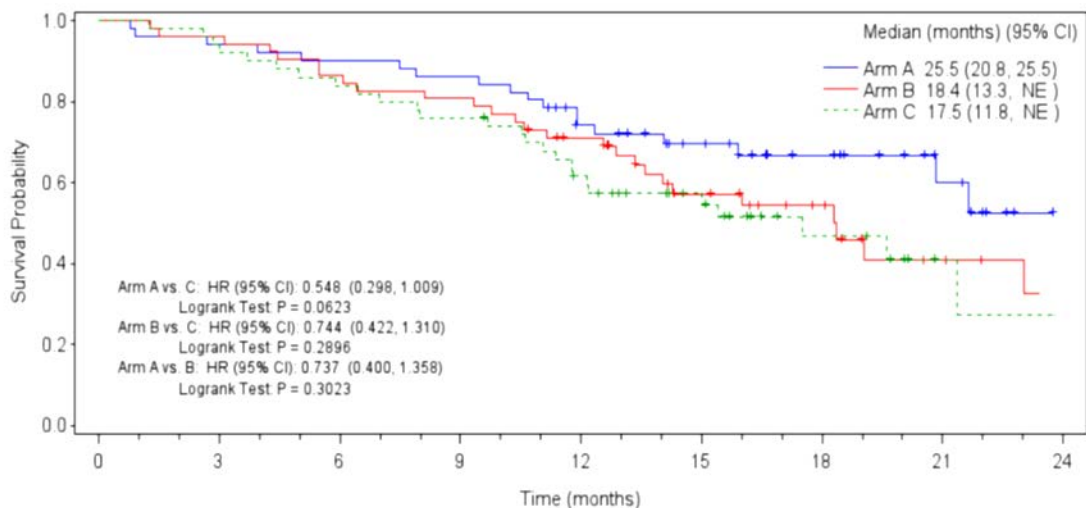
B – Overall Survival at the first updated time point (10 Dec 2014)

C - Overall Survival at the second updated time point (31 Jul 2015)
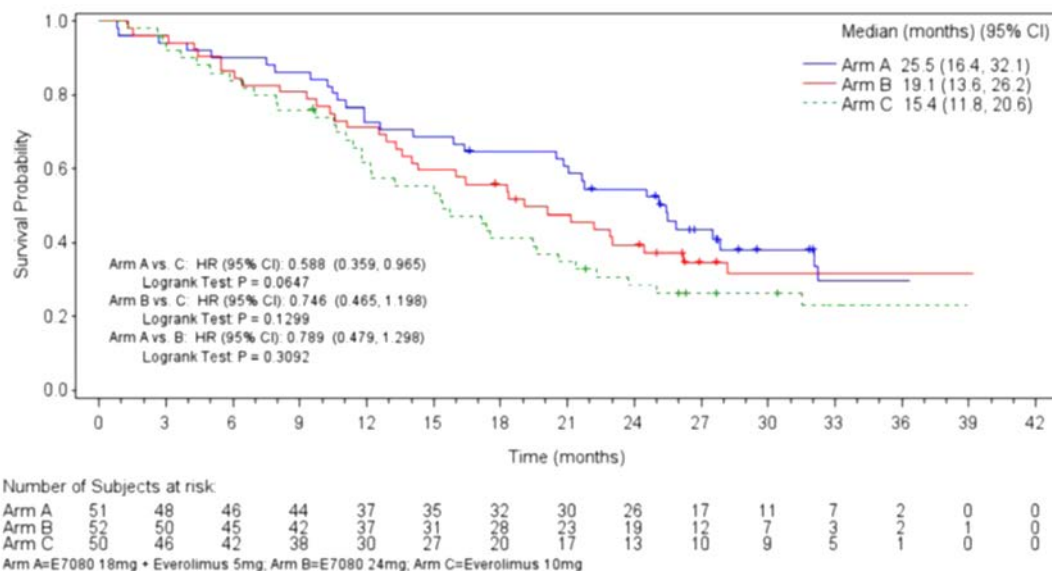
Figure 8: Kaplan-Meier Plots of Overall Survival at the Planned (A), First updated (B) and Second Updated (C) Time points – Full Analysis Set

Tumour Response (ORR, DCR, CBR and durable stable disease rate)

Table 29: Summary of Tumour Response – Investigator Assessment – Full Analysis Set

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)
Complete response (CR), n (%)	1 (2.0)	0	0
Partial response (PR), n (%)	21 (41.2)	14 a (26.9)	3 (6.0)
Stable disease (SD), n (%)	21 (41.2)	27 (51.9)	31 (62.0)
Progressive disease (PD), n (%)	2 (3.9)	3 (5.8)	12 (24.0)
Not evaluable, n (%)[a]	0	2 (3.8)	0
Not assessable, n (%)[b]	6 (11.8)	6 (11.5)	4 (8.0)

Data cut-off date = 13 Jun 2014. Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.
CI = confidence interval, CSR = clinical study report, FAS = full analysis dataset, NE = not estimable.

a: After database lock, it was discovered that 1 of the 14 subjects did not have a PR

Table 30: Summary of ORR, DCR, CBR and durable stable disease rate– Investigator Assessment – Full Analysis Set

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)
Objective Response Rate (CR + PR), n (%)	22 (43.1)	14 (26.9)	3 (6.0)
95% CI of objective response rate[c]	(29.3, 57.8)	(15.6, 41.0)	(1.3, 16.5)
Rate Ratio, P Value[d]			
Lenvatinib 18 mg + Everolimus 5 mg vs. Everolimus 10 mg	7.2 (2.3, 22.5), P<0.0001		
Lenvatinib 24 mg vs. Everolimus 10 mg		4.5 (1.4, 14.7), P=0.0067	
Lenvatinib 18 mg + Everolimus 5 mg vs. lenvatinib 24 mg	1.6 (0.9, 2.8), P=0.1007		
Duration of Objective Response (months)e			
Median (95% CI)	13.0 (3.7, NE)	7.5 (3.8, NE)	8.5 (7.5, 9.4)
1st Quartile, 3rd Quartile	3.7, NE	6.3, 12.9	7.5, 9.4
Disease Control Rate (CR + PR + SD ≥7 weeks), n (%)	43 (84.3)	41 (78.8)	34 (68.0)
95% CI of disease control rate[c]	(71.4, 93.0)	(65.3, 88.9)	(53.3, 80.5)
Durable Stable Disease Rate (SD ≥23 weeks), n (%)	13 (25.5)	20 (38.5)	18 (36.0)
95% CI of durable stable disease rate[c]	(14.3, 39.6)	(25.3, 53.0)	(22.9, 50.8)
Clinical Benefit Rate (CR + PR + durable SD), n (%)	35 (68.6)	34 (65.4)	21 (42.0)
95% CI of clinical benefit rate[c]	(54.1, 80.9)	(50.9, 78.0)	(28.2, 56.8)

Data cut-off date = 13 Jun 2014. Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.
CI = confidence interval, CSR = clinical study report, FAS = full analysis dataset, NE = not estimable.
a: Not Evaluable indicates best overall response of Not Evaluable or SD shorter than 7 weeks postrandomization.
b: Not Assessable includes early deaths and subjects with progression who discontinued treatment or were censored prior to tumour assessment scans. All of these subjects were counted as failures.
c: 95% CI was constructed using the method of Clopper and Pearson.
d: Analyses performed after database lock. Rate ratio is based on the normal approximation and P value is based on the 2 sided Fisher's exact P value.

e: Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula.
f: After database lock, it was discovered that 1 of the 14 subjects (10222003) did not have a PR

A highly statistically significant and clinically meaningful increase in ORR (43.1% vs 6%; RR=7.2 [95% CI: 2.3, 22.5]; p<0.001) was observed for the lenvatinib/everolimus combination over everolimus. In the combination arm, one subject was achieving a CR and 21 subjects a PR versus 3 subjects a PR in the everolimus arm.

Three responses, all PRs, were unconfirmed in the combination arm in the primary ORR analysis; thus, excluding these 3 responses, the confirmed ORR in the combination arm was 37% (n=19/51).

- **Ancillary analyses**

Retrospective analyses by blinded Independent Imaging Review (IIR)

As per request by and in agreement with the FDA and EMA, a retrospective analyses of the tumour scans was conducted to investigate whether the results of a blinded IIR supported the efficacy results (PFS, BOR) based on the investigator-assessed tumour responses.

The primary objective of this blinded IIR review was to compare the PFS of the combination arm versus the everolimus arm, and of the lenvatinib arm versus the everolimus arm as assessed by IIR tumour assessments, using the FAS. The secondary objectives were to assess BOR, including ORR, DCR, SD, durable SD, and CBR; and to compare PFS of the combination arm to the lenvatinib arm as assessed by IIR using the FAS.

Table 31: Summary of Key Efficacy Results Obtained by Investigator or Blinded Independent Imaging Review

	Investigator Assessment		Independent Imaging Assessment	
	Lenvatinib 18mg +Everolimus 5mg	Everolimus 10mg	Lenvatinib 18mg +Everolimus 5mg	Everolimus 10mg
PFS – Primary Analysis				
Median (months) (95% CI)[a]	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)	12.8 (7.4, 17.5)	5.6 (3.6, 9.3)
Hazard Ratio (95% CI)[b] p-value	0.40 (0.24, 0.68) 0.0005		0.45 (0.26, 0.79) 0.0029	
PFS – Sensitivity Analysis[c]				
Median (months) (95% CI)[a]	10.7 (5.6, 17.5)	5.5 (3.6, 6.4)	11.1 (7.4, 13.0)	5.3 (3.6, 6.4)
Hazard Ratio (95% CI)[b] p-value	0.40 (0.25, 0.63) 0.0001		0.48 (0.30, 0.76) 0.0017	
ORR (CR+PR)				
n (%) (95% CI)[d]	22 (43.1) (29.3, 57.8)	3 (6.0) (1.3, 16.5)	18 (35.3) (22.4, 49.9)	0 (0.0, 7.1)
Rate Ratio[e] (95%CI) p-value	7.2 (2.3, 22.5) <0.0001		NE (NE, NE) <0.0001	

	Investigator Assessment		Independent Imaging Assessment	
	Lenvatinib 24mg	**Everolimus 10mg**	**Lenvatinib 24mg**	**Everolimus 10mg**
PFS – Primary Analysis				
Median (months) (95% CI)[a]	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)	9.0 (5.6, 10.2)	5.6 (3.6, 9.3)
Hazard Ratio (95% CI)[b] p-value	0.61 (0.38, 0.98) 0.0479		0.62 (0.37, 1.04) 0.1175	
PFS – Sensitivity Analysis[c]				
Median (months) (95% CI)[a]	7.4 (5.6, 9.2)	5.5 (3.6, 6.4)	9.0 (5.5, 10.2)	5.3 (3.6, 6.4)
Hazard Ratio (95% CI)[b] p-value	0.61 (0.40, 0.94) 0.0262		0.66 (0.42, 1.03) 0.0838	
ORR (CR+PR)				
n (%) (95% CI)[d]	14 (26.9) (15.6, 41.0)	3 (6.0) (1.3, 16.5)	20 (38.5) (25.3, 53.0)	0 (0.0, 7.1)
Rate Ratio[e] (95%CI) p-value	4.5 (1.4, 14.7) 0.0067		NE (NE, NE) <0.0001	

	Investigator Assessment		Independent Imaging Assessment	
	Lenvatinib 18mg +Everolimus 5mg	**Lenvatinib 24mg**	**Lenvatinib 18mg +Everolimus 5mg**	**Lenvatinib 24mg**
PFS – Primary Analysis				
Median (months) (95% CI)[a]	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	12.8 (7.4, 17.5)	9.0 (5.6, 10.2)
Hazard Ratio (95% CI)[b] p-value	0.66 (0.39, 1.10) 0.1209		0.72 (0.42, 1.24) 0.3194	
PFS – Sensitivity Analysis[c]				
Median (months) (95% CI)[a]	10.7 (5.6, 17.5)	7.4 (5.6, 9.2)	11.1 (7.4, 13.0)	9.0 (5.5, 10.2)
Hazard Ratio (95% CI)[b] p-value	0.66 (0.41, 1.05) 0.0723		0.73 (0.46, 1.16) 0.1591	
ORR (CR+PR)				
n (%) (95% CI)[d]	22 (43.1) (29.3, 57.8)	14 (26.9) (15.6, 41.0)	18 (35.3) (22.4, 49.9)	20 (38.5) (25.3, 53.0)
Rate Ratio[e] (95%CI) p-value	1.6 (0.9, 2.8) 0.1007		0.9 (0.6, 1.5) 0.8388	

a: Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation; b: Stratified HR is based on a stratified Cox regression mode including treatment as covariate factor and baseline ECOG scores, haemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events. P-values based on stratified Log Rank test; c: All documented radiological disease progression or deaths prior to data cut-off date were used as events; d: 95% CI was constructed using the method of Clopper and Pearson. e: Rate ratio is based on the normal approximation and p-values is based on 2-sided Fisher's exact p-value.

Progression-free Survival by IIR
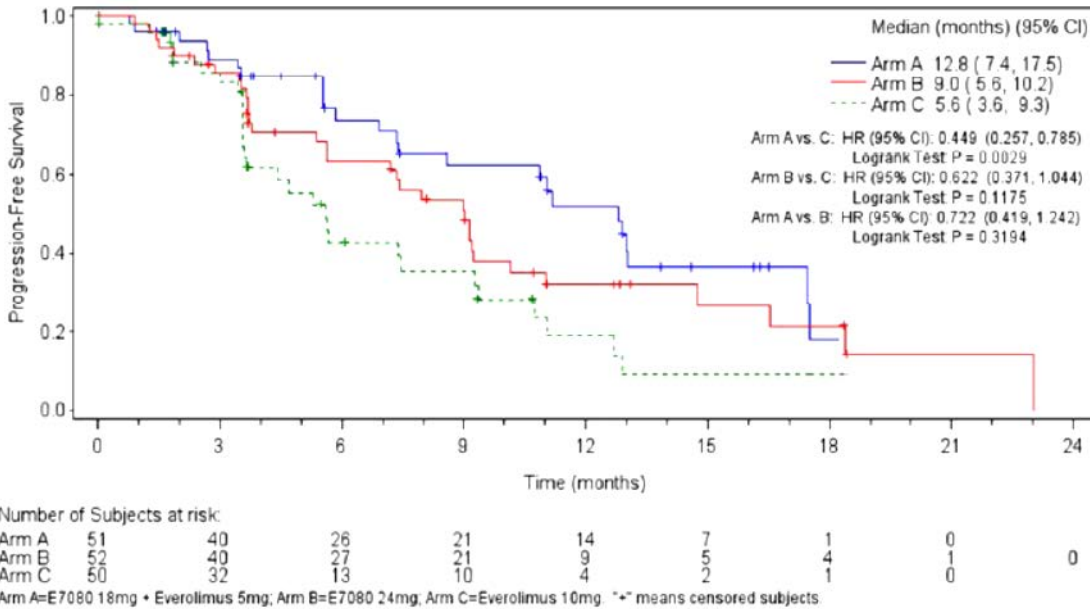
Figure 9: Kaplan-Meier Plot of Progression-Free Survival per Blinded Independent Imaging Review (IIR) — Full Analysis Set

Concordance analyses of PFS and BOR

Table 32: Progression-Free Survival assessed by Investigator and Blinded Independent Imaging Review — Full Analysis Set

	Investigator review	Independent review, n (%)	
		PD	Non PD
Overall (N=153)	PD	73 (47.7)	28 (18.3)
	Non PD	12 (7.8)	40 (26.1)
Lenvatinib 18 mg + Everolimus 5 mg (N=51)	PD	18 (35.3)	7 (13.7)
	Non PD	7 (13.7)	19 (37.3)
Lenvatinib 24 mg (N=52)	PD	28 (53.8)	8 (15.4)
	Non PD	12 (7.8)	40 (26.1)
Everolimus 10 mg (N=50)	PD	27 (54)	13 (26)
	Non PD	1 (2.0)	9 (18.0)

PD=progressive disease

Percentages are based on the total number of randomised subjects in the relevant treatment group. Tumor response was based on RECIST 1.1. Independent Reviewer responses were per the review selected by the adjudicator.

Overall, the blinded independent and the investigator results agreed on 73.8% (47.7% + 26.1%) of cases, as to whether the subject had progressed or not. Agreement was not observed for PD versus non PD in 26.1% (18.3% + 7.8%) of subjects. For 18.3% of subjects, the investigator assessed progressive disease, but this was not observed by the independent reviewer. Conversely, in 7.8% of subjects, the independent reviewer observed PD, but the investigator did not.

A high level of agreement in BOR was observed between the blinded IIR and investigator assessments. Results of the 3 treatment arms were consistent with that of the overall agreement (weighted Kappa range: 0.65 to 0.73).

Sensitivity analyses for Progression-Free Survival

A pre-planned sensitivity analysis, decided to be done after database lock, was performed using ECOG PS (0 vs 1) as an additional stratum in the stratified Cox regression model used for the primary analysis.

Table 33: Progression-Free Survival based on Investigator Assessment: Pre-planned Sensitivity Analysis based on ECOG PS as a stratum – Full Analysis Set

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Everolimus 10 mg (N=50)
Median PFS (95% CI)a	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)
P-value Based on Stratified Log-rank Test	0.0012	
Stratified Hazard Ratio (95% CI)	0.43 (0.25, 0.72)	

a: Point estimates are based on Kaplan-Meier method and 95% CI are based on Greenwood formula using log-log transformation. ECOG = Eastern Cooperative Oncology Group.   Data cut-off date = 13 Jun 2014

Ad hoc sensitivity analyses of PFS

Four ad hoc sensitivity analyses of PFS were performed to ensure that the results of the primary analysis were robust:

1. Inclusion of clinical progression as a PFS event,

2. Censored subjects with documented progression based solely on pleural effusion as a new lesion,

3. Included all subjects with disease progression and deaths as events even if a subject had missing assessments, received other anticancer therapy or treatment discontinuation due to reasons other than PD

4. Censored subjects based on the end of treatment with the last dose as entered on the study medication page of the CRF.

The results of the ad-hoc analyses were generally consistent with those of the primary PFS analysis.

Table 34: Progression-Free Survival: Ad hoc Sensitivity Analyses – Full Analysis Set

	Sensitivity Analyses							
	Clinical Progression as a PFS Event[a]		Censor Subjects with PD based only on Pleural Effusion[b]		All PDs and Deaths as PFS Events[c]		Last Dose Date from Study Medication CRF[d]	
	Lenv 18 mg + Ever 5 mg	Ever 10 mg	Lenv 18 mg + Ever 5 mg	Ever 10 mg	Lenv 18 mg + Ever 5 mg	Ever 10 mg	Lenv 18 mg + Ever 5 mg	Ever 10 mg
Median PFS months (95%CI)[e]	11.1 (5.6,17.5)	5.5 (3.6, 7.6)	14.6 (5.9,20.1)	5.5 (3.5, 7.1)	10.7 (5.6,17.5)	5.5 (3.6, 6.4)	14.7 (5.6,20.5)	5.5 (3.6, 9.3)
p-value	0.0010		0.0005		0.0001		0.0011	

based on Stratified Log Rank Test				
Stratified HR (95% CI)[f]	0.44 (0.27, 0.72)	0.40 (0.24, 0.67)	0.40 (0.25, 0.63)	0.41 (0.24, 071)

Data cut-off date = 13 Jun 2014 Lenv – lenvatinib, Ever – everolimus
The tumour assessment was based on RECIST 1.1 criteria. Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group. CRF = case report form.
a: Included clinical progression as a PFS event.
b: Censored subjects with documented progression based solely on pleural effusion as a new lesion (1 subject met this criterion).
c: Included all subjects with disease progression and deaths as events even if a subject had missing assessments, received other anticancer therapy or treatment discontinuation due to reasons other than PD (Appendix Figure 2.7.3-1)
d: Censored subjects based on the end of treatment with the last dose date as entered on the study medication page of the CRF, rather than the investigator's stated end of treatment date from the disposition page of the CRF (Appendix Figure 2.7.3-2).
e: Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.
f: Stratified hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and baseline ECOG scores, haemoglobin, and corrected serum calcium as strata. The Efron method was used for correction for tied events.

Planned Subgroup Analyses of Progression-Free Survival (Investigator)

Subgroup analyses of PFS were considered exploratory and are limited by the sample size within each subgroup.

	Events/N				Median (Months)	
	Arm A	Arm C		HR (95% CI)	Arm A	Arm C
Overall	26/51	37/50		0.401(0.239,0.675)	14.6	5.5
Hemoglobin Group						
<= 13 or 11.5(female) g/dL	18/33	23/31		0.456(0.244,0.851)	5.6	5.3
> 13 or 11.5(female) g/dL	8/18	14/19		0.248(0.102,0.600)	20.1	7.0
Corrected serum calcium						
>= 10 mg/dL	4/6	6/8		0.262(0.072,0.955)	12.9	5.3
< 10 mg/dL	22/45	31/42		0.395(0.227,0.686)	14.6	5.5
Age group						
<=65 years	15/31	30/39		0.333(0.178,0.625)	14.7	5.5
> 65 years	11/20	7/11		0.399(0.153,1.039)	7.4	5.6
Sex						
male	16/35	30/38		0.312(0.169,0.577)	14.6	5.3
female	10/16	7/12		0.610(0.230,1.617)	9.5	9.3
ECOG performance status						
0	11/27	22/28		0.271(0.130,0.562)	17.5	5.5
1	15/24	15/22		0.499(0.241,1.032)	5.6	3.6
Region						
Europe	23/46	24/36		0.385(0.215,0.692)	14.6	5.5
United States	3/5	13/14		0.464(0.132,1.637)	11.2	5.3
Baseline hypertension status						
yes	18/36	26/36		0.502(0.273,0.920)	9.5	5.7
no	8/15	11/14		0.140(0.054,0.360)	14.7	2.3

Favors Arm A   Favors Arm C

0.01   0.1   1   10

Hazard Ratio and 95% Confidence Interval

Arm A=E7080 18mg + Everolimus 5mg; Arm B=E7080 24mg; Arm C=Everolimus 10mg
Hazard ratio is based on a Cox regression model including treatment, subgroup and treatment-by-subgroup interaction as factors.

Figure 10: Forest Plot of Hazard Ratio for Progression-Free Survival by Subgroup – Full Analysis Set

Analyses by prior VEGF-targeted therapy

Based on the results of a post-hoc exploratory analysis in a limited number of patients per subgroup, the positive effect on PFS was seen regardless of which prior VEGF-targeted therapy was used: sunitinib (Hazard ratio [HR] = 0.356 [95% CI: 0.188, 0.674] or other therapies (HR = 0.350 [95% CI: 0.148, 0.828]). The results for OS also favored the combination arm over everolimus arm: sunitinib (Hazard ratio [HR] = 0.532 [95% CI: 0.303, 0.935] or other therapies (HR = 0.639 [95% CI: 0.255, 1.604]), with median OS: 21.8 and 32.1 months, with sunitinib and other therapy, respectively, in combination arm; and 12 and 21.4 months, with sunitinib and other therapy, respectively, in everolimus arm. When OS was calculated from the starting date of prior VEGF-targeted therapy, results for OS also favored the combination arm over everolimus arm.

A-Prior VEGF-targeted therapy: sunitinib
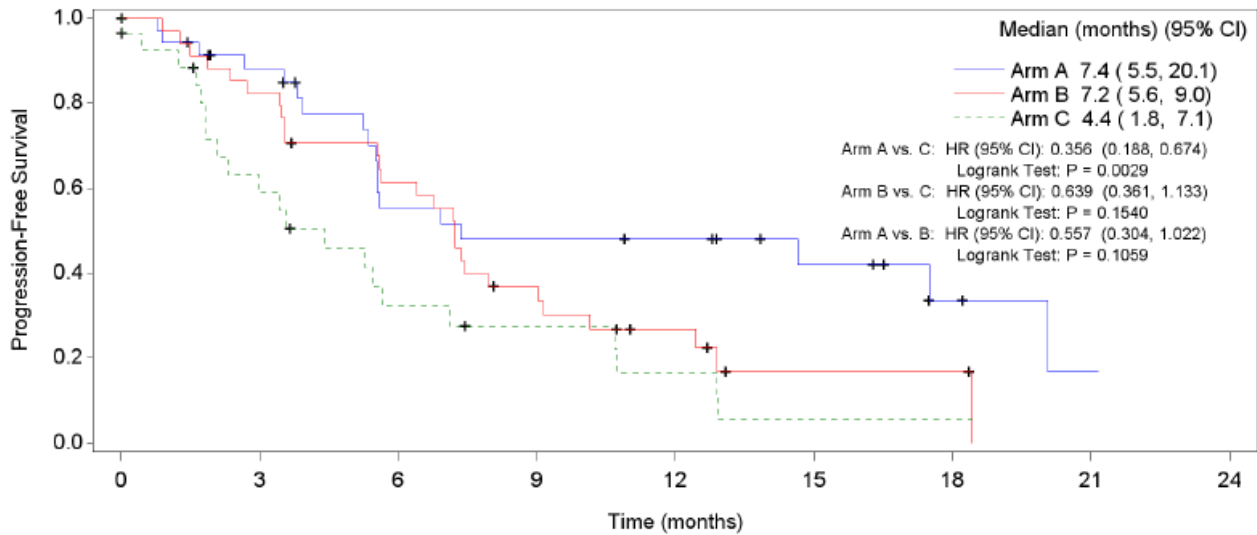
B-Prior VEGR targeted therapy: Other therapy
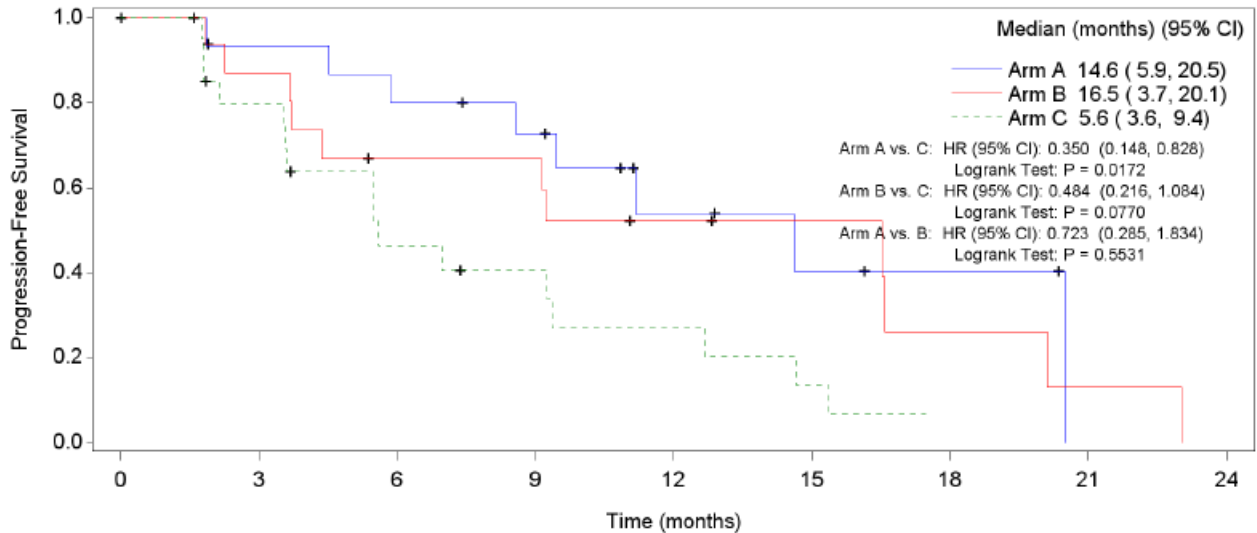
Arm A – combination, Arm B – lenvatinib, Arm C - everolimus

Figure 11: Kaplan-Meier Plot for PFS in Subjects Who Received Prior Sunitinib or Prior Vascular Endothelial Growth Factor-Targeted Therapy Other than Sunitinib in the Combination and Everolimus Treatment Arms – Study 205 Phase 2 (Full Analysis Set)

In subjects who received prior sunitinib, the ORR was 41.7% (n=15/36) for the combination arm versus 3.6% (n=1/28) for the everolimus arm as of the 13 Jun 2014 cutoff date for the primary PFS analysis. In subjects who received a different prior VEGF-targeted therapy, the ORR again favored the combination arm (46.7%, n=7/15) compared with 9.1% (n=2/22) for everolimus.

The median duration of treatment in Study 205 was 5.0 months (min, max: 0.7, 33.0) and 4.1 months (0.3, 33.6) in subjects who received prior sunitinib in the combination (n=36) and everolimus (n=28) arms, respectively, and 11.0 months (1.0, 26.5) and 4.7 months (0.6, 29.9) in subjects who received prior VEGF-targeted therapy other than sunitinib in the combination (n=15) and everolimus (n=22) arms, respectively.

In subjects who received prior sunitinib, the median duration of response was 13.0 months (95% CI: 3.7, NE) for the 15 responders in the combination arm and 9.4 months for the single responder in the everolimus arm as of the 13 Jun 2014 cutoff date for the primary PFS analysis. In subjects who received a different prior VEGF-targeted therapy, the median duration of response was 12.8 months (95% CI: 2.7, NE) for the 7 responders in the combination arm and 7.5 months (95% CI: NE, NE) for the 2 responders in the everolimus arm.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	54/153		
Non Controlled trials			

A total of 54 subjects >65years of age was enrolled in the pivotal Phase 2 portion of Study 205.
A clear benefit from treatment with lenvatinib/everolimus relative to everolimus for PFS could be observed (HR: 0.399, 95%CI: 0.153-1.039). However, the number of subjects was low and not evenly balanced between the lenvatinib/everolimus arm (n=20) and everolimus arm (n=11).

Analysis performed across trials (pooled analyses AND meta-analysis)

NA

Supportive study

Efficacy evaluation was an exploratory objective in the Phase 1b part of Study 205. The exploratory endpoint was the Best Overall Response (BOR). All 20 enrolled subjects were evaluated for objective response,

assessed by the investigator using RECIST 1.1. A total of 4 subjects, 2 in Cohort 3 and 1 in each of Cohorts 1 and 2, had their BOR categorized as "unknown." These subjects discontinued study medication early due to AEs or subject withdrew.

Table 35: Best Overall Tumour Response (BOR) of all subjects per investigator assessment by cohort - Phase 1b – Study 205 (Safety Analysis Set)

Objective Response (n, %)	Cohort 1 Lenvatinib 12 mg + Everolimus 5 mg (N=7)	Cohort 2 Lenvatinib 18 mg + Everolimus 5 mg (N=11)	Cohort 3 Lenvatinib 24 mg + Everolimus 5 mg (N=2)
Objective Response Rate (CR + PR), n (%)	2 (28.6)	4 (36.4)	0
Complete Response (CR)	0	1 (9.1)	0
Partial Response (PR)	2 (28.6)	3 (27.3)	0
Stable Disease (SD)	4 (57.1)	5 (45.5)	0
Progressive Disease (PD)	0	1 (9.1)	0
Unknown[a] n (%)	1 (14.3)	1 (9.1)	2 (100.0)

a: Unknown means no post-baseline data were available.

• **Summary of main efficacy results**

The following tables summarise the key efficacy results from the study 205 supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 36: Summary of efficacy for phase 2 portion of trial E7080-G000-205

Title: An Open-Label, Multicenter Phase 1b/2 Study of E7080 Alone, and in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment		
Study identifier	E7080-G000-205	
Design	randomized, open-label, multicenter	
	Duration of main phase:	16 March 2012 - 13 June 2014 (data cut-off date for the primary endpoint)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	ongoing
Hypothesis	superiority	
Treatments groups	Lenvatinib/everolimus combination	Lenvatinib 18 mg QD + everolimus 5 mg QD, orally, continuous 28-day cycles N=51
	Lenvatinib	Lenvatinib 24 mg QD, orally, continuous 28-day cycles N=52

	Everolimus		Everolimus 10 mg QD, orally, continuous 28-day cycles N=50
Endpoints and definitions	Primary endpoint	PFS	The time from randomization to the date of the first documented tumour progression as determined by the investigator using RECIST 1.1 criteria, or death due to any cause. Comparison groups: - combination vs. single-agent everolimus - single-agent lenvatinib vs. single-agent everolimus
	Secondary endpoint	PFS	The time from randomization to the date of the first documented tumour progression as determined by the investigator using RECIST 1.1 criteria, or death due to any cause. Comparison group: - combination vs. single-agent lenvatinib
	Secondary endpoint	OS	The time from the date of randomization until the date of death of any cause
	Secondary endpoint	ORR	The proportion of subjects who had best overall response (BOR) of complete response (CR) or partial response (PR) as determined by the investigator using RECIST 1.1 criteria
Database lock	13 June 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (=Full Analysis Set) *13 June 2014*		
Descriptive statistics and estimate variability	Treatment group	Lenvatinib 18 mg Everolimus 5 mg Combination	Lenvatinib 24 mg	Everolimus 10 mg
	Number of subjects	51	52	50
	PFS (months) median	14.6	7.4	5.5
	95% CI	(5.9,20.1)	(5.6,10.2)	(3.5,7.1)
	Number of deaths (%)	19 (37.3)	26 (50.0)	26 (52.0)
	OS (months) median	25.5	18.4	17.5
	95% CI	(20.8,25.5)	(13.3,NE)	(11.8,NE)
	ORR (%)	43.1	26.9	6.0

	95% CI		(29.3,57.8)	(15.6,41.0)	(1.3,16.5)
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Combination vs. Everolimus		
		HR	0.40		
		95% CI	(0.24,0.68)		
		P-value	0.0005		
		Comparison groups	Lenvatinib vs. Everolimus		
		HR	0.61		
		95% C	(0.38,0.98)		
		P-value	0.0479		
	Secondary endpoint PFS	Comparison groups	Combination vs. Lenvatinib		
		HR	0.66		
		95% C	(0.39,1.10)		
		P-value	0.1209		
	Secondary endpoint OS	Comparison groups	Combination vs. Everolimus		
		HR	0.55		
		95% CI	(0.30,1.01)		
		P-value	0.0623		
		Comparison groups	Lenvatinib vs. Everolimus		
		HR	0.74		
		95% CI	(0.42,1.31)		
		P-value	0.2896		
		Comparison groups	Combination vs. Lenvatinib		
		HR	0.70		
		95% CI	(0.40,1.36)		
		P-value	0.3023		
	Secondary endpoint ORR	Comparison groups	Combination vs. Everolimus		
		RR	7.2		
		95% CI	(2.3,22.5)		
		P-value	<0.0001		
		Comparison groups	Lenvatinib vs. Everolimus		
		RR	4.5		
		95% CI	(1.4,14.7)		

		P-value	0.0067
		Comparison groups	Combination vs. Lenvatinib
		RR	1.6
		95% CI	(0.9,2.8)
		P-value	0.1007

Notes	

Analysis description	**Ancillary *ad hoc* analysis: Includes results of independent review (for PFS and ORR);**
PFS combination vs. everolimus	Median (months); (95% CI)	12.8 (7.4, 17.5) Vs. 5.6 (3.6, 9.3)
	Hazard Ratio (95% CI)	0.45 (0.26, 0.79)
	p-value	0.003
ORR combination vs. everolimus	ORR: n (%)	18 (35.3) vs. 0
	Rate Ratio (95% CI)	NE (NE, NE)
	p-value	<0.0001

Analysis description	**Updated analysis for OS: First Update**		
Analysis population and time point description	Intent to treat **10 Dec 2014**		
Descriptive statistics and estimate variability	Treatment group	Lenvatinib 18 mg Everolimus 5 mg Combination	Lenvatinib 24 mg	Everolimus 10 mg
	Number of subjects	51	52	50
	Number of deaths (%)	24 (47.1)	31 (59.6)	33 (66.0)
	OS (months) median	25.5	19.1	15.4
	95% CI	(16.4,NE)	(13.6,26.2)	(11.8,19.6)

Effect estimate per comparison	Secondary endpoint OS	Comparison groups	Combination vs. Everolimus
		HR	0.51
		95% CI	(0.30,0.88)
		P-value	0.0242
		Comparison groups	Lenvatinib vs. Everolimus
		HR	0.68
		95% C	(0.41,1.14)
		P-value	0.1181
		Comparison groups	Combination vs. Lenvatinib
		HR	0.75

	95% C	(0.43,1.30)		
	P-value	0.3157		
Analysis description	**Updated analysis for OS: Second Update**			
Analysis population and time point description	Intent to treat *31 Jul 2015*			
Descriptive statistics and estimate variability	Treatment group	Lenvatinib 18 mg Everolimus 5 mg Combination	Lenvatinib 24 mg	Everolimus 10 mg
	Number of subjects	51	52	50
	Number of deaths (%)	32 (62.7)	34 (65.4)	37 (74.0)
	OS (months) median	25.5	19.1	15.4
	95% CI	(16.4,32.1)	(13.6,26.2)	(11.8,20.6)
Effect estimate per comparison	Secondary endpoint OS	Comparison groups	Combination vs. Everolimus	
		HR	0.59	
		95% CI	(0.36,0.96)	
		P-value	0.0647	
		Comparison groups	Lenvatinib vs. Everolimus	
		HR	0.75	
		95% C	(0.47,1.20)	
		P-value	0.1299	
		Comparison groups	Combination vs. Lenvatinib	
		HR	0.79	
		95% C	(0.48,1.30)	
		P-value	0.3092	

2.5.3. Discussion on clinical efficacy

The rationale for clinical evaluation of intended combination of multiple kinase inhibitor lenvatinib and mTOR inhibitor everolimus was based on biological rationale, the preliminary clinical experience with lenvatinib in metastatic RCC, established efficacy of everolimus in 2nd line treatment after VEGF-targeted therapy and expectation that combination therapy provides significant advantage over single-agent therapy.

Design and conduct of clinical studies

The pivotal study supporting the proposed indication is a Phase 1b/2 exploratory study E7080-G000-205. This is currently the only study conducted/ongoing in the proposed patient population, which includes

patients with metastatic or unresectable renal cell carcinoma after receiving at least 1 prior VEGF targeted therapy. This study was initially designed to determine whether lenvatinib and its combination with everolimus are worthy of further investigation.

However, the impressive efficacy results of the study in terms of magnitude of PFS improvement, high ORR rates and associated trend to OS benefit in combination arm led to study re-consideration by the Applicant for a MAA purpose. The proposed treatment is the combination of lenvatinib with everolimus.

The Phase 1 part of Study 205 aimed to investigate different doses of both drugs within combination using a classical designed '3+3' dose-escalation stage to determine the DLTs and MTD followed by a cohort expansion stage to confirm the MTD and to establish the RP2 dose for lenvatinib in combination with everolimus. Efficacy was an exploratory objective (BOR investigator-assessed using RECIST1.1).

The recommended dose/schedule of everolimus (10 mg once daily at continuous dosing; available as 2.5 mg, 5 mg and 10 mg tablets) is based on the dose-molecular marker responses (PD) in a Phase I trial in patients with advanced solid cancers (please refer to EPAR for Afinitor).

The MTD of single-agent lenvatinib (available as 4 mg and 10 mg hard capsules) using continuous dosing schedule was determined to be 25 mg QD in phase 1 program in advanced solid tumours and the dose 24 mg was further used for practical reasons. Importantly, concerns have been raised in regard to the starting dose of 24 mg daily (please refer to EPAR for Lenvima approved in orphan RR-DTC indication in 2015). Post-approval Study 211 aims 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 principles of the CHMP guidance available at the time of the design of the Study 205 (initiated in 2010) have been employed for DLT/MTD/RP2D determination. The dose for initiating dose escalation in combination therapy was half of the full dose for each single-agent (12 mg lenvatinib QD and 5 mg everolimus QD). The Applicant gave priority to lenvatinib for dose escalation based on preliminary evidence of lenvatinib activity in 9 RCC patients. Due to the occurrence of DLTs in the first two subjects enrolled in the Cohort 3 (lenvatinib 24 mg + everolimus 5 mg), the Cohort 4 with a full dose of everolimus 10 mg in combination with lenvatinib 24 mg was not tested. Therefore, full recommended dose of everolimus in RCC indication was not achieved. Alternative dosing schedules were not tested. The dose-finding principles for non-cytotoxic compounds are evolving, with consideration given to how the concepts of MTD and DLT are pre-defined, in order to capture relevant toxicities and arrive at a useful RP2D (EMA/CHMP/205/95 Rev.5).

Efficacy data and additional analyses

In patients with advanced RCC and disease progression following 1 prior VEGF-targeted treatment, the combination of lenvatinib 18 mg with everolimus 5 mg demonstrated statistically significant (p=0.0005) improvement in PFS compared with treatment with everolimus alone (median 14.6 months vs 5.5 months, respectively). The improvement in PFS of 9.1 months is considered clinically significant. The combination's improvement in PFS over everolimus was noted for all subgroups analysed (HRs range from 0.14 to 0.61).

The combination arm showed a statistically significant (P<0.0001) improvement in ORR (43.1%) compared with both single agent arms (26.9% for the lenvatinib arm, and 6.0% for the everolimus arm).

The combination arm showed a trend towards prolonged survival (HR = 0.55) compared with the everolimus arm that reached statistical significance (P=0.0242) in the updated OS analysis based on a 10 Dec 2014 data cut-off (HR = 0.51). Median survival was 25.5 months for the combination arm and 15.4 months for the everolimus arm.

These results support an efficacy claim for the proposed combination of lenvatinib and everolimus in the proposed indication.

The pre-planned and post hoc sensitivity analyses and the sub-group analyses produced results consistent with and supportive of the primary analyses results for the primary endpoints. The post hoc blinded independent review showed improvements in PFS and ORR with the combination over everolimus alone. Though these differences were lesser than that calculated in the primary analysis, the results are still statistically and clinically significant.

2.5.4. Conclusions on the clinical efficacy

The efficacy of the combination of lenvatinib with everolimus has been shown. Lenvatinib/everolimus combination therapy demonstrated improved PFS compared to everolimus monotherapy with a median PFS of 14.6 months vs. 5.5 months. The HR was 0.40 (95% CI: 0.24, 0.68, p=0.0005). An independent imaging review (IIR) was conducted and the results obtained, for PFS and ORR, corroborated the improvements seen in the investigator analyses with a median PFS of 12.8 months vs. 5.6 months with everolimus alone (HR= 0.45, 95% CI= 0.26,0.79, p=0.003). Additional sensitivity analyses performed confirmed the robustness of observed PFS.

Furthermore, encouraging signs of a prolonged OS were seen in patients treated with the combination of lenvatinib and everolimus combination therapy as per the primary analysis as well as the two updated analyses that span a more than 1-year period. A similar trend towards prolonged OS was also observed in favour of lenvatinib monotherapy but less obvious than with combination therapy.

2.6. Clinical safety

The main source of safety data in support of lenvatinib-everolimus combination therapy in RCC patients is Study 205 conducted in 173 patients, of which 62 patients received treatment at the intended doses/schedule of lenvatinib 18 mg plus everolimus 5 mg administered orally once daily (QD) and additional 9 patients received different doses of lenvatinib in the dose-finding part of Study 205 (12 mg – 7 patients; 24 mg – 2 patients).

In the Phase 1b part of Study 205, lenvatinib 18 mg QD plus everolimus 5 mg QD, was identified as the maximum tolerated dose (MTD) and the recommended Phase 2 (RP2) dose for the subsequent Phase 2 part of the study.

In the Phase 2 part of Study 205, the lenvatinib + everolimus combination was compared with single-agent lenvatinib at the starting dose of 24 mg QD (dose approved for the treatment of differentiated thyroid cancer [DTC]) and single-agent everolimus 10 mg QD (dose approved for the second-line treatment of advanced RCC).

The safety analysis groups within the RCC Safety Set from Study 205 are as follows:

•	RCC Phases 1b+2 combination group (N=62), hereafter referred to as the RCC combination group includes all subjects who received at least 1 dose of combination study drug (lenvatinib 18 mg QD + everolimus 5 mg QD) in either the Phase 1b (n=11) or the Phase 2 portion of Study 205 (n=51, arm A).

•	RCC lenvatinib group (N=52, arm B): all subjects who received at least 1 dose of single-agent lenvatinib 24 mg QD in the Phase 2 portion of Study 205.

•	RCC everolimus group (N=50, arm C): all subjects who received at least 1 dose of single-agent everolimus 10 mg QD in the Phase 2 portion of Study 205.

Safety data for all treatment arms in Study 205 were presented in the CSR through the data cutoff date for the primary efficacy endpoint analysis of 13 Jun 2014. The safety data from Study 205 was updated with cutoff date 31 Jul 2015 to allow for the inclusion of additional safety data for the RCC Safety Set.

The clinical program for lenvatinib, which is not approved as monotherapy in the RCC indication, includes 33 clinical studies with approximately 2150 subjects with different cancer types and 292 healthy volunteer enrolled with cutoff date 31 Jul 2015 and treated with lenvatinib either as monotherapy or as combination therapy.

The comparisons of lenvatinib safety data were done with the pooled safety data from the monotherapy studies of lenvatinib for progressive radioiodine-refractory DTC (RR-DTC), with additional supportive comparisons with the Non-DTC Safety Set:

•	All DTC Lenvatinib Monotherapy Safety Set (N=458): includes all lenvatinib-treated subjects from Studies E7080-G000-201 (DTC subjects only), E7080-J081-208 (DTC subjects only), and E7080-G000-303 (both the randomized and the optional open-label portions of the study) as of the 10 Dec 2014 data cutoff date.

•	Non-DTC Monotherapy Safety Set (N=656): includes all subjects who received single-agent lenvatinib in studies conducted in subjects with cancer as of the 15 Sep 2013 data cutoff date. Because of the small number of subjects (n=26/656, ≈ 4%) ongoing as of this cutoff date, the Applicant did not provide an update from these 26 subjects.

Patient exposure

As of the 31 Jul 2015 cut-off date for the RCC Safety Set, a total of 46 subjects (28.0%) were still ongoing in Study 205 (4 receiving treatment and 42 in follow-up), 112 subjects (68.3%) had died, and 6 subjects (3.7%) had withdrawn from the study.

The subject disposition status and primary reasons for discontinuation are summarized for the RCC, the All DTC, and the Non-DTC Safety Sets in table 380 below.

Table 37: Subject Disposition and Reasons for Discontinuation – RCC, All DTC, and Non DTC Safety Sets

	Renal Cell Carcinoma			All DTC	Non-DTC
	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62) n (%)	Lenvatinib 24 mg (N=52) n (%)	Everolimus 10 mg (N=50) n (%)	Lenvatinib (N=458) n (%)	Lenvatinib (N=656) n (%)
All Treated Subjects	62 (100.0)	52 (100.0)	50 (100.0)	458 (100.0)	656 (100)
Treatment Ongoing a	2 (3.2)	1 (1.9)	1 (2.0)	161 (35.2)	26 (4.0)

Completed Treatment – Disease Progression b	34 (54.8)	31 (59.6)	37 (74.0)	188 (41.0)	392 (59.8)
Discontinued Prematurely	26 (41.9)	20 (38.5)	12 (24.0)	109 (23.8)	238 (36.3)
Primary Reason for Premature Discontinuation of Treatment					
Adverse event	14 (22.6)	13 (25.0)	5 (10.0)	81 (17.7)	149 (22.7)
Subject choice c	3 (4.8)	0	1 (2.0)	11 (2.4)	0
Lost to follow-up	0	0	0	1 (0.2)	2 (0.3)
Administrative/Other					
Withdrawal of consent d	2 (3.2)	0	0	7 (1.5)	12 (1.8)
Pregnancy	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0
Other e	7 (11.3)	7 (13.5)	6 (12.0)	9 (2.0)	75 (11.4)

The safety data cut-off date was 31 Jul 2015 for the RCC Safety Set, 10 Dec 2014 for the All DTC Safety Set, and 15 Sep 2013 for the Non-DTC Safety Set.

CRF = case report form, DTC = differentiated thyroid cancer; RCC = renal cell carcinoma.

a: Ongoing at safety data cut-off date.

b: Disease progression was considered as completion of study treatment, as defined per protocol.

c: Subject choice indicates that the subject elected to stop treatment with the investigational drug, but agreed to further data collection, including follow-up data.

d: Withdrawal of consent indicates that the subject did not agree to allow collection of any additional data.

e: "Other" was a category on the CRF. For Study 205, this includes palliative therapy and withdrawal due to poor compliance; for the All DTC and the Non-DTC Safety Sets, no further information is available.

The overall exposure to lenvatinib by mean daily dose and duration of exposure, as of the 31 Jul 2015 safety data cut-off date for Study 205, is presented in the table 39 below.

Table 38: Summary of Study Drug Exposure for Lenvatinib – RCC, All DTC, and Non-DTC Safety Sets

Parameter Statistic	Renal Cell Carcinoma		All DTC a	Non-DTC b
	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62)	Lenvatinib 24 mg (N=52)	Lenvatinib (N=458)	Lenvatinib (N=656)
Number of Cycles Received, n				
Mean (SD)	12.1 (9.57)	10.2 (7.72)	17.8 (12.47)	7.0 (8.98)
Median	9.5	8.5	16.0	4.0
Q1, Q3	4.0, 18.0	4.0, 14.5	7.0, 29.0	2.0, 8.0
Min, Max	1, 36	1, 32	1.0, 66.0	1, 98
Cumulative Dose of Lenvatinib, mg				
Mean (SD)	4142 (3787.9)	4625 (3606.5)	7402.5 (5781.24)	3143.7 (4005.04)
Median	2731	3898	6114.0	1784.0
Q1, Q3	954.0, 6376	1886, 6291	2702.0, 11366.0	816.0, 3932.0
Min, Max	252, 15462	96, 17032	60.0, 28224.0	1.6, 32245.5
Lenvatinib Average Daily Dose, e mg/day				
Mean (SD)	13.2 (3.71)	18.9 (5.02)	16.6 (5.24)	18.8 (6.00)
Median	13.5	20.3	16.1	20.5
Q1, Q3	10.6, 16.9	15.1, 23.9	12.7, 21.0	15.2, 24.0
Min, Max	6, 18	7, 24	4.4, 25.5	0.2, 32.0
Percentage of Intended Lenvatinib Dose, f %				
Mean (SD)	73.5 (20.62)	78.7 (20.91)	69.9 (22.09)	84.5 (18.82)
Median	75.0	84.5	68.1	92.3
Q1, Q3	58.9, 93.8	62.9, 99.5	53.3, 90.0	73.7, 100.0
Min, Max	31, 100	28, 100	22.3, 106.2	2.8, 100.0

The safety data cut-off date was 31 Jul 2015 for the RCC Safety Set, 10 Dec 2014 for the All DTC Safety Set, and 15 Sep 2013 for the Non-DTC Safety Set.

AE = adverse event, DTC = differentiated thyroid cancer, Max = maximum, Min = minimum, NAv = not available, Q1 = 1st quartile, Q3 = 3rd quartile, QD = once a day, RCC = renal cell carcinoma, SD = standard deviation, SY = subject-years, TEAE = treatment-emergent adverse event.

a: The lenvatinib starting dose was 24 mg QD except for 32 subjects who had a starting dose of 20 mg QD.

b: The lenvatinib starting dose was 24 mg QD for 508 subjects; it was <14 mg QD for 93 subjects, 14 – <20 mg QD for 12 subjects, 20 – <24 mg QD for 12 subjects, and >24 mg QD for 3 subjects.

c: Duration of treatment (in months) is defined as (Last dose date – First dose date + 1)×12/365.25, and includes dose interruptions.

d: SY of treatment = sum of duration of treatment (in years) for all subjects in each category. These values are used for treatment adjustment of TEAEs to calculate the AE Rate of episodes/SY.

e: Mean Daily Dose (mg/day) = Total cumulative dose (mg) / (last dose date - 1st dose date + 1).

f: Percentage of Intended Dose = Mean daily dose / planned starting dose.

Duration of treatment was defined as the number of days the subject received treatment, including dose interruptions.

Table 39: Duration of treatment, months – RCC, All DTC, and Non DTC Safety Sets

	Renal Cell Carcinoma			All DTC a	Non-DTC b
	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62) n (%)	Lenvatinib 24 mg (N=52) n (%)	Everolimus 10 mg (N=50) n (%)	Lenvatinib (N=458) n (%)	Lenvatinib (N=656) n (%)
Duration of Treatment, c months					
0 - <6 months, n (%)	29 (46.8)	22 (42.3)	32 (64.0)	142 (31)	479 (73.0)
≥6 months, n (%)	33 (53.2)	30 (57.7)	18 (36.0)	316 (69)	177 (27.0)
Mean (SD)	10.7 (8.81)	8.9 (7.21)	6.7 (6.81)	15.9 (11.46)	6.1 (8.25)
Median	8.0	7.4	4.1	14.7	3.5
Q1, Q3	3.7, 16.6	3.2, 13.0	1.9, 10.0	5.7, 26.6	1.6, 7.4
Min, Max	0.5, 33.0	0.1, 29.4	0.3, 33.6	0.1, 60.7	0.0, 89.6
SY of Treatment d	55.2	38.8	27.7	608.1	331.1

The safety data cut-off date was 31 Jul 2015 for the RCC Safety Set, 10 Dec 2014 for the All DTC Safety Set, and 15 Sep 2013 for the Non-DTC Safety Set.

AE = adverse event, DTC = differentiated thyroid cancer, Max = maximum, Min = minimum, NAv = not available, Q1 = 1st quartile, Q3 = 3rd quartile, QD = once a day, RCC = renal cell carcinoma, SD = standard deviation, SY = subject-years, TEAE = treatment-emergent adverse event.

a: The lenvatinib starting dose was 24 mg QD except for 32 subjects who had a starting dose of 20 mg QD.

b: The lenvatinib starting dose was 24 mg QD for 508 subjects; it was <14 mg QD for 93 subjects, 14 – <20 mg QD for 12 subjects, 20 – <24 mg QD for 12 subjects, and >24 mg QD for 3 subjects.

c: Duration of treatment (in months) is defined as (Last dose date – First dose date + 1)×12/365.25, and includes dose interruptions.

d: SY of treatment = sum of duration of treatment (in years) for all subjects in each category. These values are used for treatment adjustment of TEAEs to calculate the AE Rate of episodes/SY

Duration of exposure

Duration of exposure was defined as the number of days the subject received treatment, excluding dose interruptions.

Table 40: Patient exposure to lenvatinib by duration of exposure

	Renal Cell Carcinoma						All DTC	
	Lenvatinib 18 mg + Everolimus 5 mg Phases Ib+II (N=62)		Lenvatinib 18mg + Everolimus 5mg Phase II (N=51)		Lenvatinib 24mg (N=52)		Lenvatinib (N=656)	
Duration of Exposure	n (%)	Subj-year	n (%)	Subj-year	n (%)	Subj-year	n (%)	Subject-year
1 day to < 1 week	0	0	0	0	1 (1.9)	0	3 (0.7)	0
1 week to < 3 months	17(27.4)	2.1	14 (27.5)	1.7	12(23.1)	1.4	81(17.7)	10.3
3 months to < 6 months	15(24.2)	5.3	13 (25.5)	4.7	10(19.2)	3.7	58(12.7)	21.8
6 months to < 1 year	8(12.9)	6.6	5 (9.8)	3.9	15(28.8)	10.1	84(18.3)	61.6
1 year to < 2 years	17(27.4)	24.3	15 (29.4)	21.7	12(23.1)	16.2	120(26.2)	182.2
>= 2 years	5(8.1)	12.0	4 (7.8)	9.7	2(3.8)	4.3	112(24.5)	273.0
Total	62 (100.)	50.2	51 (100.)	41.8	52 (100.)	35.8	81(17.7)	10.3

Table 41: Patient exposure to everolimus by duration of exposure

Duration of Exposure	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b + 2 (N=62)[a]		Lenvatinib 18 mg + Everolimus 5 mg Phase 2 (N=51)		Everolimus 10 mg (N=50)	
	n (%)	Subject-year	n (%)	Subject-year	n (%)	Subject-year
1 week to <3 months	16 (25.8)	1.9	13 (25.5)	1.5	19 (38.0)	2.4
3 months to <6 months	15 (24.2)	5.2	13 (25.5)	4.7	14 (28.0)	5.1
6 months to <1 year	9 (14.5)	7.1	6 (11.8)	4.5	9 (18.0)	7.0
1 year to <2 years	17 (27.4)	24.3	15 (29.4)	21.7	6 (12.0)	6.8
≥2 years	5 (8.1)	12.0	4 (7.8)	9.7	2 (4.0)	5.1
Total	62 (100.0)	50.4	51 (100.0)	42.1	50 (100.0)	26.4

Adverse events

The overall TEAE profile in all safety data sets is summarized below.

Table 42: Overview of Treatment-Emergent Adverse Events – RCC, All DTC, and Non DTC Safety Sets

	Renal Cell Carcinoma			All DTC	Non-DTC
	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62) n (%)	Lenvatinib 24 mg (N=52) n (%)	Everolimus 10 mg (N=50) n (%)	Lenvatinib (N=458) n (%)	Lenvatinib (N=656) n (%)
TEAEs [a]	62 (100.0)	52 (100.0)	50 (100.0)	457 (99.8)	647 (98.6)
Treatment-related TEAEs [b]	62 (100.0)	51 (98.1)	49 (98.0)	4446 (97.4)	610 (93)
TEAEs with CTCAE Grade >=3	49 (79.0)	46 (88.5)	27 (54.0)	397 (56.7)	472 (72.0)
Treatment-related TEAEs with CTCAE Grade >=3	43 (69.4)	35 (67.3)	21 (42.0)	344 (75.1)	360 (54.9)
Serious TEAEs [c]	38 (61.3)	28 (53.8)	21 (42.0)	263 (57.4)	314 (47.9)
Deaths	1 (1.6)	1 (2.0)	3 (5.8)	34 (7.4)	54 (8.2)
Other SAEs	37 (59.7)	29 (56.9)	27 (51.9)	257 (56.1)	331 (50.5)
Life threatening	2 (3.2)	2 (3.9)	2 (3.8)	25 (5.5)	22 (3.4.8)
Requires inpatient hospitalization or prolongation of existing hospitalization	36 (58.1)	28 (54.9)	25 (48.1)	240 (52.4)	322 (49.1)
Persistent or significant disability or incapacity	0	0	0	0	0
Congenital anomaly / birth defect	0	0	0	188 (41.0)	392 (59.8)
Important medical events	5 (8.1)	3 (5.9)	5 (9.6)	35 (7.6)	31 (4.7)
TEAEs leading to study drug dose adjustment [d]	58 (93.5)	47 (90.4)	30 (60.0)	427 (93.2)	477 (72.7)
TEAEs leading to study drug withdrawal	18 (29.0)	16 (30.8)	6 (12.0)	96 (21.0)	168 (25.6)
TEAEs leading to study drug dose reduction	42 (67.7)	30 (57.7)	8 (16.0)	298 (65.1)	186 (28.4)
TEAEs leading to study drug interruption	47 (75.8)	36 (69.2)	25 (50.0)	371 (81)	364 (55.5)
TEAEs leading to study drug dose reduction and/or interruption	55 (88.7)	41 (78.8)	27 (54.0)	403 (88.0)	

The overall TEAE profile in in Phase 1b part of the Study 205 is summarized below.

Table 43: Overview of Treatment-Emergent Adverse Events – Safety Analysis Set -Phase 1b part of Study 205

	Lenvatinib 12 mg + everolimus 5 mg (N=7) n (%)	Lenvatinib 18 mg + everolimus 5 mg (N=11) n (%)	Lenvatinib 24 mg + everolimus (N=2) n (%)
TEAEs	7 (100.0)	11 (100.0)	2 (100.0)
TEAEs with CTCAE Grade >=3	7 (100.0)	10 (90.9)	1 (50.0)
Serious TEAEs	6 (85.7)	8 (72.7)	0
Deaths [a]	1[a]	1[a]	2[a]
Other SAEs [b]	6 (85.7)	8 (72.7)	0
Requires inpatient hospitalization or prolongation of existing hospitalization	5 (71.4)	8 (72.7)	0
Important medical events	1 (14.3)	2 (18.2)	0
	Lenvatinib 12 mg + everolimus 5 mg (N=7) n (%)	Lenvatinib 18 mg + everolimus 5 mg (N=11) n (%)	Lenvatinib 24 mg + everolimus (N=2) n (%)
TEAEs leading to study drug dose adjustment [c]	5 (71.4)	11 (100.0)	1 (50.0)
TEAEs leading to study drug withdrawal	0	168 (25.6)	168 (25.6)
TEAEs leading to study drug dose reduction	2 (28.6)	7 (63.6)	1 (50.0)
TEAEs leading to study drug interruption	5 (71.4)	9 (81.8)	0

Percentages are based on the total number of subjects in the relevant treatment arm. Data cutoff date 13 Jun 2014. For each row category, a subject with 2 or more TEAEs in that category is counted only once.

a: Two subjects (10011005 and 70011001) died within 30 days of the last dose of study medication due to their underlying cancer (progressive disease), however, the investigator did not report the death as an adverse event. Therefore, these subjects are not included in the overall incidence of SAEs.

b: Subjects may have had more than 1 SAE or an SAE that met more than 1 criterion.

c: Study treatment adjustment includes study treatment withdrawal, dose reduction, and/or interruption.

Common adverse events

In the RCC combination group the most frequently reported TEAEs (any grade), occurring in at least 30% of subjects, were diarrhoea (80. 6%), fatigue (59.7%), decreased appetite (53.7%), vomiting (48.4%), nausea (45.2%), hypertension (40.3%), hypertriglyceridemia (40.3%), cough (37.1%), stomatitis (35.5%), peripheral oedema (33.9%), decreased weight (33.9%), dyspnea (30.6%), and hypercholesterolemia (30.6%).

The most frequently reported Grade 3 or 4 TEAEs, occurring in at least 5% of subjects in the RCC combination group, were diarrhoea (19.4%), fatigue (12.9%), hypertension (12.9%), hypertriglyceridemia (12.9%), acute renal failure (8.1%), anaemia (8.1%), dehydration (8.1%), proteinuria (8.1%), and vomiting (6.5%).

In a larger lenvatinib monotherapy safety data set the most commonly reported TEAEs (≥ 30% of subjects, any grade) (All DTC safety set), in descending order of frequency, were hypertension, diarrhoea, decreased appetite, weight decreased, fatigue, nausea, proteinuria, stomatitis, vomiting, dysphonia, headache, and palmar-plantar erythrodysesthesia (PPE) syndrome.

The overall safety profile of everolimus is also well established. The most frequently reported (≥10%) AEs with everolimus in clinical trials were stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, hyperglycaemia, weight decreased, pruritus, asthenia, peripheral oedema, hypercholesterolemia, epistaxis, and headache.

Table 44: Per-Subject Incidence Rate of Treatment-Emergent Adverse Events Occurring in 10% or More of Subjects for Any AE Grade or at Least 5% for AE Grades 3 and 4

| System Organ Class Preferred Term | Renal Cell Carcinoma | | | | | | All DTC | | Non-DTC | |
| | Lenvatinib + Everolimus 18mg + 5mg (N = 62)* n (%) | | Lenvatinib 24 mg (N = 52) n (%) | | Everolimus 10 mg (N= 50) n (%) | | Lenvatinib (N= 458) n (%) | | Lenvatinib (N-656) n (%) | |
	Grade Any	Grade 3/4	Grade Any	Grade 3/4	Grade Any	Grade 3/4	Grade Any	Grade 3/4	Grade Any	Grade 3/4
Subjects with Any TEAE	62 (100.)	48 (77.4)	52 (100.0)	46 (88.5)	50 (100.0)	27 (54.0)	457 (99.8)	394 (86.0)	647 (98.6)	462 (70.4)
Blood and lymphatic system disorders										
Anaemia	11 (17.7)	5 (8.1)	4 (7.7)	1 (1.9)	13 (26.0)	6 (12.0)	37 (8.1)	7 (1.5)	50 (7.6)	15 (2.3)
Thrombo-cytopenia	7 (11.3)	3 (4.8)	1 (1.9)	0	4 (8.0)	0	37 (8.1)	8 (1.7)	70 (10.7)	11 (1.7)
Endocrine disorders										
Hypothyroidism	15 (24.2)	0	19 (36.5)	1 (1.9)	1 (2.0)	0	24 (5.2)	0	110 (16.8)	7 (1.1)
Gastrointestinal disorders										
Abdominal Pain	15 (24.2)	2 (3.2)	12 (23.1)	2 (3.8)	1 (2.0)	0	93 (20.3)	9 (2.0)	146 (22.3)	27 (4.1)
Abdominal Pain Upper	9 (14.5)	1 (1.6)	7 (13.5)	0	3 (6.0)	0	85 (18.6)	3 (0.7)	88 (13.4)	6 (0.9)
Constipation	10 (16.1)	0	19 (36.5)	0	9 (18.0)	0	122 (26.6)	1 (0.2)	172 (26.2)	6 (0.9)
Diarrhoea	50 (80.6)	12 (19.4)	37 (71.2)	6 (11.5)	17 (34.0)	1 (2.0)	307 (67.0)	46 (10.0)	270 (41.2)	33 (5.0)
Dyspepsia	10 (16.1)	0	6 (11.5)	1 (1.9)	6 (12.0)	0	57 (12.4)	1 (0.2)	49 (7.5)	0
Nausea	28 (45.2)	3 (4.8)	32 (61.5)	4 (7.7)	8 (16.0)	0	207 (45.2)	10 (2.2)	271 (41.3)	21 (3.2)
Oral Pain	8 (12.9)	0	5 (9.6)	0	1 (2.0)	0	38 (8.3)	1 (0.2)	43 (6.6)	2 (0.3)
Stomatitis	22 (35.5)	1 (1.6)	13 (25.0)	1 (1.9)	21 (42.0)	1 (2.0)	169 (36.9)	12 (2.6)	141 (21.5)	10 (1.5)
Vomiting	30 (48.4)	4 (6.5)	20 (38.5)	2 (3.8)	6 (12.0)	0	163 (35.6)	11 (2.4)	209 (31.9)	18 (2.7)
General disorders and administration site conditions										
Asthenia	15 (24.2)	2 (3.2)	8 (15.4)	1 (1.9)	3 (6.0)	1 (2.0)	115 (25.1)	29 (6.3)	67 (10.2)	21 (3.2)

Fatigue	37 (59.7)	8 (12.9)	21 (40.4)	4 (7.7)	16 (32.0)	0	213 (46.5)	23 (5.0)	333 (50.8)	80 (12.2)
Oedema Peripheral	21 (33.9)	1 (1.6)	9 (17.3)	0	9 (18.0)	0	96 (21.0)	2 (0.4)	81 (12.3)	2 (0.3)
Pyrexia	13 (21.0)	1 (1.6)	5 (9.6)	0	5 (10.0)	1 (2.0)	69 (15.1)	1 (0.2)	68 (10.4)	2 (0.3)

Infections and infestations

Nasopharyngitis	7 (11.3)	0	4 (7.7)	0	6 (12.0)	0	46 (10.0)	0	27 (4.1)	0

Investigations

Blood Thyroid Stimulating Hormone Increased	7 (11.3)	0	2 (3.8)	0	1 (2.0)	0	28 (6.1)	0	55 (8.4)	1 (0.2)
Weight Decreased	21 (33.9)	2 (3.2)	26 (50.0)	3 (5.8)	4 (8.0)	0	241 (52.6)	55 (12.0)	144 (22.0)	22 (3.4)

Metabolism and nutrition disorders

Decreased Appetite	33 (53.2)	3 (4.8)	30 (57.7)	2 (3.8)	9 (18.0)	0	246 (53.7)	24 (5.2)	238 (36.3)	15 (2.3)
Dehydration	8 (12.9)	5 (8.1)	1 (1.9)	0	1 (2.0)	0	44 (9.6)	17 (3.7)	66 (10.1)	27 (4.1)
Hypercholester-olaemia	19 (30.6)	2 (3.2)	6 (11.5)	1 (1.9)	8 (16.0)	0	15 (3.3)	2 (0.4)	9 (1.4)	0
Hyperglycaemia	11 (17.7)	0	3 (5.8)	0	12 (24.0)	5 (10.0)	23 (5.0)	1 (0.2)	29 (4.4)	10 (1.5)
Hypertriglyc-eridaemia	25 (40.3)	8 (12.9)	7 (13.5)	2 (3.8)	12 (24.0)	4 (8.0)	17 (3.7)	2 (0.4)	14 (2.1)	2 (0.3)
Hypokalaemia	8 (12.9)	3 (4.8)	1 (1.9)	1 (1.9)	1 (2.0)	0	49 (10.7)	13 (2.8)	42 (6.4)	11 (1.7)

Musculoskeletal and connective tissue disorders

Arthralgia	18 (29.0)	0	13 (25.0)	0	7 (14.0)	0	141 (30.8)	5 (1.1)	130 (19.8)	3 (0.5)
Back Pain	15 (24.2)	2 (3.2)	11 (21.2)	0	7 (14.0)	0	91 (19.9)	10 (2.2)	104 (15.9)	7 (1.1)
Musculoskeletal Chest Pain	11 (17.7)	1 (1.6)	8 (15.4)	2 (3.8)	2 (4.0)	0	57 (12.4)	1 (0.2)	38 (5.8)	2 (0.3)
Pain In Extremity	10 (16.1)	0	6 (11.5)	1 (1.9)	3 (6.0)	0	83 (18.1)	5 (1.1)	79 (12.0)	7 (1.1)

Nervous system disorders

Dizziness	7 (11.3)	0	4 (7.7)	0	2 (4.0)	0	74 (16.2)	1 (0.2)	88 (13.4)	0
Headache	12 (19.4)	1 (1.6)	14 (26.9)	3 (5.8)	5 (10.0)	1 (2.0)	164 (35.8)	12 (2.6)	198 (30.2)	13 (2.0)

Psychiatric disorders

Insomnia	10 (16.1)	1 (1.6)	8 (15.4)	0	1 (2.0)	0	62 (13.5)	0	57 (8.7)	1 (0.2)

Renal and urinary disorders

Proteinuria	18 (29.0)	5 (8.1)	16 (30.8)	10 (19.2)	7 (14.0)	1 (2.0)	178 (38.9)	48 (10.5)	197 (30.0)	37 (5.6)
Renal Failure Acute	5 (8.1)	5 (8.1)	5 (9.6)	3 (5.8)	0	0	11 (2.4)	4 (0.9)	14 (2.1)	6 (0.9)

Respiratory, thoracic and mediastinal disorders

Cough	23 (37.1)	0	9 (17.3)	1 (1.9)	15 (30.0)	0	124 (27.1)	1 (0.2)	104 (15.9)	4 (0.6)
Dysphonia	11 (17.7)	0	19 (36.5)	0	2 (4.0)	0	163 (35.6)	4 (0.9)	192 (29.3)	1 (0.2)
Dyspnoea	19 (30.6)	3 (4.8)	12 (23.1)	1 (1.9)	11 (22.0)	4 (8.0)	83 (18.1)	11 (2.4)	108 (16.5)	14 (2.1)

	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Epistaxis	14 (22.6)	0	4 (7.7)	0	12 (24.0)	0	75 (16.4)	1 (0.2)	67 (10.2)	0
Oropharyngeal Pain	7 (11.3)	0	2 (3.8)	0	2 (4.0)	0	71 (15.5)	1 (0.2)	53 (8.1)	1 (0.2)
Skin and subcutaneous tissue disorders										
Dry Skin	7 (11.3)	0	3 (5.8)	0	3 (6.0)	0	52 (11.4)	0	71 (10.8)	0
Pruritus	8 (12.9)	0	3 (5.8)	0	7 (14.0)	0	26 (5.7)	0	34 (5.2)	0
Rash	14 (22.6)	0	8 (15.4)	0	11 (22.0)	0	89 (19.4)	1 (0.2)	77 (11.7)	0
Vascular disorders										
Hypertension	25 (40.3)	8 (12.9)	25 (48.1)	9 (17.3)	5 (10.0)	1 (2.0)	321 (70.1)	170 (37.1)	347 (52.9)	163 (24.8)

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 group or safety set.

The safety data cut-off date was 31 Jul 2015 for the RCC Safety Set, 10 Dec 2014 for the All DTC Safety Set, and 15 Sep 2013 for the Non-DTC Safety Set.

CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, MedDRA = Medical Dictionary for Regulatory Activities, PPE = palmer-plantar erythrodysesthesia syndrome, RCC = renal cell carcinoma, TEAE = treatment-emergent adverse event, TSH = thyroid stimulating hormone.

Clinically Significant Adverse Events (CSEs)

Clinically significant events (CSEs) previously defined for the DTC MAA included hypertension, proteinuria, arterial and venous thromboembolic events, posterior reversible encephalopathy syndrome (PRES), renal events, liver events, gastrointestinal (GI) perforation and fistula formation, QTc prolongation, decreased ejection fraction (EF), hypocalcemia, haemorrhage, and PPE. Weight loss and cytopenias were also evaluated.

The combination arm of study 205 had a higher level of clinically significant TEAE than everiolimus arm (79% and 62%, respectively).

Table 45: Summary of Clinically Significant Adverse Events

TEAE, n (%)	RCC Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62) All Grades	Grade ≥3	RCC Lenvatinib 24 mg (N=52) All Grades	Grade ≥3	RCC Everolimus 10 mg (N=50) All Grades	Grade ≥3	All DTC Lenvatinib 24 mg (N=458) All Grades	Grade ≥3
Subjects with any clinically significant AE	49 (79.0)	26 (41.9)	49 (94.2)	28 (53.8)	31 (62.0)	6 (12)	423 (92.4)	272 (59.4)
Hypertension	26 (41.9)	8 (12.9)	25 (48.1)	9 (17.3)	5 (10)	1 (2)	336 (73.4)	179 (39.1)
Arterial thromboembolic events	1 (1.6)	1 (1.6)	4 (7.7)	4 (7.7)	3 (6.0)	2 (4.0)	25 (5.5)	14 (3.1)
Venous thromboembolic events	4 (6.5)	2 (3.2)	7 (13.5)	3 (5.8)	2 (4.0)	1 (2.0)	24 (5.2)	18 (3.9)
QTc prolongation	4 (6.5)	0	3 (5.8)	0	0	0	56 (12.2)	5 (1.1)
Decreased EF and	3	2	4	1	2	1	32	13

TEAE, n (%)	RCC Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62)		RCC Lenvatinib 24 mg (N=52)		RCC Everolimus 10 mg (N=50)		All DTC Lenvatinib 24 mg (N=458)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
cardiac failure	(4.8)	(3.2)	(7.7)	(1.9)	(4.0)	(2.0)	(7.0)	(2.8)
Hemorrhage	24 (38.7)	5 (8.1)	15 (28.8)	1 (1.9)	14 (28.0)	1 (2)	185 (40.4)	13 (2.8)
PRES (posterior reversible encephalopathy syndrome)	0	0	1 (1.6)	1 (1.6)	0	0	1 (0.2)	1 (0.2)
Renal events	11 (17.7)	6 (9.7)	8 (15.4)	3 (5.8)	6 (12.0)	1 (2.0)	59 (12.9)	12 (2.6)
Proteinuria	19 (30.6)	5 (8.1)	16 (30.8)	10 (19.2)	7 (14.0)	1 (2.0)	178 (38.9)	48 (10.5)
Liver events	9 (14.5)	2 (3.2)	7 (13.5)	1 (1.9)	7 (14.0)	1 (2.0)	110 (24.0)	25 (5.5)
Hypocalcemia	5 (8.1)	2 (3.2)	3 (5.8)	0	2 (4.0)	0	60 (13.1)	20 (4.4)
PPE Palmar plantar erythro-dysesthesia	10 (16)	0	11 (21.2)	0	6 (12.0)	0	162 (35.4)	15 (3.3)
GI perforation/ Fistula Formation	1 (1.6)	1 (1.6)	3 (5.8)	1 (1.9)	0	0	11 (2.4)	8 (1.7)

Cardiovascular events

Cardiovascular toxicity includes events such as hypertension, cardiac failure, arterial and venous thromboembolic events, QTc prolongation and haemorrage. These are considered to be clinically significant events for lenvatinib+everolimus and are subject to routine Pharmacovigilance reporting. A summary of the incidence of cardiovascular TEAEs in the lenvatinib RCC combination group and All DTC Safety Set is provided in Table above.

Hypertension

Hypertension was experienced at a lower incidence rate and intensity in the RCC combination group (42%) than in the lenvatinib single arm (48%) and in the All DTC Safety set (73%) but was still higher than in the everolimus only arm (10%). AEs grade 3 or above occurred in 13% of the RCC combination group.

There were no Grade 4 or Grade 5 TEAEs, no SAEs, and no discontinuations due to AEs related to hypertension in the RCC combination group and thus hypertension was sufficiently manageable in the RCC combination group.

The median time to onset of hypertension was 4.9 weeks (any grade) and 6.9 weeks (Grade ≥ 3) in the RCC combination group, which is later than in the All DTC safety set (2 weeks). The highest proportion of subjects

experienced an episode of hypertension in Cycle 1 in the RCC combination group (21.0%) as was the case in the All DTC Safety Set (45.6%).

Thromboembolic events

Thromboembolic events are known to occur with VEGF/VEGFR-targeted therapies.

One Arterial thromboembolic events (ATE) per SGQ of grade 3 occurred in the RCC combination group to compare to 4 in the lenvatinib alone group (7.7%, 3 grade 3 and 1 grade 5) and in 5.5% of the DTC patients. There were no interruption, reduction or discontinuation due to ATE in the RCC combination group.

The time to onset of arterial thromboembolic events for the 1 subject in the RCC combination group was 69.6 weeks (Grade 3). In the RCC combination group, the 1 episode of an arterial thromboembolic event occurred in Cycle 18. Although episodes of arterial thromboembolic events per SGQ occurred throughout treatment in the All DTC Safety Set, a higher percentage tended to occur within the first 2 cycles of treatment.

Four venous thromboembolic events occurred in the RCC combination group (6.5%), one of each of grades 1, 2, 3 and 4, two being SAEs. One led to an interruption of the studied combination of drugs. The lenvatinib alone arm showed higher figures with 7 AEs (13.5%) of grade 1, 2 and 3 which is significantly higher than the profile of VTEs in DTC patients (at least for the grade 1 and 2 AEs). The median time to onset of venous thromboembolic events was 28.1 weeks (any grade) and 20.6 weeks (Grade $\geq$ 3) in the RCC combination group

Of the TEAEs contributing to the SGQ for venous thromboembolic events, deep vein thrombosis, pulmonary embolism, thrombophlebitis, and venous thrombosis each occurred in 1 subject in the RCC combination group. Pulmonary embolism was the most frequent event in the All DTC (2.8%) and the Non DTC (3.0%) Safety Sets. The incidence rate and severity of venous thromboembolic events in the RCC combination group is consistent with the known safety profile of lenvatinib.

The median time to onset of venous thromboembolic events was 28.1 weeks (any grade) and 20.6 weeks (Grade $\geq$ 3) in the RCC combination group.

QTc prolongation

In the RCC study in the subjects with baseline and postbaseline data avaliabale (92%), respectively 11.3% , 24% and 56% had increase of >60 ms, between 30 and 61 ms, and below 31 ms in the RCC combination group. Data are similar for the RCC lenvatinib group but with a significantly lower number of patients with increase of > 60 ms (2; 3.8%). The incidence of QTc interval greater than 500 ms was 6% in the lenvatinib plus everolimus-treated group. No reports of QTc interval prolongation greater than 500 ms or increases greater than 60 ms occurred in the everolimus-treated group.

The median time to onset of QTc prolongation was 35.1 weeks (any grade) in the RCC combination group. In the RCC combination group, episodes occurred sporadically from Cycle 2 through Cycle 18.

Decreased ejection fraction and cardiac failure

"Decreased ejection fraction and cardiac failure" occurred in 3 subjects (4.8%) in the RCC combination group, 4 subjects (7.7%) in the RCC lenvatinib group and 7% in the DTC safety set. The only TEAE contributing to the CSE of decreased EF and cardiac failure that occurred in more than 2% of subjects in the RCC

combination group was decreased EF (3.2%) as in the all-DTC safety set (4.8%). Cardiac failure was reported in 1 patient (1.6%) of the combination group.

So far the incidence rate and severity of cardiac failure and decreased EF events in the RCC combination group is consistent with the known safety profile of lenvatinib per the approved Lenvima SmPC.

The median time to onset of decreased EF and cardiac failure per SGQ was 15.7 weeks (any grade) and 32.8 weeks (Grade ≥ 3) in the RCC combination group. Episodes of decreased EF and cardiac failure per SGQ tended to occur sporadically throughout treatment for both the RCC combination group and the All DTC Safety Set.

Haemorrhage

Haemorrhage is a well-known AE associated with treatment with TKIs. Two distinctive types of bleeding have been described: mild spontaneous mucocutaneous bleeding and serious tumour related bleeding.

Haemorrhage accounted for 2 discontinuations, 2 drug reductions and 2 drug interruptions in the RCC combination arm, 1 discontinuation in the RCC lenvatinib arm and 1 dose reduction in the everolimus arm. One patient in both RCC combination and lenvatinib arms had a grade 5 event.

In the RCC study haemorrhage was reported in 38.7% (8.1% were Grade ≥ 3) of patients in the lenvatinib plus everolimus-treated group, notably epistaxis (22.6%), haematuria (4.8%), haematoma (3.2%), and gastric haemorrhage (3.2%). The median time to first onset of was 10.2 weeks (any grade) and 7.6 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. The rate of haemorrhage was the highest at the beginning of treatment (12% of subjects) then decreased to a plateau after 3 cycles. There might be a second period of higher occurrence (5% of subjects) between the 6th and the 10th cycle. The chronology of the events is slightly different than the one of the DTC patients.

The incidence of serious haemorrhage was 4.8% (cerebral haemorrhage, gastric haemorrhage and haemarthrosis). Discontinuation due to haemorrhagic events occurred in 3.2% of patients in the lenvatinib plus everolimus-treated group. There was one case of fatal cerebral haemorrhage in the lenvatinib plus everolimus-treated group and one case of fatal intracranial haemorrhage in the lenvatinib-treated group.

Renal and urinary disorders

Renal events including renal failure, blood creatinine increased, blood urea increased, creatinine renal clearance decreased and toxic nephropathy toxic were reported in 17.7% of patients in the combination group (11 events, 15 episodes, 0.27 episodes/SY) in the RCC combination group, 12.9% (8 events, 11 episodes, 0.14 episodes/SY) in the All DTC Safety Set, and 7.5% (0.25 episodes/SY) in the Non DTC Safety Set. In the 11 subjects of the RCC combination group, no subjects discontinued treatment, 2 had a dose reduction and 3 a dose interruption. One subject discontinued treatment in the arm B/ RCC lenvatinib group.

There was a higher rate of SAEs for renal events in the RCC combination group (11.3%) compared with the All DTC (2.6%) and the Non DTC (2.1%) Safety Sets. The incidence rate and severity of renal events was similar in the RCC combination group and the RCC lenvatinib group.

The median time to onset of renal events was 8.1 weeks (any grade and Grade ≥ 3) in the RCC combination group. More than half of the episodes occurred within the first 3 cycles (RCC combination group, 7 of 12 episodes) or first 4 cycles (All DTC Safety Set, 35 of 76 episodes). Thus, although episodes of renal events tended to occur throughout treatment, they more frequently did so early in treatment.

Of the renal events, acute renal failure (8.1%) and increased blood creatinine (4.8%) were the most frequent for the RCC combination group. In the All DTC Safety Set, acute renal failure and increased blood creatinine occurred in 2.4% and 6.6% of subjects, respectively.

Renal failure and impairment

In the combination group 8.1% of patients developed renal failure and 3.2% developed renal impairment, (9.7% of patients had a Grade 3 event of renal failure or impairment). In the everolimus monotherapy group 2.0% of patients developed renal failure (2.0% were Grade 3).
In the DTC study, 5.0% of patients developed renal failure and 1.9% developed renal impairment, (3.1% of patients had a Grade ≥ 3 event of renal failure or impairment).
Grade 3 acute renal failure events occurred at a higher rate in the RCC combination group (5 subjects, 8.1%) than in the lenvatinib alone mRCC group (5.8%) or in the All DTC Safety Set (4 subjects, 0.9%). There were no Grade 4 or grade 5 acute renal failure events in the RCC safety.

Serious renal events occurred at a higher rate in the RCC combination group (11.3%) and the RCC lenvatinib group (7.7%) compared with the All DTC Safety Set (2.6%).

Proteinuria

Proteinuria was reported in 30.6% of patients in the combination group (8.1% were Grade ≥ 3) and 14.0% of patients in the everolimus-treated group (2.0% were Grade ≥3). The median time to onset of proteinuria was 6.1 weeks (any grade) and 20.1 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Proteinuria led to permanent treatment discontinuation in 4.8% of patients. The highest proportion of subjects experienced an episode of proteinuria in the first 2 cycles of treatment.

Liver Events

TEAEs occurred in 9 (14.5%), 7 (13.5%) and 5 (10%) of subjects of respectively the RCC combination, the RCC lenvatinib and the RCC everolimus arms to compare to 24% with the DTC patients. In the mRCC group 2 patients discontinued treatment, and one each had an interruption or a dose reduction. In the mRCC lenvatinib group 1 patient had a dose reduction. SAEs occurred in 2 patients of the mRCC combination group: increased blood bilirubin (Grade 3) and increased transaminases (Grade 3). The median time to onset of liver events was 6.7 weeks (any grade) and 14.2 weeks (Grade ≥ 3) in the RCC combination group. The worst grade and first occurrence of the event generally occurred within the first 7 treatment cycles in a similar pattern than with the all DTC safety group. The rate of liver event episodes per SY was slightly higher in the RCC combination group compared with that in the All DTC Safety. SAEs and discontinuations due to liver events occurred for a slightly higher percentage of subjects in the RCC combination group than in the All DTC and the Non DTC Safety Sets, this difference representing a few subjects in the RCC group. The episodes per SY and severity of liver events were higher in the RCC combination group than in the RCC lenvatinib group.

Of the TEAEs contributing to liver events in the RCC combination group, increased alanine aminotransferase (ALT) was the most frequent (9.7% any Grade and 1.6% Grade ≥ 3), followed by increased aspartate aminotransferase (AST; 4.8% any Grade and 1.6% Grade ≥ 3) and increased blood alkaline phosphatase (ALP; 4.8% any Grade, no Grade ≥ 3).

There were no subjects identified in the safety database who met the criteria for possible Hy's Law.

Electrolyte disturbances

Table 46: Summary of electrolyte disturbances

Parameter (CTCAE Preferred Term)	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62)		Lenvatinib 24 mg Phase 2 (N=52)		Everolimus 10 mg Phase 2 (N=50)	
Grade of Lab Value:	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Hypercalcemia	1 (1.6)	0	0	0	1 (2.0)	0
Hypocalcemia	5 (8.1)	2 (3.2)	3 (5.8)	0	2 (4.0)	0
Hyperkalemia	5 (8.1)	3 (4.8)	3 (5.8)	0	1 (2.0)	0
Hypokalemia	8 (12.9)	3 (4.8)	1 (1.9)	1 (1.9)	1 (2.0)	0
Hyponatremia	2 (3.2)	2 (3.2)	1 (1.9)	0	0	0
Hypermagnesemia	0	0	0	0	1 (2.0)	0
Hypomagnesemia	2 (3.2)	1 (1.6)	4 (7.7)	1 (1.9)	0	0
Hypophosphatemia	0	0	1 (1.9)	0	1 (2.0)	0

The incidence rate and episodes per SY of TEAEs for hypocalcemia per SGQ were comparable in the RCC combination group (5 subjects; 8.1%; 0.16), the RCC lenvatinib group (3 subjects; 5.8%; 0.08) and the Non DTC (4.6%; 0.11) Safety Sets, and numerically lower than that in the All DTC Safety Set (60 subjects; 13.1%; 0.15).

No subjects required treatment interruptions or discontinued treatment because of abnormalities in sodium, magnesium or calcium. One subject in the combination group required a dose reduction and discontinued treatment because of hypokalemia

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. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia. (SmPC section 4.4). Hypocalcemia and hypokalemia are important identified risks in RMP.

Palmar-Plantar Erythrodysesthesia Syndrome

The incidence rate of TEAEs for PPE was lower in the RCC combination group (16.1%) and in the RCC everolimus arm than that in the RCC lenvatinib arm (21%) and in the All DTC Safety Set (35.4%). There were no Grade 3 TEAEs in the RCC combination group; Grade 3 TEAEs were reported for 15 subjects (3.3%) in the All DTC Safety Set. There were no SAEs and no treatment discontinuations due to PPE in the RCC or All DTC Safety Sets. Two patients (3.2%) had and interruption in the RCC combination arm, 1 in the

lenvatinib arm and 9% in the All-DTC safety set. Episodes of PPE tended to occur throughout treatment. The median time to onset of PPE was 7.2 weeks in the RCC combination group.

Gastrointestinal perforation and fistula formation

One case (1.6%; grade 3, perforated appendicitis) of gastrointestinal perforation and fistula formation occurred in the mRCC combination group, 3 in the mRCC lenvatinib group (6%) and 2.4% in the all-DTC safety group.

Pancreatitis

Six (9.7%) subjects of the RCC combination arm had a potential risk of pancreatitis. One had a dose reduction and one an interruption. No SAE was described. A higher incidence (9.7%) of "Lipase increased" is observed in the RCC combination arm while "Amylase increased", "Hyperamylasaemia", "hyperlipasaemia", "pancreatic pseudocyst" and "pancreatitis" are not different from the All DTC group.

Interstitial Lung Disease

The TEAEs for potential risk of interstitial lung diseases (ILD) are pneumonitis, lung infiltration, acute respiratory distress syndrome and pulmonary sarcoidosis. In study 205 phase 2, pneumonitis occurred in 3 (6%) 1 and 6 patients of the RCC combination, lenvatinib and everolimus groups respectively. While the worst grade was 2 for two patients of the combination arm (1 SAE), it was 3 for three patients of the everolimus arm. Lung infiltration occurred once in the everolimus arm (grade < 3). Two (4.0%) subjects in the RCC everolimus group discontinued treatment because of pneumonitis. The frequency of pneumonitis reported in the RCC everolimus group is not inconsistent with the known frequency reported in the approved AFINITOR SmPC. The incidence (4, 6.5%) of ILD is higher in the RCC combination (phase 1b +2) than in the All DTC patients (6 events; 1.3%).

Hypothyroidism

Thyroid dysfunction is a known class effect of TKIs due to the antiangiogenetic effect on the thyroid blood vessels of the drugs in this class. Hypothyroidism occurred in 24% of patients in the lenvatinib plus everolimus-treated group and 2% of patients in the everolimus-treated group. All events of hypothyroidism in the combination group were of Grade 1 or 2. There were no severe (Grade 3 or 4) TEAEs, SAEs, or treatment discontinuations associated with the important risk of hypothyroidism in the RCC combination group and the All DTC Safety Set; however, all 3 types of events were observed for the Non DTC Safety Set (1.2%, 0.6%, and 0.3%, respectively). In patients with a normal TSH at baseline, an elevation of TSH level was observed post baseline in 60.5% of lenvatinib plus everolimus-treated patients as compared with none in patients receiving everolimus alone.

New or Worsening Safety Signals for Lenvatinib Plus Everolimus Combination Therapy

The potential for new or worsening safety signals with combination lenvatinib/everolimus therapy in RCC was evaluated in comparison with the known safety profiles of lenvatinib and everolimus as single agents.

The following criteria have been applied in order to make a meaningful comparison and assessment of potential new or worsening events based on the sample size in the RCC Safety Set:

• Events were only considered for evaluation if the frequency in the RCC combination group was ≥ 10% subjects for any grade TEAE or ≥ 5% subjects for any Grade 3 or 4 TEAE.

• These events were only considered potential new or worsening signals if they occurred at ≥ 10% (any grade) AND there was a relative risk of 2 or greater when the RCC combination group was compared with the All DTC Safety Set OR if they occurred at ≥ 5% (Grade 3 or 4) AND there was a relative risk of 2 or greater when the RCC combination group was compared with the All DTC Safety Set. The relative risk of 2 was chosen as the cutoff because a lower relative risk cutoff would likely result in many false signals due to the size of the RCC Safety Set.

Table 47: Summary of Potential New or Worsening Safety Signals for Lenvatinib Plus Everolimus Combination Therapy in the RCC Population

Preferred Term	Renal Cell Carcinoma						All DTC		Approved LENVIMA SmPC	Approved AFINITOR SmPC
	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62) n (%)		Lenvatinib 24 mg (N=52) n (%)		Everolimus 10 mg (N=50) n (%)		Lenvatinib 24 mg (N=458) n (%)		Lenvatinib 24 mg (DTC) (N=452) %	Everolimus 10 mg (all indications, including RCC) (N=2,470) %
Grade of TEAE:	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Any Grade
Potential New Safety Signals										
Event not in Approved LENVIMA SmPC or Approved AFINITOR SmPC										
No events identified										
Event in Approved AFINITOR SmPC but not in Approved LENVIMA SmPC										
Hypertriglyceridaemia	**25 (40.3)**	**8 (12.9)**	7 (13.5)	2 (3.8)	12 (24.0)	4 (8.0)	17 (3.7)	2 (0.4)	-	≥1% to <10%
Anaemia	**11 (17.7)**	**5 (8.1)**	4 (7.7)	1 (1.9)	13 (26.0)	6 (12.0)	37 (8.1)	7 (1.5)	-	≥10%
Hyperglycaemia	**11 (17.7)**	0	3 (5.8)	0	12 (24.0)	5 (10.0)	23 (5.0)	1 (0.2)	-	≥10%
Pruritus	**8 (12.9)**	0	3 (5.8)	0	7 (14.0)	0	26 (5.7)	0	-	≥10%
Potential Worsening Safety Signals										
Event in Both Approved LENVIMA SmPC and Approved AFINITOR SmPC										
Diarrhoea [a]	50 (80.6)	12 (19.4)	37 (71.2)	6 (11.5)	17 (34.0)	1 (2.0)	307 (67.0)	46 (10.0)	≥10%	≥10%
Fatigue	37 (59.7)	**8 (12.9)**	21 (40.4)	4 (7.7)	16 (32.0)	0	213 (46.5)	23 (5.0)	≥10%	≥10%
Vomiting	30 (48.4)	**4 (6.5)**	20 (38.5)	2 (3.8)	6 (12.0)	0	163 (35.6)	11 (2.4)	≥10%	≥1% to <10%
Hypercholesterolemia	**19 (30.6)**	2 (3.2)	6 (11.5)	1 (1.9)	8 (16.0)	0	15 (3.3)	2 (0.4)	≥1% to <10%	≥10%
Dehydration	8 (12.9)	**5 (8.1)**	1 (1.9)	0	1 (2.0)	0	44 (9.6)	17 (3.7)	≥1% to <10%	≥1% to <10%
Renal Failure Acute	5 (8.1)	**5 (8.1)**	5 (9.6)	3 (5.8)	0	0	11 (2.4)	4 (0.9)	≥1% to <10%b	≥10%c
Event in Approved LENVIMA SmPC but not in Approved AFINITOR SmPC										
Hypothyroidism	**15 (24.2)**	0	19 (36.5)	1 (1.9)	1 (2.0)	0	24 (5.2)	0	≥1% to <10%	-

All events that met the following criteria for a potential new or worsening event are shown in **bold**: events were only considered for evaluation if the frequency in the RCC Phase 1b+2 combination group was ≥10% subjects for any grade TEAE or ≥5% subjects for any Grade 3 or 4 TEAE. These events were only considered potential new or worsening signals if they occurred at ≥10% (any grade) AND there was a relative risk of 2 or greater when the RCC Phase 1b+2 combination group was compared with the All DTC Safety Set **OR** if they occurred at ≥5% (Grade 3 or 4) AND there was a relative risk of 2 or greater when the RCC Phase 1b+2 combination group was compared with the All DTC Safety Set.

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 group or safety set.

The safety data cut-off date was 31 Jul 2015 for the RCC Safety Set, 10 Dec 2014 for the All DTC Safety Set, and 15 Sep 2013 for the Non-DTC Safety Set.

DTC = differentiated thyroid cancer, RCC = renal cell carcinoma, SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event, TKI = tyrosine kinase inhibitor, TSH = thyroid stimulating hormone.

a: Diarrhoea is included for consideration because it occurred at a high frequency, although it did not meet the above criteria.

b: Approved LENVIMA (lenvatinib) SmPC: renal failure cases include acute prerenal failure, renal failure, renal failure acute, and renal tubular necrosis.

c: Approved AFINITOR (everolimus) SmPC: renal failure (≥10%) is shown for comparison to the approved LENVIMA SmPC, which includes combined terms (see above). The frequency of acute renal failure reported in the approved AFINITOR SmPC is ≥0.1% to <1%.

Eleven events were identified: diarrhea, hypercholesterolemia, hypothyroidism, hypertriglyceridemia, fatigue, vomiting, acute renal failure, dehydration, anemia, hyperglycemia and pruritus. Diarrhea has also been included for consideration because it occurred at a high frequency, although it did not meet the specified criteria.

Potential new safety signals with the combination

No new safety signals have been identified with combination therapy in the RCC Safety Set that are not already known for either lenvatinib or everolimus.

New Safety Signals Not Known for Lenvatinib

Hypertriglyceridemia, anaemia, hyperglycaemia, and pruritus were reported with an increased frequency in the RCC combination relative to All DTC Safety set. These 4 events are well known AEs associated with everolimus therapy and are all included in the approved AFINITOR SmPC. There was an increased frequency in the RCC combination group relative to the All DTC Safety Set, which fulfilled the criteria for a new signal for the combination therapy. However, the frequencies seen in the RCC everolimus group were generally higher than that in the RCC combination and RCC lenvatinib groups, which supports the conclusion that these events are attributable to everolimus and, therefore, not considered to be a new signal for the combination therapy.

Hypertriglyceridemia

Hypertriglyceridemia has a higher incidence in mRCC patients (lenvatinib arm; 13.5%) than in the DTC patients (3.7%). Although single agent everolimus has a causal effect (24%); the combination shows the highest values (40.3%) suggesting a synergetic effect of everolimus and lenvatinib.

Anaemia

Anaemia, described as "very common" in the Afinitor SmPC, had the highest incidence in the RCC everolimus group (26%). Its incidence in the RCC lenvatinib group and in the DTC safety set is identical (8.1%), but it is twice as more frequent in the RCC combination group (17.7%). Of note the half AEs are of grade 3 or 4 AEs in the combination arm.

Anaemia was the most frequently reported AE that led to dose reduction and/or interruption in the everolimus arm. This event led to dose reduction and/or interruption in 1 subject in each of the combination (2.0%) and lenvatinib (1.9%) arms, and in 6 subjects (12.0%) in the everolimus arm. Anaemia resulting in dose reduction and/or interruption was Grade 3 or 4 in 1 subject in each of the combination and lenvatinib arms, and in 4 subjects (8.0%) in the everolimus arm.

Hyperglycaemia

The incidence of hyperglycaemia is described as 'very common' in the SmPC of Afinitor. Its incidence (any grade) was much higher in the RCC combination group (17.7%) compared with that in the All DTC Safety Set (5.0%). No Grade 3 or 4 events were reported in the RCC combination group. Hyperglycaemia (any grade; Grade 3 or 4) was reported in the RCC lenvatinib group (5.8%; 0%) and in the RCC everolimus group (24.0%; 10.0%).

Pruritus

The incidence of pruritus is described as very common in the SmPC of Afinitor. Its incidence (any grade) was much higher in the RCC combination group (12.9%) compared with that in the All DTC Safety Set (5.7%). No Grade 3 or 4 events were reported in the RCC combination group. Pruritus Grade 1 or 2, but no grade 3 or 4 events have been reported in the RCC lenvatinib group (5.8%) and in the RCC everolimus group (14.0%).

Safety signals already known for both lenvatinib and everolimus

Fatigue, vomiting, hypercholesterolemia, dehydration, and acute renal failure were reported with an increased frequency in the RCC combination group relative to the All DTC Safety Set. Diarrhoea was added because of its high frequency.

Diarrhoea

In the RCC study, diarrhoea was reported in 80.6% of patients in the combination group (21.0% were Grade ≥ 3) and in 34.0% of patients in the everolimus-treated group (2.0% were Grade ≥ 3). The median time to onset was 4.1 weeks (any grade) and 8.1 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Diarrhoea was the most frequent cause of dose interruption/reduction and recurred despite dose reduction. Diarrhoea resulted in discontinuation in one patient. The increased frequency of severe diarrhoea in the RCC combination group appears to represent an additive effect of the 2 therapies, a worsening safety signal for the combination therapy and can be managed with dose reductions and medical therapy, including prompt institution of antidiarrheal medication at the first onset of this TEAE.

Vomiting

Vomiting showed a similar pattern with incidences of 12%, 38.5% and 48.4% in the everolimus, lenvatinib and combination groups. No discontinuation was due to this AE. The incidence of vomiting that led to dose reduction and/or interruption was 19.6% (n=10) in the combination, 5.8% (n=3) in the lenvatinib and in 0% in the everolimus arm. Grade 3 or 4 vomiting led to dose reduction and/or interruption in 3 subjects (5.9%) in the combination and 2 subjects (3.8%) in the lenvatinib arms.

Fatigue

Similarly to diarrhoea but in a much lower extent, the combination appears to exert additional effects on fatigue according to the incidences of 32%, 40.4% but 59.7% in the RCC everolimus, lenvatinib and combination groups respectively (incidences of 0%, 7.7% and 12.9 % for grade 3 and 4 AEs, respectively). No discontinuation was due to this AE. Another constitutional symptom asthenia was reported in 24.2% of subjects in the combination group, 15.4% in the lenvatinib group, and 6.0% in the everolimus group. There was only 1 event of Grade 4 asthenia, which occurred in the everolimus group (there were only 1 or 2 events of Grade ≥ 3 asthenia in each of the 3 groups). Weight loss was reported in 33.9% of subjects in the combination group, 50.0% in the lenvatinib group, and 8.0% in the everolimus group. Unlike the trend observed for fatigue and asthenia, lenvatinib and everolimus combination treatment did not demonstrate increase in the observed incidence of weight loss compared to the single agents alone. There were no treatment discontinuations due to asthenia or weight loss in any of the 3 treatment groups.

Table 48: Summary of constitutional symptoms

Parameter (CTCAE Preferred Term)	Lenvatinib 18 mg + Everolimus 5 mg Phases 1b+2 (N=62)		Lenvatinib 24 mg Phase 2 (N=52)		Everolimus 10 mg Phase 2 (N=50)	
Grade of Lab Value:	**Any Grade n (%)**	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**
Fatigue	37 (59.7)	8 (12.9)	21 (40.4)	4 (7.7)	16 (32.0)	0
Asthenia	15 (24.2)	2 (3.2)	8 (15.4)	1 (1.9)	3 (6.0)	1 (2.0)
Weight Loss	21 (33.9)	2 (3.2)	26 (50.0)	3 (5.8)	4 (8.0)	0

Hypercholesterolemia and dyslipedemia

The incidence rate of hypercholesterolemia (any grade) was much higher in the RCC combination group (30.6%) compared with that in the All DTC Safety Set (3.3%), with that of the RCC lenvatinib arm (11.5%) or with that of the RCC everolimus arm (16%) and the increased incidence is a worsening safety signal for the combination therapy.

The most frequent events within the dyslipidemia SMQ were hypertriglyceridemia (40.3% in the RCC combination group, 13.5% in the RCC lenvatinib group, and 24.0% in the RCC everolimus group), hypercholesterolemia (30.6%, 11.5%, and 16.0%, respectively), and increased blood cholesterol (8.1%, 3.8%, and 6.0%, respectively). Dyslipidemia caused 5 interruptions and 2 reductions of drug in the RCC combination group but only one drug reduction in the lenvatinib arm.

Dehydration

The incidence of grade 3 or 4 dehydration (5 pts; 8.1%) in the combination arm is significantly higher than in the lenvatinib arm and the everolimus arm (both 0%).

Acute renal failure

This AE is described above in the section on significant AEs.

Abdominal pain

Abdominal pain (upper) led to dose reduction and/or interruption in 9.8% (n=5), 3.8% (n=2) and 0% in the combination, lenvatinib, and everolimus arms, respectively. One subject (2.0%) in the combination arm had Grade 3 upper abdominal pain that led to dose reduction/interruption.

Long-Term Safety

Long-term safety data for the combination are currently limited to the results available from Study 205.

Table 49: Overall Adverse Event Profile for the Combination Arm by Study Drug Treatment Period – Study 205 (Phase 2 + Proposed Dose Pooled Safety Set)

Category	0–6 mo N=62 n (%)	>6–12 mo N=33 n (%)	>12–18 mo N=24 n (%)	>18–24 mo N=12 n (%)	>24 mo N=7 n (%)
TEAEs	62 (100.0)	33 (100.0)	23 (95.8)	12 (100.0)	6 (85.7)
Treatment-related TEAEs	62 (100.0)	32 (97.0)	23 (95.8)	12 (100.0)	6 (85.7)
Grade ≥3 TEAEs	44 (71.0)	8 (24.2)	10 (41.7)	3 (25.0)	2 (28.6)
Treatment-related Grade ≥3 TEAEs[a]	38 (61.3)	8 (24.2)	8 (33.3)	2 (16.7)	2 (28.6)
SAEs	28 (45.2)	5 (15.2)	7 (29.2)	2 (16.7)	0 (0.0)
Deaths	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nonfatal SAEs	27 (43.5)	5 (15.2)	7 (29.2)	2 (16.7)	0 (0.0)
TEAEs leading to study drug dose adjustment[b]	54 (87.1)	15 (45.5)	16 (66.7)	5 (41.7)	1 (14.3)
TEAEs leading to study drug withdrawal	13 (21.0)	1 (3.0)	3 (12.5)	0 (0.0)	1 (14.3)
TEAEs leading to study drug dose reduction	39 (62.9)	3 (9.1)	5 (20.8)	1 (8.3)	0 (0.0)
TEAEs leading to study drug dose interruption	43 (69.4)	13 (39.4)	11 (45.8)	4 (33.3)	1 (14.3)

For each row category, a subject with 2 or more AEs in that category in each interval is counted only once for that time interval. However, if a subject had more than 1 episode of the same AE across multiple intervals, episodes are counted separately as new events for each relevant interval. Only subjects with a specific AE reported in a given interval are counted for that interval. Percentages are based on total number of subjects at risk in each period.

a: Treatment-related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality.

b: Dose adjustment includes study drug withdrawal, dose reduction, and/or interruption. Subjects may be counted in multiple categories.

As of the 31 Jul 2015 cutoff date for the RCC Safety Set, a total of 46 subjects (28.0%) were still ongoing (4 receiving treatment and 42 in follow-up) in Study 205. The pharmacovigilance database was reviewed with the cutoff date of 27 Apr 2016. One of the 4 follow-up reports for SAEs pertained to a fatal event with the time to onset of 844 days after the subject's first dose. Based on additional follow-up information this was a case of myocardial infarction. The coroner's postmortem report confirmed the immediate cause of death as being attributed to acute plaque haemorrhage of the left descending artery. The subject had advanced atherosclerosis of the coronary vessels and a medical history of hypercholesterolemia and Type 2 diabetes.

Given that long-term safey data with lenvatinib and its combination with everolimus are limited in the RCC patients, long-term safety data for lenvatinib monotherapy are of particular relevance to inform on lenvatinib safety at long term and to compare safety profiles of the combination versus single-agent therapies. In the lenvatinib monotherapy All DTC safety set, 139 subjects ($\approx$ 30%) received lenvatinib for longer than 24 months. Of these 139 subjects, 28.8% had a severe (Grade 3 or 4) TEAE after 24 months of treatment, most commonly hypertension (8 subjects, 5.8%) and diarrhea (5, 3.6%). The most frequently reported CSEs ($\geq$ 10% of subjects) after 24 months of lenvatinib treatment in Lenvatinib either the All DTC (N=139) or Non-DTC (N=26) safety sets were hypertension, proteinuria, hemorrhage, liver events, and PPE.

Serious adverse event/deaths/other significant events

Table 50: Serious Adverse Events That Occurred in 3% or More of Subjects in the RCC Phases 1b+2 Combination Group – RCC, All DTC, and Non DTC Safety Sets

Preferred Term	Renal Cell Carcinoma			All DTC	Non-DTC
	Lenvatinib + Everolimus 18mg + 5mg (N = 62)* n(%)	Lenvatinib 24mg (N = 52) n(%)	Everolimus 10mg (N = 50) n(%)	Lenvatinib (N = 458) n(%)	Lenvatinib (N = 656) n(%)
Subjects with at least One Serious TEAE	38 (61.3)	28 (53.8)	21 (42.0)	263 (57.4)	314 (47.9)
Dehydration	6 (9.7)	0	0	15 (3.3)	19 (2.9)
Renal Failure Acute	5 (8.1)	4 (7.7)	0	6 (1.3)	9 (1.4)
Anaemia	4 (6.5)	1 (1.9)	4 (8.0)	2 (0.4)	2 (0.3)
Diarrhoea	3 (4.8)	0	0	3 (0.7)	14 (2.1)
Dyspnoea	3 (4.8)	1 (1.9)	2 (4.0)	7 (1.5)	9 (1.4)
Thrombocytopenia	3 (4.8)	0	0	1 (0.2)	3 (0.5)
Vomiting	3 (4.8)	0	0	6 (1.3)	19 (2.9)
Confusional State	2 (3.2)	1 (1.9)	0	3 (0.7)	7 (1.1)
General Physical Health Deterioration	2 (3.2)	0	0	8 (1.7)	12 (1.8)
Hyperkalaemia	2 (3.2)	0	0	0	1 (0.2)
Musculoskeletal Chest Pain	2 (3.2)	1 (1.9)	0	2 (0.4)	1 (0.2)
Pyrexia	2 (3.2)	0	1 (2.0)	3 (0.7)	8 (1.2)
Renal Impairment	2 (3.2)	0	0	1 (0.2)	0

Deaths

Table 51: Table Listing of Fatal Adverse Events – Safety Analysis Set (Phase 2)

Subject ID Age (yr), Sex, Race	Fatal Adverse Event Preferred term/ (Investigator Term)	Relationship to Study Drug[a]	Study Day of AE Onset/ Death[b]	Last Dose Before Death (mg)	Duration of Treatment (days)[c]	Day of Death in Relation to Last Dose[d]
Combination Arm (Lenvatinib 18mg + Everolimus 5 mg)						
	Cerebral haemorrhage (Brain hemorrhage)	Probably related	27 / 27	24 / 5e	26	2

Subject ID Age (yr), Sex, Race	Fatal Adverse Event Preferred term/ (Investigator Term)	Relationship to Study Drug[a]	Study Day of AE Onset/ Death[b]	Last Dose Before Death (mg)	Duration of Treatment (days)[c]	Day of Death in Relation to Last Dose[d]
Lenvatinib 24 mg						
	Myocardial infarction (Myocardial infarction)	Possibly related	700 / 700	10	700	1
	Haemorrhage intracranial (Intracranial hemorrhage)	Not related	195/ 195	20	168	28
	Sepsis (Sepsis)	Not related	37 / 37	24	33	5
Everolimus 10 mg						
	Acute respiratory failure (Acute respiratory failure)[f]	Not related	447 / 457	10	446	12
	Escherichia sepsis (Sepsis E. coli)	Not related	38 / 38	10	26	13

Adverse event terms were coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) version 16.1. Includes treatment-emergent fatal AEs as of the data cutoff date (13 Jun 2014). Age is age at informed consent. AE = adverse event, F = female, M = male, W = white, yr = year.
a: As assessed by the investigator.
b: Study Day of Death = date of death – date of first dose of study drug +1
c: Duration of Treatment = date of last dose of study drug – date of first dose of study drug +1
d: Number of days between end of treatment with study drug and death.
e: Lenvatinib dose / everolimus dose. Lenvatinib dose corrected post DBL to 18 mg in database (lenvatinib dosing in combination arm).
f: Acute respiratory failure was secondary to pneumonia.

There were 6 subjects with fatal AEs: 1 in the combination arm, 3 in the lenvatinib arm and 2 in the everolimus arm. None of these subjects had progressive disease reported as the cause of death by the investigator. In 1 subject in the lenvatinib arm, the investigator did not specify whether progressive disease was present at the time of death.

The subject in the combination arm died of a cerebral haemorrhage that was considered probably related to study medication by the investigator. A 58-year-old White female diagnosed with metastatic clear cell renal cell carcinomahad medical history of anaemia, constipation and fatigue. Previous anticancer therapy included sunitinib. Concomitant medications included iron, magnesium and senna alexandrina. ECOG performance status at screening was 0. The subject was admitted to the hospital due to severe headache, hypertension and vomiting. Within one hour of admission, the subject became noncommunicative. A CT of the brain showed cerebral haemorrhage. The study medication was withdrawn and the subject received the last dose of study medication. Later that day, one day after the last dose, the subject died due to cerebral haemorrhage. The Investigator considered this event serious and probably related to the study medication.

Of the 3 subjects that had fatal AEs in the lenvatinib group:

• 1 subject with a history of aortic arteriosclerosis and atherosclerotic calcification of coronary arteries died of a myocardial infarction that was considered possibly related to lenvatinib treatment by the investigator.

• 1 subject died of an intracranial haemorrhage that was considered not related to lenvatinib treatment; the investigator did not specify whether progressive disease was present at the time of death. This subject had a

history of hypertension, craniotomy for microsurgical resection of brain metastases, and prior radiotherapy to the left frontal lobe.

• 1 subject died of sepsis that was considered not related to lenvatinib treatment by the investigator. The subject was hospitalized for both acute renal failure and sepsis (etiology unknown) at the time of death.

In the everolimus arm, one subject died of respiratory failure and the other subject died of E.coli sepsis. The first subject had pneumonia (Grade 3) that resulted in respiratory failure with pericardial effusion (Grade 3) and cardiac tamponade (Grade 4) as contributing factors.

One subject died of myocardial infarction in the combination arm after data cutoff date of 31July 2015 (see 'Long-term safety' section above).

Laboratory findings

Table 52: Treatment Emergent Markedly Abnormal Laboratory Results – study 205 (Phase 2)

Laboratory Test Statistic	RENAL Cell Carcinoma				All DTC
	Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N=62)*	Lenvatinib 18mg + Everolimus 5mg Phase II (N=51)	Lenvatinib 24mg (N=52)	Everolimus 10mg (N=50)	Lenvatinib (N=458)
HEMATOLOGY					
Hemoglobin					
Study Overall, n [a]	62	51	51	50	447
Markedly Abnormal High	1 (1.6)	1 (2.0)	1 (2.0)	0	5 (1.1)
Markedly Abnormal Low	6 (9.7)	5 (9.8)	2 (3.9)	12 (24.0)	21 (4.7)
Platelets					
Study Overall, n [a]	61	50	51	50	446
Markedly Abnormal Low	9 (14.8)	7 (14.0)	1 (2.0)	1 (2.0)	22 (4.9)
Leukocytes					
Study Overall, n [a]	62	51	51	50	447
Markedly Abnormal Low	6 (9.7)	5 (9.8)	2 (3.9)	5 (10.0)	33 (7.4)
Neutrophils					
Study Overall, n [a]	61	51	51	50	429
Markedly Abnormal Low	6 (9.8)	5 (9.8)	3 (5.9)	0	34 (7.9)
Lymphocytes					
Study Overall, n [a]	61	51	51	50	423
Markedly Abnormal High	3 (4.9)	2 (3.9)	1 (2.0)	0	9 (2.1)
Markedly Abnormal Low	20 (32.8)	15 (29.4)	12 (23.5)	14 (28.0)	105 (24.8)
CHEMISTRY					
Creatinine					
Study Overall, n [a]	62	51	51	50	449
Markedly Abnormal High	8 (12.9)	7 (13.7)	5 (9.8)	6 (12.0)	57 (12.7)
Aspartate Aminotransferase					
Study Overall, n [a]	62	51	51	50	449
Markedly Abnormal High	5 (8.1)	4 (7.8)	2 (3.9)	0	26 (5.8)

Alanine Aminotransferase					
Study Overall, n [a]	62	51	51	48	449
Markedly Abnormal High	6 (9.7)	4 (7.8)	2 (3.9)	2 (4.2)	32 (7.1)
Alkaline Phosphatase					
Study Overall, n [a]	62	51	51	50	449
Markedly Abnormal High	5 (8.1)	4 (7.8)	3 (5.9)	1 (2.0)	17 (3.8)
Bilirubin					
Study Overall, n [a]	62	51	51	50	421
Markedly Abnormal High	1 (1.6)	1 (2.0)	1 (2.0)	0	24 (5.7)
Potassium					
Study Overall, n [a]	62	51	51	50	449
Markedly Abnormal High	5 (8.1)	5 (9.8)	6 (11.8)	3 (6.0)	25 (5.6)
Markedly Abnormal Low	4 (6.5)	4 (7.8)	4 (7.8)	1 (2.0)	27 (6.0)
Sodium					
Study Overall, n [a]	62	51	51	50	449
Markedly Abnormal High	0	0	1 (2.0)	0	4 (0.9)
Markedly Abnormal Low	7 (11.3)	5 (9.8)	3 (5.9)	3 (6.0)	27 (6.0)
Calcium					
Study Overall, n [a]	62	51	51	50	449
Markedly Abnormal High	1 (1.6)	1 (2.0)	1 (2.0)	1 (2.0)	17 (3.8)
Markedly Abnormal Low	8 (12.9)	6 (11.8)	7 (13.7)	3 (6.0)	101 (22.5)
Phosphate					
Study Overall, n [a]	62	51	51	49	425
Markedly Abnormal Low	7 (11.3)	7 (13.7)	2 (3.9)	3 (6.1)	6 (1.4)
Glucose Chemistry					
Study Overall, n [a]	61	50	51	48	425
Markedly Abnormal High	6 (9.8)	5 (10.0)	8 (15.7)	11 (22.9)	30 (7.1)
Markedly Abnormal Low	1 (1.6)	0	1 (2.0)	1 (2.1)	14 (3.3)
Triglycerides					
Study Overall, n [a]	62	51	51	50	271
Markedly Abnormal High	18 (29.0)	15 (29.4)	11 (21.6)	15 (30.0)	20 (7.4)
Cholesterol					
Study Overall, n [a]	62	51	51	50	279
Markedly Abnormal High	19 (30.6)	15 (29.4)	6 (11.8)	6 (12.0)	36 (12.9)
Albumin					
Study Overall, n [a]	62	51	51	50	449
Markedly Abnormal Low	5 (8.1)	4 (7.8)	6 (11.8)	1 (2.0)	96 (21.4)
Magnesium					
Study Overall, n [a]	62	51	51	50	425
Markedly Abnormal High	0	0	0	0	4 (0.9)
Markedly Abnormal Low	3 (4.8)	3 (5.9)	6 (11.8)	0	17 (4.0)
Creatine Kinase					
Study Overall, n [a]	57	48	48	44	409
Markedly Abnormal High	8 (14.0)	6 (12.5)	3 (6.3)	6 (13.6)	24 (5.9)
Triacylglycerol Lipase					
Study Overall, n [a]	57	48	48	44	362
Markedly Abnormal High	9 (15.8)	8 (16.7)	6 (12.5)	8 (18.2)	20 (5.5)

* Includes all subjects who received lenvatinib 18 mg + everolimus 5 mg dose from both Phase I and Phase II portion of study E7080-G000-205. [a] Indicates the number of subjects with non-missing baseline and post-baseline data; this number is used to calculate percentages within each laboratory test. Markedly abnormal is defined as a value that is above or below the normal range and the CTCAE grade increased from baseline by 2 or more grades, except for phosphate which must have shifted by 3 or more grades. Subjects are counted only once for each row. Laboratory Results were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The data cut off date for the RCC set is 31JUL2015, data cut off date for the All DTC set is 10DEC2014.

Safety in special populations

Age

Overall there was no meaningful difference in the AE profile between the older (≥ 65 years) and younger (< 65 years) subjects for the RCC combination group. The findings for the RCC combination group were comparable with those for the All DTC and the Non DTC Safety Sets.

Gender

No meaningful differences between male and female subjects for the RCC combination group with the exception of a trend toward a higher rate of treatment discontinuation among female subjects (44%) compared with male subjects (22.7%). However the numbers are low and no firm conclusion can be drawn.

Race

The studied population was essentially white, other races were underrepresented.

Weight

The RCC combination group showed similar mean decreases in body weight (maximum mean change: minus 15.83 kg) compared with that for the RCC lenvatinib group (maximum mean change: minus 12.60 kg) at time points for which more than 2 subjects contributed data. The selected RCC patients had relatively high BMI and were not representative of patients with lower weight. An analysis of weight loss by body mass index done in the All DTC Safety Set indicated that weight loss was greater for subjects in the obese and overweight categories at Baseline than for subjects in the underweight or normal weight categories. The number of patients is too low to draw firm conclusions.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions

Please refer to the PK assessment report and PD section (Section 2.4) of this report.

Drug-disease interactions

The safety of lenvatinib in combination with everolimus was evaluated in subjects with potential baseline disease risk factors. These include renal impairment, hepatic impairment, hypertension, and diabetes.

The CSE of Renal Events tended to occur at a higher incidence rate in subjects with baseline renal impairment compared with those without baseline renal impairment for the RCC combination group (27.8% vs. 13.6%). This difference was also observed for the All DTC Safety Set (24.5% vs. 11.5%); a similar trend was observed for the Non-DTC Safety Set 11.5% vs. 6.9%).

The safety of lenvatinib in combination with everolimus in subjects with RCC was evaluated by baseline hepatic function: Not Impaired and Impaired subgroups. Subjects were considered to have baseline hepatic impairment if their baseline AST, ALT, or bilirubin levels were a CTCAE Grade 1 or higher (Impaired subgroup). For the RCC Safety Set groups, the number of subjects with impaired hepatic function at baseline

was very small: 6 subjects overall; 3 (4.8%) of 62 subjects in the RCC combination group and 3 (5.8%) of 52 subjects in the RCC lenvatinib group. Because the percentage of subjects in the RCC combination group was less than 5%, no meaningful comparisons can be made. Therefore, baseline hepatic function was not further discussed.

Baseline hypertension (yes vs no subgroups) was evaluated as risk factor. The overall incidence rate of SAEs for the RCC Safety Set, were similar (63.0% vs. 56.3%) in subjects with and without baseline hypertension. Patients with baseline hypertension had a higher incidence of Grade 3 or 4 dehydration, fatigue, and hypertension (SmPC section 4.8). The following higher incidence rate in subjects with baseline hypertension than in those without in the RCC combination group were reported: dehydration (10.9% vs. 0%), fatigue (15.2% vs. 6.3%), and hypertension (17.4% vs. 0%).

Subjects were considered to have baseline diabetes if they had a medical history of diabetes or hyperglycaemia or received any prior diabetic medications. Although the number of subjects with baseline diabetes was small (n=9) in the RCC combination group, severe acute renal failure (22.2% vs. 5.7%), hypertension (22.2% vs. 11.3%), and hypertriglyceridemia (33.3% vs. 9.4%) tended to be reported at a higher incidence rate in subjects with baseline diabetes than in those without baseline diabetes. Of note, severe diarrhea and fatigue occurred more frequently in subjects without baseline diabetes than in those with baseline diabetes in the RCC combination group. The following common TEAEs were reported at a higher incidence rate in subjects with baseline diabetes than in those without baseline diabetes for the RCC combination group: abdominal distension (22.2% vs. 5.7%), acute renal failure (22.2% vs. 5.7%), asthenia (33.3% vs. 22.6%), hyperglycaemia (33.3% vs. 15.1%), hyperkalemia (22.2% vs. 5.7%), hypertriglyceridemia (55.6% vs. 37.7%), musculoskeletal chest pain (33.3% vs. 15.1%), nausea (55.6% vs. 43.4%), and vomiting (66.7% vs. 45.3%). Therefore, the SmPC section 4.8 states that patients with baseline diabetes had a higher incidence of Grade 3 or 4 hypertension, hypertriglyceridemia and acute renal failure.

Discontinuation due to adverse events

In the RCC study 18 (29%) of patients discontinued treatment due to adverse events. Most individual AEs leading to study treatment discontinuation were reported in not more than 1 subject; the only AEs that led to discontinuation in more than 1 subject were thrombocytopenia in 2 (3.9%) subjects in the combination arm, myocardial infarction/acute myocardial infarction in 2 (3.9%) subjects in the lenvatinib arm, and pneumonitis in 2 (4.0%) subjects in the everolimus arm. Five (9.8%) subjects in the combination arm, 8 (15.4%) subjects in the lenvatinib arm, and 3 (6.0%) subjects in the everolimus arm discontinued study medication as a result of Grade 3 or 4 AEs.

The rate of discontinuation due to TEAEs in the Phase 1b+2 combination arm as of 31 Jul 2015 was similar before Cycle 5 (5 subjects; 0.24/subject year [SY]) and after Cycle 5 (9 subjects; 0.26/SY).

Eight subjects, 3 in each of the combination and lenvatinib arms, and 2 in the everolimus arm, discontinued study medication due to 1 or more Grade 4 or 5 AEs. These events included a) Grade 4 hypokalemia, Grade 4 dyspnoea, and Grade 5 cerebral haemorrhage in 1 subject each in the combination arm, b) Grade 5 myocardial infarction, Grade 4 intracranial haemorrhage, and Grade 4 sepsis in 1 subject each in the lenvatinib arm and c) Grade 4 pulmonary embolism and Grade 4 Escherichia sepsis in 1 subject each in the everolimus arm.

Table 53: Adverse Events Leading to Study Treatment Discontinuation by Preferred Term – Study 205 (Phase 2)

MedDRA Preferred Term	Lenvatinib + Everolimus 18mg + 5mg (N = 51) n (%)			Lenvatinib 24 mg (N = 52) n (%)			Everolimus 10 mg (N = 50) n (%)		
	All Grade	Gr 3	Gr 4	All Grade	Gr 3	Gr 4	All Grade	Gr 3	Gr 4
Subjects with any TEAEs Leading to Treatment Discontinuation[a]	13 (25.5)			16 (30.8)			6 (12.0)		
Thrombocytopenia	2 (3.9)								
Alanine Aminotransferase Increased	1 (2.0)	1 (2.0)		1 (2.0)					
Arthralgia	1 (2.0)								
Aspartate Aminotransferase Increased	1 (2.0)	1 (2.0)							
Cerebral Haemorrhage[b]	1 (2.0)								
Confusional State	1 (2.0)	1 (2.0)							
Convulsion	1 (2.0)	1 (2.0)							
Diarrhoea	1 (2.0)	1 (2.0)							
Dyspnoea	1 (2.0)		1[e] (2.0)				1 (2.0)		
Gastric Haemorrhage	1 (2.0)	1 (2.0)							
Hepatic Pain	1 (2.0)								
Hyperkalaemia	1 (2.0)		1 (2.0)						
Hypokalaemia	1 (2.0)								
Hypomagnesaemia	1 (2.0)	1 (2.0)							
Penile Oedema	1 (2.0)								
Proteinuria	2 (3.9)			3 (5.8)	1 (1.9)				
Weight Decreased	1 (2.0)			1 (1.9)					
Acute Myocardial Infarction				1 (1.9)	1 (1.9)				
Back Pain				1 (1.9)					
Cholecystitis				1 (1.9)					
Ejection Fraction Decreased				1 (1.9)					
Escherichia Sepsis							1 (2.0)		1 (2.0)
Haemorrhage Intracranial				1 (1.9)		1 (1.9)			
Inappropriate Antidiuretic Hormone Secretion				1 (1.9)	1 (1.9)				
Metastatic Pain[c]				1 (1.9)					
Myocardial Infarction[b]				1 (1.9)					
Osteolysis				1 (1.9)	1 (1.9)				
Pneumonitis							2 (4.0)	1 (2.0)	
Posterior Reversible Encephalopathy Syndrome				1 (1.9)	1 (1.9)				
Pulmonary Embolism							1 (2.0)		1 (2.0)
Renal Failure Acute				1 (1.9)	1 (1.9)				
Sepsis				1 (1.9)[b]		1 (1.9)			
Spinal Cord Compression[d]							1 (2.0)		

Data cutoff date = 13 Jun 2014 and 31 jul 2015 (yellow) . Percentages are based on the total number of subjects in the Safety Analysis Set within relevant treatment group. Display is in decreasing order of frequency of TEAEs in the (lenvatinib + everolimus) arm. Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.1.

Gr = grade, TEAE = treatment-emergent adverse event.

a: Subjects with 2 or more adverse events in the same preferred term are counted only once for that preferred term.
b: Grade 5. See Table 32 for a listing of subjects with fatal adverse events.
c: Subject had clinical progression (rib lesion) at the time of the event.
d: Subject had progressive disease (L2 vertebral body lesion) at the time of the event.
e: Investigator reported term was shortness of breath due to disease progression.

Dose modifications (reductions and interruptions)

Table 54: Time to First Dose Reduction among Subjects with Dose Reduction

	Renal Cell Carcinoma				All DTC
	Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N = 62)*	Lenvatinib 18mg + Everolimus 5mg Phase II (N = 51)	Lenvatinib 24mg (N = 52)	Everolimus 10mg (N = 50)	Lenvatinib (N = 458)
Subjects with Any Dose Reduction[1], n (%)	44 (71.0)	36 (70.6)	32 (61.5)	13 (26.0)	357 (77.9)
Time to Dose Reduction (Months)					
Median (95% CI)	1.8 (1.3, 2.5)	1.7 (1.1, 2.5)	2.3 (1.8, 3.3)	2.5 (1.9, 7.8)	2.3 (1.8, 2.8)
Q1, Q3	1.1 ,3.7	1.0 ,3.6	1.5 ,4.0	2.1 ,7.8	0.9 ,5.1

* Includes all subjects who received lenvatinib 18 mg + everolimus 5 mg dose from both Phase I and Phase II portion of study E7080-G000-205. [1] Includes subjects with dose reduction in either lenvatinib or everolimus. [2] Includes subjects with dose reduction in lenvatinib. [3] Includes subjects with dose reduction in everolimus. 95% CI was estimated using the log-log transformation from Kaplan-Meier method. Percentages are based on total number of subjects in each treatment group within each safety analysis set. The data cut off date for the RCC set is 31JUL2015, data cut off date for the All DTC set is 10DEC2014.

- *Lenvatinib*

Table 55: Summary of Last Dose Levels for Lenvatinib – Safety Analysis Set

Last Dose Levels [a]	Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N=62)* n(%)	Lenvatinib 18mg + Everolimus 5mg Phase II (N=51) n(%)	Lenvatinib 24mg (N=52) n(%)
24 mg	0 (0.0)	0 (0.0)	20 (38.5)
20 mg	0 (0.0)	0 (0.0)	15 (28.8)
18 mg	18 (29.0)	15 (29.4)	0 (0.0)
14 mg	19 (30.6)	15 (29.4)	6 (11.5)
10 mg	14 (22.6)	12 (23.5)	8 (15.4)
8 mg	10 (16.1)	8 (15.7)	2 (3.8)
4 mg	1 (1.6)	1 (2.0)	1 (1.9)

Table 55: Summary of Last Dose Levels for Lenvatinib – Safety Analysis Set

Last Dose Levels [a]	Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N=62)* n(%)	Lenvatinib 18mg + Everolimus 5mg Phase II (N=51) n(%)	Lenvatinib 24mg (N=52) n(%)

* Includes all subjects who received lenvatinib 18 mg + everolimus 5 mg dose from both Phase I and Phase II portion of study E7080-G000-205.
Percentages are based on the total number of subjects in the safety analysis set within relevant treatment group.
[a] This is the last non-zero dose.

Table 56: Dose reductions and interruptions in lenvatinib (data cutoff 31Jul2015)

	Renal Cell Carcinoma			All DTC
	Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N = 62)* n (%)	Lenvatinib 18mg + Everolimus 5mg Phase II (N = 51) n (%)	Lenvatinib 24mg (N = 52) n (%)	Lenvatinib (N = 458) n (%)
Dose Reduction				
Total Number of Subjects with Dose Reduction	44 (71.0)	36 (70.6)	32 (61.5)	357 (77.9)
Cycle of First Dose Reduction (until cycle 10)				
Cycle 1	6 (9.7)	6 (11.8)	4 (7.7)	92 (20.1)
Cycle 2	16 (25.8)	13 (25.5)	6 (11.5)	70 (15.3)
Cycle 3	8 (12.9)	6 (11.8)	10 (19.2)	29 (6.3)
Cycle 4	3 (4.8)	2 (3.9)	3 (5.8)	35 (7.6)
Cycle 5	1 (1.6)	1 (2.0)	3 (5.8)	28 (6.1)
Cycle 6	4 (6.5)	3 (5.9)	2 (3.8)	21 (4.6)
Cycle 7	1 (1.6)	1 (2.0)	1 (1.9)	24 (5.2)
Cycle 8	2 (3.2)	2 (3.9)	2 (3.8)	7 (1.5)
Cycle 9	1 (1.6)	1 (2.0)	-	9 (2.0)
Cycle 10	-	-	-	6 (1.3)
Frequency of Dose Reductions [1]				
1	19 (30.6)	15 (29.4)	15 (28.8)	98 (21.4)
2	14 (22.6)	12 (23.5)	6 (11.5)	115 (25.1)
3	10 (16.1)	8 (15.7)	8 (15.4)	94 (20.5)
>=4	1 (1.6)	1 (2.0)	3 (5.8)	50 (10.9)
Dose Interruptions				
Total Number of Subjects with Dose Interruptions	50 (80.6)	41 (80.4)	39 (75.0)	282 (61.6)
Cycle of First Dose Interruption (until cycle 10)				
Cycle 1	18 (29.0)	16 (31.4)	11 (21.2)	54 (11.8)

Cycle 2	15 (24.2)	11 (21.6)	10 (19.2)	39 (8.5)
Cycle 3	6 (9.7)	6 (11.8)	5 (9.6)	39 (8.5)
Cycle 4	3 (4.8)	2 (3.9)	6 (11.5)	33 (7.2)
Cycle 5	2 (3.2)	2 (3.9)	3 (5.8)	18 (3.9)
Cycle 6	4 (6.5)	3 (5.9)	-	12 (2.6)
Cycle 7	2 (3.2)	1 (2.0)	3 (5.8)	9 (2.0)
Cycle 8	-	-	-	5 (1.1)
Cycle 9	-	-	-	15 (3.3)
Cycle 10	-	-	1 (1.9)	11 (2.4)
Frequency of Dose Interruptions				
1	17 (27.4)	13 (25.5)	10 (19.2)	83 (18.1)
2	9 (14.5)	7 (13.7)	10 (19.2)	50 (10.9)
3	4 (6.5)	4 (7.8)	8 (15.4)	37 (8.1)
>=4	20 (32.3)	17 (33.3)	11 (21.2)	112 (24.5)
Dose Discontinuation				
Drug Discontinuation due to AE	18 (29.0)	13 (25.5)	16 (30.8)	96 (21.0)
Cycle of Drug Discontinuation (until cycle 10)				
Cycle 1	1 (1.6)	1 (2.0)	2 (3.8)	16 (3.5)
Cycle 2	1 (1.6)	1 (2.0)	1 (1.9)	10 (2.2)
Cycle 3	1 (1.6)	1 (2.0)	2 (3.8)	10 (2.2)
Cycle 4	2 (3.2)	1 (2.0)	1 (1.9)	10 (2.2)
Cycle 5	2 (3.2)	1 (2.0)	-	7 (1.5)
Cycle 6	3 (4.8)	2 (3.9)	1 (1.9)	4 (0.9)
Cycle 7	3 (4.8)	3 (5.9)	2 (3.8)	7 (1.5)
Cycle 8	-	-	-	1 (0.2)
Cycle 9	1 (1.6)	1 (2.0)	1 (1.9)	5 (1.1)
Cycle 10	-	-	2 (3.8)	4 (0.9)
Cycle 11	-	-	-	1 (0.2)
Cycle 13	-	-	-	1 (0.2)
Cycle 14	-	-	-	1 (0.2)
Cycle 15	1 (1.6)	-	-	1 (0.2)
Cycle 16	-	-	-	2 (0.4)
Cycle 18	1 (1.6)	-	-	1 (0.2)
Cycle 19	-	-	-	1 (0.2)
Cycle 20	1 (1.6)	1 (2.0)	1 (1.9)	-
Cycle 21	-	-	-	2 (0.4)
Cycle 22	-	-	1 (1.9)	3 (0.7)
Cycle 23	-	-	-	1 (0.2)
Cycle 25	-	-	2 (3.8)	2 (0.4)
Cycle 30	1 (1.6)	1 (2.0)	-	-
Cycle 32	-	-	-	3 (0.7)
Cycle 33	-	-	-	2 (0.4)
Cycle 45	-	-	-	1 (0.2)

* Includes all subjects who received lenvatinib 18 mg + everolimus 5 mg dose from both Phase I and Phase II portion of study E7080-G000-205. [1] Dose reductions calculated directly from the dosing record (based on the planned dose). Drug discontinuation is based on AE data. Percentages are based on total number of subjects in each treatment group within each safety analysis set. The data cut off date for the RCC set is 31JUL2015, data cut off date for the All DTC set is 10DEC2014.

- *Everolimus.*

In the RCC combination group, 77.4% of subjects had 1 or more dose interruptions of everolimus compared to 54% of subjects in everolimus arm. Drug discontinuation occurred in 12% of patients in the everolimus group and it was 29% in the combination group.

Table 57: Dose interruptions in everolimus (data cutoff 31Jul2015)

	Renal Cell Carcinoma		
	Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N = 62)* n (%)	Lenvatinib 18mg + Everolimus 5mg Phase II (N = 51) n (%)	Everolimus 10 mg (N = 50) n (%)
Total Number of Subjects with Dose Reduction	1 (1.6)	1 (2.0)	13 (26)
Cycle of First Dose Reduction (until cycle 10)			
Cycle 2	0	6 (11.8)	2 (4.0)
Cycle 3	0	13 (25.5)	5 (10.0)
Cycle 6	1 (1.6)	1 (2.0)	1 (2.0)
Cycle 7	0	2 (3.9)	1 (2.0)
Cycle 9	0	1 (2.0)	1 (2.0)
Cycle 11	0	3 (5.9)	2 (4.0)
Cycle 12	0	1 (2.0)	1 (2.0)
Frequency of Dose Reductions [1]			
1	1 (1.6)	1 (2.0)	13 (26.0)
2	0	0	0
3	0	0	0
>=4	0	0	0
Total Number of Subjects with Dose Interruptions	48 (77.4)	39 (76.5)	27 (54.0)
Cycle of First Dose Interruption (until cycle 10)			
Cycle 1	18 (29.0)	16 (31.4)	4 (8.0)
Cycle 2	14 (22.2)	10 (19.6)	8 (16.0)
Cycle 3	4 (6.5)	4 (7.8)	6 (12.0)
Cycle 4	3 (4.8)	2 (3.9)	3 (6.0)
Cycle 5	2 (3.2)	2 (3.9)	1 (2.0)
Cycle 6	4 (6.5)	3 (5.9)	1 (2.0)
Cycle 7	2 (3.2)	1 (2.0)	1 (2.0)
Cycle 8	0	0	1 (2.0)
Cycle 9	1 (1.6)	1 (2.0)	0
Cycle 10	0	0	1 (2.0)
Cycle 11	0	0	1 (2.0)
Frequency of Dose Interruptions			
1	16 (25.8)	12 (23.5)	15 (30.0)

2	9 (14.5)	7 (13.7)	8 (16.0)
3	3 (4.8)	3 (5.9)	1 (2.0)
>=4	20 (32.3)	17 (33.3)	3 (6.0)
Drug discontinuation due to AEs	18 (29.0)	13 (25.5)	6 (12.0)

Adverse events that required dose reduction or interruption

The treatment-emergent adverse event (TEAE) that most frequently led to dose reduction was diarrhoea. Dose reductions for diarrhoea occurred at a higher frequency in the RCC combination arm (21.0%) compared with the RCC lenvatinib arm (13.5%) as well as for the All DTC (10.5%) and Non-DTC (3.5%) safety sets.

Table 58: Treatment-Emergent Adverse Events That Led to Dose Reduction in Greater Than 3% of Subjects for the RCC Phases 1b+2 Combination Group – RCC, All DTC, and Non DTC Safety Sets

	Renal Cell Carcinoma			All DTC	Non-DTC
Preferred Term	**Lenvatinib + Everolimus 18mg + 5mg** **(N = 62)*** **n (%)**	**Lenvatinib 24mg** **(N = 52)** **n (%)**	**Everolimus 10mg** **(N = 50)** **n (%)**	**Lenvatinib** **(N = 458)** **n (%)**	**Lenvatinib** **(N = 656)** **n (%)**
Subjects with at least 1 TEAE that led to dose reduction	42 (67.7)	30 (57.7)	8 (16.0)	298 (65.1)	186 (28.4)
Diarrhoea	13 (21.0)	7 (13.5)	-	48 (10.5)	23 (3.5)
Thrombocytopenia	4 (6.5)	-	-	8 (1.7)	6 (0.9)
Vomiting	4 (6.5)	1 (1.9)	-	13 (2.8)	7 (1.1)
Fatigue	3 (4.8)	3 (5.8)	1 (2.0)	42 (9.2)	35 (5.3)
Nausea	3 (4.8)	4 (7.7)	-	23 (5.0)	8 (1.2)
Proteinuria	3 (4.8)	3 (5.8)	1 (2.0)	50 (10.9)	21 (3.2)
Abdominal Pain Upper	2 (3.2)	-	-	4 (0.9)	-
Asthenia	2 (3.2)	2 (3.8)	1 (2.0)	21 (4.6)	9 (1.4)
Decreased Appetite	2 (3.2)	3 (5.8)	-	36 (7.9)	18 (2.7)
Hypertriglyceridaemia	2 (3.2)	-	-	-	-
Stomatitis	2 (3.2)	1 (1.9)	-	20 (4.4)	13 (2.0)
Weight Decreased	2 (3.2)	1 (1.9)	-	37 (8.1)	13 (2.0)

* Includes all subjects who received lenvatinib 18 mg + everolimus 5 mg dose from both Phase I and Phase II portion of study E7080-G000-205. Percentages are based on the total number of subjects in the safety analysis set within relevant treatment group. TEAE = Treatment-emergent Adverse Event. Subjects with two or more adverse events in the same preferred term are counted only once for that preferred term. Preferred terms are sorted in descending frequency based on the incidence rate in the RCC Phases 1b+2 combination group. If the incidence rate of 2 or more preferred terms was identical, the preferred terms have been sorted alphabetically. Adverse events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 for RCC Phase II + Proposed Dose Pooled Safety Set and All DTC Lenvatinib Safety Set and version 16.1 for Non-DTC Monotherapy Safety Set. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The data cut off date for the RCC set is 31JUL2015, data cut off date for the All DTC set is 10DEC2014 and 15SEP2013 for the Non-DTC set.

Adverse events leading to dose reduction and/or interruption as an action occurred with frequency of 88.7%, 78.8% and 54% respectively in the combination group, lenvatinib and everolimus arms. Gastrointestinal events, including diarrhea, vomiting and upper abdominal pain, resulted in dose reduction and/or interruption more often in the combination than in the lenvatinib and everolimus arms. Grade 3 or 4 diarrhea led to dose reduction and/or interruption in 7 subjects (11.3%) in the combination, 5 subjects (9.6%) in the lenvatinib, and 1 subject (2.0%) in the everolimus arm.

Table 59: Treatment-Emergent Adverse Events Leading to Dose Reduction and/or Dose Interruption in at Least 2 subjects in the Phase 2 part of Study 205 or 2% of All DTC Lenvatinib Safety Set.

| | Renal Cell Carcinoma | | | | | | All DTC | |
| | Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N=62)* | | Lenvatinib 24mg (N=52) | | Everolimus 10mg (N=50) | | Lenvatinib (N=458) | |
Preferred Term	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4
Subjects with any TEAEs Leading to Dose Reduction and/or Interruption	55 (88.7)	39 (62.9)	41 (78.8)	29 (55.8)	27 (54.0)	15 (30.0)	403 (88.0)	293 (64.0)
Diarrhoea	24(38.7)	7(11.3)	15(28.8)	5 (9.6)	1 (2.0)	1 (2.0)	104(22.7)	33(7.2)
Vomiting	11(17.7)	3 (4.8)	3 (5.8)	2 (3.8)	-	-	36 (7.9)	5 (1.1)
Fatigue	9 (14.5)	2 (3.2)	6 (11.5)	3 (5.8)	4 (8.0)	-	61(13.3)	20(4.4)
Decreased Appetite	7 (11.3)	3 (4.8)	7(13.5)	2 (3.8)			65(14.2)	21 (4.6)
Proteinuria	6 (9.7)	3 (4.8)	8 (15.4)	7(13.5)	1 (2.0)	1 (2.0)	87(19.0)	43 (9.4)
Abdominal Pain Upper	5 (8.1)	1 (1.6)	2 (3.8)	-	-	-	12 (2.6)	1 (0.2)
Asthenia	5 (8.1)	1 (1.6)	5 (9.6)	1 (1.9)	1 (2.0)	1 (2.0)	46(10.0)	20 (4.4)
Nausea	5 (8.1)	2 (3.2)	7 (13.5)	2 (3.8)	-	-	52(11.4)	7 (1.5)
Stomatitis	5 (8.1)	1 (1.6)	1 (1.9)	1 (1.9)	-	-	33 (7.2)	10 (2.2)
Thrombocytopenia	5 (8.1)	3 (4.8)	-	-	1 (2.0)	-	14 (3.1)	7 (1.5)
Hypertriglyceridaemia	4 (6.5)	4 (6.5)	-	-	-	-	1 (0.2)	-
Pyrexia	4 (6.5)	1 (1.6)	-	-	2 (4.0)	1 (2.0)	4 (0.9)	-
Renal Failure Acute	4 (6.5)	3 (4.8)	-	-	-	-	3 (0.7)	1 (0.2)
Weight Decreased	4 (6.5)	1 (1.6)	3 (5.8)	1 (1.9)	-	-	72(15.7)	28 (6.1)
Dehydration	3 (4.8)	3 (4.8)	-	-	-	-	15 (3.3)	9 (2.0)
Hypertension	3 (4.8)	2 (3.2)	6 (11.5)	4 (7.7)	-	-	97(21.2)	68 (14.8)
Abdominal Discomfort	2 (3.2)	-	-	-	-	-	-	-
Abdominal Pain	2 (3.2)	1 (1.6)	5 (9.6)	2 (3.8)	-	-	18(3.9)	3 (0.7)
	Renal Cell Carcinoma						All DTC	
	Lenvatinib 18mg + Everolimus 5mg Phase Ib + Phase II (N=62)*		Lenvatinib 24mg (N=52)		Everolimus 10mg (N=50)		Lenvatinib (N=458)	
Preferred Term	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4	All Grade	Grade 3 or 4
Blood Creatine Phosphokinase Increased	2 (3.2)	2 (3.2)	-	-	1 (2.0)	1 (2.0)	5 (1.1)	1 (0.2)
Dyspnoea	2 (3.2)	-	1 (1.9)	-	2 (4.0)	1 (2.0)	8 (1.7)	-
Gingivitis	2 (3.2)	-	-	-	-	-	1 (0.2)	-
Hypercholesterolaemia	2 (3.2)	2 (3.2)	1 (1.9)	1 (1.9)	-	-	-	-
Hypotension	2 (3.2)	-	-	-	-	-	12 (2.6)	6 (1.3)

Lethargy	2 (3.2)	1 (1.6)	1 (1.9)	-	1 (2.0)	-	1 (0.2)	-
Pneumonitis	2 (3.2)	-	-	-	3 (6.0)	2 (4.0)	1 (0.2)	-
Anaemia	1 (1.6)	1 (1.6)	1 (1.9)	1 (1.9)	6 (12.0)	4 (8.0)	4 (0.9)	1 (0.2)
Arthralgia	1 (1.6)	-	1 (1.9)	-	-	-	22 (4.8)	1 (0.2)
Cough	1 (1.6)	-	-	-	2 (4.0)	-	6 (1.3)	-
Dysphonia	1 (1.6)	-	-	-	-	-	15 (3.3)	4 (0.9)
Ejection Fraction Decreased	1 (1.6)	-	3 (5.8)	1 (1.9)	-	-	6 (1.3)	2 (0.4)
Hypothyroidism	1 (1.6)	-	2 (3.8)	1 (1.9)	-	-	-	-
Lipase Increased	1 (1.6)	1 (1.6)	2 (3.8)	2 (3.8)	-	-	6 (1.3)	6 (1.3)
Lower Respiratory Tract Infection	1 (1.6)	-	-	-	4 (8.0)	1 (2.0)	2 (0.4)	2 (0.4)
Palmar-Plantar Erythrodysaesthesia Syndrome	1 (1.6)	-	1 (1.9)	-	1 (2.0)	-	60 (13.1)	15 (3.3)
Pneumonia	1 (1.6)	-	1 (1.9)	1 (1.9)	-	-	13 (2.8)	8 (1.7)
Dizziness	-	-	-	-	-	-	9 (2.0)	1 (0.2)
Electrocardiogram Qt Prolonged	-	-	-	-	-	-	9 (2.0)	5 (1.1)
Headache	-	-	1 (1.9)	1 (1.9)	-	-	19 (4.1)	7 (1.5)
Hypocalcaemia	-	-	-	-	-	-	9 (2.0)	6 (1.3)
Malaise	-	-	1 (1.9)	-	-	-	9 (2.0)	-
Mouth Ulceration	-	-	-	-	2 (4.0)	1 (2.0)	-	-
Myalgia	-	-	1 (1.9)	1 (1.9)	-	-	12 (2.6)	3 (0.7)
Oedema Peripheral	-	-	-	-	-	-	10 (2.2)	1 (0.2)
Pain In Extremity	-	-	1 (1.9)	-	-	-	9 (2.0)	1 (0.2)
Upper Respiratory Tract Infection	-	-	3 (5.8)	-	2 (4.0)	-	5 (1.1)	-

* Includes all subjects who received lenvatinib 18 mg + everolimus 5 mg dose from both Phase I and Phase II portion of study E7080-G000-205. Any TEAEs leading to dose reduction and/or dose interruption not having at least 2 subjects in any treatment arm in the RCC safety set are listed only if the incidence is >=2% in the All DTC set. TEAE = Treatment-emergent adverse event. Dose reduction and/or dose interruption in (Lenvatinib + Everolimus) arm refer to dose reduction and/or interruption in Lenvatinib or Everolimus or both. Percentages are based on the total number of subjects in the safety analysis set within relevant treatment group. Display is in decreasing order of frequency of TEAEs in the (Lenvatinib + Everolimus) Phase Ib + Phase II pooled group. Subject with two or more adverse events in the same preferred term is counted only once for that preferred term. Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. The data cut off date for the RCC set is 31JUL2015, data cut off date for the All DTC set is 10DEC2014.

Post marketing experience

Lenvatinib has been approved for marketing in over 35 countries for the indication of RR-DTC and is sold under the brand name, LENVIMA®. Approximately 1000 new patients have been exposed to lenvatinib since the International Birth Date of 13 Feb 2015 through 12 Aug 2015, the cut-off date for the most recent Periodic Safety Update Report (Oct 2015).

Most of the exposure has been in patient support programs in the US and in a post-marketing surveillance study in Japan. The most frequently reported adverse reactions post-marketing have been dehydration, hypertension, diarrhoea, fatigue, and nausea. These are consistent with the adverse reactions observed in the clinical studies included in the original MAA for DTC and are consistent with the safety profile of lenvatinib as reflected in the current product information.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The assessment of clinical safety is based on the results of the phase 1b/2 study 205 which enrolled overall 62 patients with RCC treated with the intended dosing regimen of lenvatinib-everolimus combination. Data for lenvatinib monotherapy was provided from studies in other indications and is supported by data from lenvatinib monotherapy arm of Study 205. The safety profile of everolimus is well-established in the second-line RCC patients. The open-label nature of Study 205, in addition to its relatively small sample size, further diminished the value of safety data analysis from randomised treatment arms. Comparison exercise between combination arm and respective monotherapy arms is further complicated by lower doses of components used within combination than in single-agent arms. The submitted data did not allow evaluation of potential PD and/or PK interactions that could result in higher toxicity in certain patient subgroups.

Safety data from the randomised part of Study 205 were supported by safety data coming from the dose-finding part of the same study.

The most frequently reported TEAEs (any grade), occurring in at least 30% of subjects in the combination group were diarrhoea (80. 6%), fatigue (59.7%), decreased appetite (53.7%), vomiting (48.4%), nausea (45.2%), hypertension (40.3%), hypertriglyceridemia (40.3%), cough (37.1%), stomatitis (35.5%), peripheral oedema (33.9%), decreased weight (33.9%), dyspnoea (30.6%), and hypercholesterolemia (30.6%). There is an overlap with safety profiles of both lenvatinib (associated with hypertension, diarrhoea, decreased appetite, weight decreased, fatigue, nausea, proteinuria, stomatitis, vomiting, dysphonia, headache, and palmar-plantar erythrodysesthesia (PPE) syndrome) and everolimus (stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, hyperglycemia, weight decreased, pruritus, asthenia, peripheral edema, hypercholesterolemia, epistaxis, and headache).

The most frequently reported Grade 3 or 4 TEAEs, occurring in at least 5% of subjects in the RCC combination group, were diarrhoea (19.4%), fatigue (12.9%), hypertension (12.9%), hypertriglyceridemia (12.9%), acute renal failure (8.1%), anaemia (8.1%), dehydration (8.1%), proteinuria (8.1%), and vomiting (6.5%). In the lenvatinib arm, the most common grade 3 or 4 treatment-emergent adverse event was proteinuria (19%) and in patients assigned to single-agent everolimus it was anaemia (12%).

Grade 3 and 4 events occurred in higher proportion of patients allocated to lenvatinib plus everolimus arm (71%) and single-agent lenvatinib arm (79%) compared to single-agent everolimus (50%).

SAEs were reported in 38 subjects (61.3%) in the combination group (n=62), in 28 subjects (53.8%) in the lenvatinib arm, and in 21 subjects (42.0%) in the everolimus arm. Among the most frequent SAEs (>5% subjects) reported in the combination arm were dehydration (9.7%) and renal failure (8.1%). Other most serious adverse events include dyspnea, gastrointestinal AEs (diarrhea and vomitig) and haematological events (anaemia and thrombocytopenia). Anaemia was more frequently reported in the combination and everolimus arms (in 4 subjects each).

Six fatal AEs were reported, including one cerebral haemorrhage in the combination group and one myocardial infarction with single-agent lenvatinib. Longer follow-up data in patients with RCC reported additional SAE of myocardial infaction with fatal outcome one day post-treatment.

Clinically significant events (CSEs) previously defined for the DTC MAA included hypertension, proteinuria, arterial and venous thromboembolic events, posterior reversible encephalopathy syndrome (PRES), renal events, liver events, gastrointestinal (GI) perforation and fistula formation, QTc prolongation, decreased

ejection fraction (EF), hypocalcaemia, haemorrhage, and PPE. Weight loss and cytopenias were also evaluated.

For the majority of CSEs, there was no significant change to the known safety profiles of lenvatinib or everolimus, but the available data do not allow to make definitive conclusions since some events are rarer and would not be adequately addressed by available safety database. No Hy's Law cases occurred. However, the frequency of renal events and cytopenias (anaemia, thrombocytopenia), did increase in the RCC safety set. Renal failure, renal impairment and proteinuria were reported in substantial proportion of patients, with about 10% incidence of grade 3 or greater.

Consistency with safety profile of VEGFi and mTORi

The AEs observed with combination lenvatinib/everolimus in Study 205 are consistent with the known toxicities of each individual agent.

Furthermore, lenvatinib has a safety profile that is consistent with other VEGF/VEGFR-targeted therapies, although the nature and extent of various AEs differ among the approved compounds, described as follows.

Combination lenvatinib/everolimus tends to be associated most frequently with hypertension; GI events such as diarrhoea, nausea, and vomiting; hypothyroidism; and hypercholesterolemia. These events can be controlled with dose modifications and prompt medical treatment.

Everolimus was also associated with high rates of hyperglycaemia as well as anaemia, lymphopenia, and dyslipidaemia, and the SmPC contains special precautions for non-infectious pneumonitis, renal failure events, stomatitis, and wound healing complications.

Safety in comparison to other TKIs use in second line treatment of mRCC

Common treatment-related adverse events associated with VEGF-targeted therapies and TKIs in general include fatigue and asthenia, GI symptoms (e.g., diarrhoea, stomatitis), skin toxicities (e.g., hand-foot syndrome, hair depigmentation, rash), cardiovascular toxicities (e.g., hypertension), and a variety of metabolic and laboratory abnormalities (Schmidinger, 2013). Although there are a number of known class effects, targeted agents differ regarding their individual side effect profiles. These differences may be attributed to the drug's mode of action, the number of targets inhibited, the type of inhibited target(s) (e.g., VEGF vs. PDGF vs.Flt-3), and the strength of target inhibition (affinity to the tyrosine kinase, "on-" and "off-" target toxicities) (Chen and Cleck, 2009; Haraldsdottir and Shah, 2014; Schmidinger, 2013).

Some toxicities have been linked to the inhibition of a specific target, e.g., hypertension and VEGF; however, the association of other side effects with a particular target is less clear (e.g., stomatitis, diarrhoea). Moreover, single-nucleotide polymorphisms may influence the incidence and severity of side effects in different patient populations (Schmidinger, 2013).

Events regarded as class effects that occurred infrequently, rarely, or not at all with combination lenvatinib/everolimus included arterial and venous thromboembolic events, interstitial lung disease, cardiac failure, PRES, PPE, and impaired wound healing. However, the number of patients was limited and serious adverse events should be closely monitored.

Hypertension was commonly reported with all of the approved agents and appears to be dose-dependent (Schmidinger, 2013). Axitinib was also associated with high rates of elevated TSH and GI events such as nausea and diarrhoea. Sorafenib was associated with higher rates of PPE, rash, alopecia, and bleeding

events. Pazopanib was associated with higher rates of hyperglycaemia, haemorrhagic events, and liver events (including elevations in liver transaminase values).

In clinical trials of TKIs, amylase and lipase elevations were also reported frequently (often by more than 30% of subjects) and are considered a class effect, whereas acute pancreatitis occurred in fewer than 5% of subjects (Pezzilli, et al., 2010). Another review of clinical trials of TKIs reported increased amylase and lipase levels in approximately 50% of subjects (Schmidinger, 2013). In Study 205, elevations in lipase and amylase concentrations occurred in approximately 10% and 3% of subjects in the RCC combination arm, respectively, but there were no cases of pancreatitis.

Potential for new or worsening safety

The potential for new or worsening safety signals with combination lenvatinib/everolimus therapy in RCC was evaluated in comparison with the known safety profiles of lenvatinib and everolimus as single agents.

No new safety signals have been identified with combination therapy in the RCC Safety Set, which was not already known for either lenvatinib or everolimus.

Hypertriglyceridemia, anaemia, hyperglycaemia, and pruritus were reported with an increased frequency in the RCC combination group relative to the All DTC Safety Set and fulfilled the criteria for a potential new safety signal with combination therapy in the RCC population that is not already known for lenvatinib.

Fatigue, vomiting, hypercholesterolemia, dehydration, and acute renal failure were reported with an increased frequency in the RCC combination group relative to the All DTC Safety Set.

Diarrhoea has also been included for consideration because it occurred at a high frequency (81% in the combination arm), although it did not meet one of the prespecified criteria (relative risk of 2 or greater when the RCC combination group was compared with the All DTC Safety Set). Grade 3 or 4 diarrhea occurred in about 19% of patients. It also triggered dose adjustments being the most frequent cause of dose reductions and/or interruptions and resulting in discontinuation of treatment in one patient. Although not studied directly, the MOA for the worsening of diarrhea with the combination is postulated to be mediated by the impairment of intestinal function related to the MOAs for the individual agents – VEGF/VEGFR and c-KIT inhibition by lenvatinib coupled with mTOR/NHE3 inhibition by everolimus.

Electrolyte imbalance, mucocutaneous toxicities and constitutional symptoms are observed, although at varying frequencies with both VEGFR TKIs and mTOR inhibitors and, in some cases the combination treatment may alter the frequencies of observed toxicities with the single agents. Drugs that act on the VEGF pathway may induce renal abnormalities, as a consequence of their intrinsic mode of action and nephrotoxicity associated with everolimus has been reported (Launay-Vacher et al., 2015). The renal toxicity of VEGF inhibitors is mainly renovascular in nature, including hypertension (HTN), proteinuria, and decreased glomerular filtration rate (GFR). Renal events were observed in higher proportion of patients in the combination group (17.7%) than in lenvatinib arm (15.4%) and everolimus arm (12%), with higher rate of grade 3 and more events (9.7%, 5.8% and 2%, respectively). Grade 3 acute renal failure events occurred at a higher rate in the RCC combination group (5 subjects, 8.1%) than in the lenvatinib alone mRCC group (5.8%) or in the All DTC Safety Set (4 subjects, 0.9%).

The incidence rate of hypothyroidism (any grade) was much higher in the RCC combination group (24.2%) compared with that in the everolimus group (2%). In addition, the incidence rate of increased blood TSH (any grade) in the RCC combination group (11.3%) was higher than that in the All DTC Safety Set. Impairment of exogenous thyroid suppression is included in the Warnings and Precautions section of the

approved LENVIMA SmPC. The rate of hypothyroidism for combination lenvatinib/everolimus was within the range reported for other agents in the same class.

Both hypothyroidism and increased blood TSH are known class effects of TKIs (Haraldsdottir and Shah, 2014; Pezzilli, et al., 2010). The rate of hypothyroidism may be dose dependent as it was reported at a higher rate in the RCC lenvatinib group (24 mg lenvatinib: 36.5%) compared with the RCC combination group (18 mg lenvatinib: 24.2%). Furthermore, 75% of patients in the lenvatinib plus everolimus-treated group were not receiving exogenous thyroid replacement, and of these, 71% had normal baseline thyroid stimulating hormone (TSH) levels. In patients with a normal TSH at baseline, an elevation of TSH level was observed post baseline in 63% of lenvatinib plus everolimus-treated patients as compared with none in patients receiving everolimus alone.

Unexpected onset of AEs due to potential pharmacokinetic and/or pharmacodynamic interactions and their late detection is not excluded given that experience with VEGFi-mTORi combinations is limited to date mainly to early phase studies, with few data at long term.

Investigation of safety data from Studies 307 and 218 in regard to potentially worsening AEs will be further conducted in a manner similar to that applied to the data from Study 205. The frequency of all treatment-emergent adverse events (TEAEs) (any grade) and Grade 3 or 4 TEAEs. The first review to be conducted will be of first-line data in Study 307 (which is estimated to be available by 2020) against the known safety profile of treated subjects in DTC and second-line RCC, followed, in 2021, by a comparison of the second- and third-line data in RCC Study 218. The Study 218 data will also be pooled with the 2 previous data sets in support of the addition of these data to the SmPC. This will allow analysis of safety data across the breadth of the RCC population covered in Studies 307, 218, and 205, and will provide a useful view of the safety profile across the proposed range of use from first-line through third-line settings. Any differences in incidence or severity from the existing AE profile or between different subgroups will be identified, discussed, and if warranted, proposed for inclusion in the SmPC.

The following methodology was proposed to further characterise potential worsening of AEs. Events will be considered potential new or worsening signals if: they occur at ≥5% (any grade) AND there is a relative risk of 2 or greater when the RCC combination group is compared either with the everolimus EPAR pooled data set or the incidences of the events which are ADRs in the Kisplyx SmPC;-OR for Grade 3 or 4 events, or clinically significant adverse events, if they occur at ≥1% AND there is a relative risk of 2 or greater when the RCC combination group is compared either with the everolimus EPAR pooled data set or the incidences of the events which are ADRs in the Kisplyx SmPC.

Long-term safety
Long-term safety data for the combination are currently available from Study 205 and are limited by the number of subjects in the study and, consequently, by the number of patients who received treatment for more than one year. The combination treatment appear to prolong overall survival in patients in the pivotal study, with median OS of about 2 years observed. Of the 62 subjects in the combination arm, 22 subjects (35.5%) had 1 year or more of treatment (36.3 SY) and 5 subjects (8.1%) had ≥ 2 years of treatment (12.0 SY). However, long-term safety will be more comprehensively assessed in a lager safety database in the planned studies. In particular, potential cumulative toxicity and time-dependent intolerability and toxicity could emerge at longer term. Additional combination-therapy trials (Studies 218, 307 and 221) are planned, which will provide additional data on longer-term safety and allow comparison with single agent safety profiles. Moreover, real-world data will become available from the EU and US upon approval of the combination.

Given the limited number of patients treated with combination, no meaningful conclusions in regard to long-term toxicity can be drawn. Higher proportion of all types of AEs appears to be observed within first 6 months, but some increase in toxicity might occur at more than 1 year of exposure. Collection of long-term safety data is of continuous importance also for lenvatinib monotherapy and several studies are ongoing. Long-term data with other VEGF-targeted therapies (eg Rini et al, 2015) indicate increase in cardiovascular toxicity, which is a key element in B/R of these agents (Shah et al, 2015). Long–term data on the safety profiles of the TKIs axitinib and sunitinib used as monotherapy in RCC have been analysed. Of a total of 108 patients had received axitinib for ⩾2 years, and interval analysis showed that most AEs occurred during the first 6 months of treatment, with rates stable or decreased over time. However, incidence rates increased over time for proteinuria, peripheral edema, and increased blood creatinine. Common Grade ⩾3 AE rates declined or plateaued over time, except for increased amylase and myocardial infarction. The median times to onset for increased amylase and myocardial infarction were 8.1 months and 22.1 months, respectively (Rini, et al., 2015). In regard to long-term safety of sunitinib, hypothyroidism increased by interval analysis from 6% at 0 <6 months to 42% at 5–<6 years and by cumulative analysis from 14% at 0–<1 year to 36% over 6 years. Grade 3/4 treatment-related AEs in patients during long-term treatment peaked during the first year and then steadily decreased (Porta, et al., 2016).

Based upon review of the available literature on long-term use of TKIs as single agents in mRCC, the majority of AEs occurred within the first 6-12 months, and the incidence of most AEs decreased or remained stable over time. The exceptions to these observations were proteinuria, peripheral oedema, increased blood creatinine, and hypothyroidism. The severe (Grade ⩾3) AEs that increased in incidence over time were increased amylase and myocardial infarction, and these AEs tended to occur later on in treatment (>8 months).

Dose

When therapeutic goal is prolongation of survival, it is important to reduce toxicities and to maximize overall time on treatment. The duration of treatment (including dose interruptions) was 8.0 months in the combination group (n=62) (7.6 months in the combination arm in the Study 205), 7.4 months in the lenvatinib group (n=52) and 4.1 months in the everolimus group. Most of the AEs observed up to now with the combination treatment are manageable and further optimisation of strategies to reduce rate of premature discontinuation of treatment due to toxicity is encouraged to allow patients to benefit from highly effective treatment.

The results from the study 205 show efficacy in mRCC patients with the starting dose of 18 mg QD of lenvatinib and 5 mg everolimus, however 88.7% of patients require dose modifications (dose reduction and/or interruption) and 29% of patients discontunied treatment due to AEs, indicating poor tolerability of the combination. Similarly, overall 89.7% of lenvatinib-treated patients had dose modifications of lenvatinib in DTC Study 303. Data on safety and activity of lower starting doses for lenvatinib monotherapy 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 (ORR6M) as assessed by the investigator according to RECIST 1.1).

In the RCC indication, a study comparing lower dose of lenvatinib within combination is requested. Study 218 is a randomised dose-finding phase 2 trial in advanced RCC patients which aims to compare lower dose of

lenvatinib– 14 mg, with possibility to increase the dose up to 18 mg if well tolerated. The 14-mg starting dose will be escalated to 18 mg if no Grade 2 (intolerable) or any Grade ⩾3 treatment-emergent adverse events that require dose reduction are observed in the first cycle (4 weeks) of treatment. Further characterisation and use of appropriate biomarkers and PK/PD models is also expected (see discussion on clinical pharmacology and RMP).

In order to investigate correctly the potential of lenvatinib for CYP3A4 inhibition/induction, an in vivo study with midazolam as a probe substrate for CYP3A4, the applicant is requested to conduct a drug-drug interaction study to investigate the potential of lenvatinib for CYP3A4 inhibition/induction (study 109).

Further, in order to further charactrerise the combination safety profile, Study 307, 218 and study 221 are planned in addition to the ongoing safety studies for lenvatinib monotherapy (Studies 303, 208 and 211).

Study 218 will further evaluate the safety of lenvatinib-everolimus combination and further contribute to knowledge on PK and PK/PD of lenvatinib and everolimus and their PK and PD interactions It will also establish exposure-safety and exposure-efficacy relationships and better inform the choice of the optimal starting dose, the results of the integrated and mechanism-based PK/PD modelling should be submitted at the time of submission of the CSR.

Study 307 is requested to further characterise the safety and tolerability profile of the combination therapy and further contribute to knowledge on PK and PK/PD of lenvatinib and everolimus and their PK and PD interactions.

Study 221 will continue to characterize safety for the combination treatment in patients with non clear cell renal carcinoma.

The studies requested for Lenvima will also provide relevant safety information for this application. Study 303 will evaluate the long-term safety of lenvatinib in patients with RR-DTC in a randomized, double-blind, placebo-controlled Phase 3 study. This will enable to continue to characterize/ confirm current and long-term safety profile of lenvatinib in monotherapy in another indication (DTC). Study 208 will contribute to the long-term safety profile of lenvatinib in patients with advanced thyroid cancer. Study 211 will 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).

For further details on the above mentioned studies, please see RMP section 2.7 below.

2.6.2. Conclusions on the clinical safety

The overall safety profile of lenvatinib-everolimus combination is consistent with known safety profiles of its components observed either in other indications (for lenvatinib) or in the intended indication (for everolimus). The reported toxicity was in general predictable and manageable. No new safety signal has been reported. The incidences and severity of some of the adverse events are increased due to an additive and/or synergic effect of the combination. However, most of these were well managed by dose reduction, interruption or by additional medical treatment.

However, precaution is warranted given a small size of safety database, a limited information on long-term toxicity, and a limited data on PK/PD interactions together with indication on potential for worsening toxicity for VEGFRi -mTOR inhibitor combinations in general. Although toxicity appears to be manageable with the

intended combination, an onset of more frequent or severe toxicity may occur in a larger database and/or at longer term.

Poor tolerability of the combination is manifest with high rates of discontinuations due to AEs and dose modifications.

Therefore, further studies need to be conducted in relevant clinical setting in order to provide comprehensive data and to improve tolerability profile of the combination in view of a limited safety database for the combination treatment at intended doses/schedule, related uncertainties and poor tolerability of the combination (high rate of treatment discontinuation and dose modifications).

The CHMP considers the following measures necessary to address issues related to safety (please see section 2.7 of the RMP):

Study 307 is requested to further characterise the safety and tolerability profile of the combination therapy and further contribute to knowledge on PK and PK/PD of lenvatinib and everolimus and their PK and PD interactions.

Study 218 will further evaluate the safety of lenvatinib-everolimus combination and contribute to knowledge on PK and PK/PD of lenvatinib and everolimus and their PK and PD interactions. It will also establish exposure-safety and exposure-efficacy relationships and better inform on the choice of the optimal starting dose. The results of the integrated and mechanism-based PK/PD modelling should be submitted at the time of submission of the CSR.

Study 221 will continue to characterize safety for the combination treatment in patients with non clear cell renal carcinoma.

Study 010 will assess in vitro lenvatinib protein binding, determine the unbound drug concentrations in order to define correctly the dose-adjustment in patients with severe hepatic and renal impairment.

Studies requested for Lenvima will also provide relevant safety information for this application (please see section 2.7 of the RMP). Study 303 will evaluate the long-term safety of lenvatinib in patients with RR-DTC in a randomized, double-blind, placebo-controlled Phase 3 study. Study 208 will determine the long-term safety profile of lenvatinib in patients with advanced thyroid cancer. Study 211 will determine whether a lower starting dose of lenvatinib 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). Study 109 will investigate correctly the potential of lenvatinib for CYP3A4 inhibition/induction.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypertension
	Proteinuria
	Renal failure or impairment

Summary of safety concerns	
	Hypokalaemia
	Cardiac failure
	Posterior reversible encephalopathy syndrome (PRES)
	Hepatotoxicity
	Haemorrhagic events
	Arterial thromboembolic events (ATEs)
	QTc prolongation
	Hypocalcemia
	Hypothyroidism
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 paediatric population
	Impaired wound healing
	Interstitial Lung Disease (ILD)-like conditions
	Potential of lenvatinib for induction/inhibition of CYP-3A4 Mediated Drug Metabolism
	Overdose (concomitant everolimus) (RCC)
Missing information	Use in the paediatric 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
	Long-term use

Pharmacovigilance 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 109 (Interventional Clinical Study:	A drug-drug interaction (DDI) study to investigate the potential of lenvatinib for	To investigate correctly the potential of lenvatinib for CYP3A4 inhibition/induction,	Planned	Mar 2018

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
Category 3)	CYP3A4 inhibition/induction	an in vivo study with midazolam as a probe substrate for CYP3A4.		
Study E7080-A001-010 (Interventional Clinical Study: Category 3)	A Multicenter Phase 0 Study In Healthy Subjects As Well As Subjects With Either Hepatic Or Renal Impairment To Obtain Plasma To Assess In Vitro Lenvatinib Protein Binding	To define correctly the dose-adjustment in patients with severe hepatic and renal impairment and determine unbound drug concentration	Planned	30 June 2019
DTC				
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	Continue to characterize/ confirm current safety profile of lenvatinib in DTC	Completed*	Feb 2014
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. To assess bone growth and height during and after discontinuation of treatment with lenvatinib.	Use in paediatric population aged 2 to <18 years	Start date: 29 Dec 2014, first dose of lenvatinib 15 Jan 2015	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.	Continue to characterize/ confirm current safety profile of lenvatinib in DTC	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 randomized, double-blind, placebo-controlled Phase 3 study.	Continue to characterize/ confirm current safety profile of lenvatinib in DTC	Completed*	Ongoing

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 211 (Interventional Clinical Study: Category 3)	**Primary Objective** • To determine whether a starting dose of lenvatinib 20 mg or 14 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 6 months [ORR6M]) with an improved safety profile compared to 24 mg QD (based on treatment-emergent adverse events [TEAEs] of Grade 3 or higher in the first 6 months after randomization). Secondary Objectives: • To evaluate PFS • To evaluate PFS2 • To evaluate safety and tolerability • To evaluate PK-PD relationship between exposure and biomarkers /efficacy/safety • To evaluate impact on HR QOL Exploratory Objectives: • To explore OS •To explore TSH, and other serum biomarkers as potential biomarkers for tumor response • To explore DNA sequence variants in genes that may influence PK, safety, or pharmacodynamics data	Characterize/ confirm safety profile of lenvatinib in DTC at lower doses, to determine whether a lower dose starting dose of lenvatinib will provide comparable efficacy with an improved safety profile	Planned	31 Aug 2020
RCC				

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 205 (Interventional Clinical Study: Category 3)*	An Open-Label, Multicenter Phase Ib/2 Study of Lenvatinib Alone, and in Combination with Everolimus in subjects with unresectable advanced or metatstatic renal cell carcinoma following one prior VEGF targeted treatment.	To continue to characterize/confirm the current safety profile of lenvatinib either as monotherapy or in combination with everolimus in advanced RCC.	Ongoing	Dec 2018
Study 218 (Interventional Clinical Study: Category 3)	Primary objective: •To assess whether a starting dose of lenvatinib 14 mg in combination with everolimus 5 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 24 weeks [ORR24W]) with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg (based on treatment-emergent intolerable Grade 2 or any ≥Grade 3 adverse events in the first 24 weeks after randomization). Secondary objectives: •To assess PFS •To assess ORR •To determine the tolerability and safety profile of lenvatinib in combination with everolimus •To assess proportion of subjects who discontinued treatment due to toxicity •To assess time to treatment failure •To assess PK profiles of lenvatinib and everolimus during combination therapy and to assess PK and PD drug-drug interactions •To evaluate OS •To evaluate impact on QOL	To continue to characterize/confirm the current safety profile of lenvatinib either as monotherapy or in combination with everolimus in advanced RCC	Planned	Final protocol and data analysis plan submission: Nov 2016 Study completion: Nov 2020 Periodic interim analyses by independent Data Monitoring Committee Final report submission: Jul 2021
Study 221 (Interventional Clinical Study:	Primary Objective: •To evaluate objective	To characterize the safety profile of lenvatinib + everolimus	Final protocol 13	Final report submission:

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
Category 3)	response rate (ORR) of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease Secondary Objectives: •To assess safety and tolerability of lenvatinib in combination with everolimus •To evaluate progression-free survival (PFS) •To evaluate overall survival (OS) •To assess the pharmacokinetic (PK) profiles of lenvatinib and everolimus during combination therapy in subjects with nccRCC. Exploratory Objectives: • To explore clinical benefit rate (CBR) • To explore disease control rate (DCR) • To explore duration of response (DOR) •To identify and explore tumor and blood biomarkers that correlate with clinical outcomes, including efficacy •To explore the relationship of population PK derived exposure parameters to biomarker, safety, and efficacy data using a model-based approach	in subjects with nccRCC who have not received any chemotherapy for advanced disease	May 2016	Q4 2019
Study 307 (Interventional Clinical Study: Category 3)	Primary Objective: • To demonstrate that lenvatinib in combination with everolimus (Arm A) or	To continue to characterize/confirm the current safety profile of lenvatinib in combination with everolimus in	Planned	The protocol and the data analysis plan for PK/PD should be

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
	pembrolizumab (Arm B) is superior compared to sunitinib alone (Arm C) in improving progression-free survival (PFS) (by independent imaging review [IIR] using Response Evaluation Criteria In Solid Tumors [RECIST 1.1]) as first-line treatment in subjects with advanced renal cell carcinoma (RCC). Secondary Objectives: [The secondary objectives are under review and will be updated when finalized].	advanced RCC		submitted by: 30/11/2016 Periodic interim analyses by independent Data Monitoring Committee Final report submission of study results: 15 July 2020

* Completed for primary efficacy analysis and CSR submitted.
**Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Hypertension	SmPC sections 4.2, 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Proteinuria	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Renal failure or impairment	SmPC sections 4.2, 4.4 and 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
Hypokalaemia	SmPC section 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Cardiac failure	SmPC sections 4.4 and 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)	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hepatotoxicity	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hemorrhagic events	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Arterial thromboembolic events (ATEs)	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
QTc prolongation	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hypocalcemia	SmPC sections 4.4 and 4.8	None planned.
Hypothyroidism	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Gastrointestinal perforation and fistula formation	SmPC sections 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned.
Venous thromboembolic events (VTEs)	SmPC section 4.8	None planned.

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Abnormal pregnancy outcome, excretion in breast milk	SmPC section 4.6 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Male and female fertility	SmPC sections 4.6 and 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	SmPC sections 4.2 and 5.3 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
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

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Overdose (concomitant everolimus) (RCC)	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 paediatric population	SmPC section 4.2 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in severe hepatic impairment	SmPC section 4.2 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in severe renal impairment	SmPC section 4.2 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	SmPC sections 4.2 and 4.4 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in patients aged ≥75 years	SmPC sections 4.2, 4.4 and 4.8 Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Long-term use	AEs such as cardiovascular events may emerge during long-term treatment, and continuous collection of long-term safety data is relevant for all indications. In RCC, no risk minimization measures are recommended at present as the duration of exposure to the combination covers the lifespan of the treated patient population: 72% of total subject-years of exposure were contributed by patients treated for at least 12 months, whilst median survival for mRCC patients treated with this comibination is 25.5 months. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies	None planned

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Conclusion

The CHMP and PRAC considered that the risk management plan version 8.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

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. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lenvatinib (lenvatinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initially claimed indication is:

"Lenvatinib is indicated in combination with everolimus for the treatment of patients with unresectable advanced or metastatic renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy".

The agreed indication is:

"Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted prior therapy".

Renal cell carcinoma is the third leading urologic cancer. About 30% of patients with RCC have metastatic disease at the time of diagnosis, and a significant proportion of patients with localized disease treated with curative nephrectomy relapse subsequently with metastatic disease. Metastatic RCC is associated with a high quality-of-life burden. About 8% to 22.5% of mRCC patients survive for five years or more as compared to 90% of patients with localized renal cancer, but survival rates increase with the use of new therapies and depend on several prognostic factors. Patient population is heterogeneous in terms of clinical (prognostic factors) and molecular determinants.

The incidence of mRCC is increasing, and the disease is still considered incurable. The most frequent locations of metastases are the lungs, mediastinum, bone, liver, and brain.

In patients with advanced RCC, the aim of therapy is to prolong PFS, to achieve high response rate, to prolong survival and to improve quality of life. In second line setting only few agents could demonstrate benefit in terms of OS (e.g. nivolumab) and most of therapies approved in second line could show PFS benefit in randomised phase 3 trials, although with different magnitude of effect (median PFS ranging from 4 to 7 months).

3.1.2. Available therapies and unmet medical need

Current approved treatments for metastatic RCC in the first-line setting comprise targeted therapies, either tyrosine kinase inhibitors (TKI; sunitinib; pazopanib) or mammalian target of rapamycin (mTOR) inhibitors (temsirolimus) administered as single agents, bevacizumab + interferon, or high-dose interleukin-2.

Approved second-line agents include TKIs: sorafenib, sunitinib, axitinib, and pazopanib and the mTOR inhibitor everolimus.

A novel immunotherapeutic agent, belonging to a class of immune checkpoint inhibitors (PD-1/PD-L1), has been recently granted approval by the EC. Opdivo (nivolumab) as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Afinitor, intended to be used at a half of the recommended dose in combination with lenvatinib, is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy. The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

3.1.3. Main clinical studies

The application is based on a Phase 1b/2 study 205 (n=173) consisting of dose-finding part to determine DLTs/MTD/RP2D (n=20) and randomised open-label 3-arm part (n=153), with lenvatinib-everolimus combination (18mg/5mg), single-agent lenvatinib (24mg QD) and single-agent everolimus (10mg QD) arms.

3.2. Favourable effects

Beneficial effects

The combination of lenvatinib plus everolimus significantly prolonged PFS compared to single-agent everolimus with a median PFS of 14.6 months (95% CI: 5.9, 20.1) for the combination versus 5.5 months (95% CI: 3.5, 7.1) for everolimus (HR=0.40, 95% CI: 0.24, 0.68, p=0.0005), by investigator assessment and analysis. An independent imaging review (IIR) was conducted and the results obtained, for PFS and ORR, corroborated the improvements seen in the investigator analyses. The IIR results showed PFS of 12.8 months with the proposed combination compared to 5.6 months with everolimus alone (HR= 0.45, 95% CI= 0.26,0.79, p=0.003).

The observed PFS benefit was consistent with results for secondary endpoints of OS and ORR.

At 3 different time points, the combination of lenvatinib plus everolimus consistently showed a trend towards prolonged survival compared with everolimus, with HRs (95%CI; p-value) of 0.55 (0.30, 1.01; p=0.06), 0.51 (0.30, 0.88; p=0.02), and 0.59 (0.36, 0.96; p=0.06), respectively.

The ORR for the combination was greater than the ORR for everolimus with 43.1% (1 CR and 21 PRs) and 6% (3 PRs), respectively. The independent imaging review analyses showed an ORR of 35.3% for the combination compared to 0% in the everolimus arm.

3.3. Uncertainties and limitations about favourable effects

The Study 205 is of modest size (153 patients) and was not powered to demonstrate OS benefit. Due to a small sample size the benefit in subgroups could not be comprehensively assessed. Of note, patient reported outcomes have not been collected and impact on quality of life is uncertain.

3.4. Unfavourable effects

Diarrhoea, hypercholesterolemia, and hypothyroidism were identified as worsening safety signals with the combination treatment compared with lenvatinib and everolimus as monotherapy.

Grade 3 and 4 events occurred in higher proportion of patients allocated to lenvatinib plus everolimus arm (79%) compared to single-agent everolimus (54%).

SAEs were reported in 38 subjects (61.3%) in the combination safety group and in 21 subjects (42.0%) in the everolimus arm.

The rate of discontinuations due to AEs was reported as 29% in pooled safety data set with intended dosing regimen and as 12 % in the everolimus arm.

Adverse events leading to dose reductions, interruptions and modifications (redaction and/or interruptions) were reported respectively in 68%, 76% and 89 % of patients in combination group and in 16 %, 50 and 54% of patients in the everolimus arm.

The overall safety profile of the combination was consistent with known safety profiles of individual components, toxicity was predictable and in general manageable. No new safety signals were identified to date.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is limited in terms of sample size (62 patients treated in the intended indication with the intended dose regimen, including 11 in dose-finding part of the study) and in terms of duration of exposure.

It is unknown whether worsening of toxicity, earlier onset or higher severity of ADRs might occur in larger sample size population and whether underlying PK and/or PD interactions could contribute to such worsening.

Insufficient knowledge on PK and PD drug-drug interactions between lenvatinib and everolimus confers risk of potentially higher toxicity. With regard to potential interactions between lenvatinib and everolimus, further exploration is still needed.

In order to better understand the combination safety profile, including long-term toxicity, Studies 307, 218 and 221 are planned in addition to the already ongoing safety studies for lenvatinib monotherapy (Studies 303, 208 and 211).

It is unknown whether alternative dose/regimen will result in better tolerability of the combination. Study 218 will assess whether a starting dose of lenvatinib 14 mg in combination with everolimus 5 mg once daily (QD) will provide comparable efficacy with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg, and to assess PK and PK/PD of the two drugs and related interactions. It will also establish exposure-safety and exposure-efficacy relationships and better inform the choice of the optimal starting dose, the results of the integrated and mechanism-based PK/PD modelling should be submitted at the time of submission of the CSR.

Study 307 is requested to further characterise the safety profile and tolerability of the combination therapy and will contribute to understanding of PK, PK/PD of both drugs and their interactions.

Study 221 will assess the safety and efficacy of the combination therapy in non-clear cell RCC patients, the MAH should conduct and submit the results of this Phase 2 Trial.

The level of lenvatinib protein binding is yet not known while the assessment of renal and hepatic impairment should be based on free fraction. Study 010 will provide data to better define the dose-adjustments in patients with severe hepatic and renal impairment.

3.6. Effects Table

Table 60: Effects Table for Lenvatinib in combination with everolimus.

Effect	Short Description	Unit	Treatment Combination LEV+EVE	Control EVE	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS (median)	Patients alive and free of progression	Months	14.5	5.5	Open label design, but consistent and significant effect among primary (data cutoff 13 Jun 2014) and sensitivity analyses	See clinical efficacy section of this AR
			HR=0.40 95% CI: 0.24, 0.68, p=0.0005			

Effect	Short Description	Unit	Treatment Combination LEV+EVE	Control EVE	Uncertainties/ Strength of evidence	References
ORR	Anti-tumour activity (CR+PR)	%	43.1	6.0	Significant effect	
OS (median) Cut-off 13 June 2014	Gain in survival	Months	25.5	17.5	Not powered for OS, but trend towards prolonged survival confirmed by data from two successive more mature analyses (10 Dec 2014 and 31 Jul 2015)	
			HR=0.548 (0.298, 1.009) 0.0623			

Unfavourable Effects

Effect		Unit	Treatment Combination LEV+EVE	Control EVE	Uncertainties/ Strength of evidence	References
At least 1 AE		%	100	100	Open label design, small sample size	See clinical safety AR table 4.3.1
AE grade 3-5		%	79	54	"	"
Serious AE		%	61.3	21	"	"
AE leading to dose interruption		%	75.8	50	"	"
AE leading to dose reduction		%	67.7	16	"	"
AE leading to dose reduction and/or interruption		%	87.7	54	"	"
AE leading to discontinuation		%	29.0	12	"	"
Number of AE with fatal outcome		%	1.6	4	"	"
Diarrhoea		%	80.6	34.0	"	"
Hypertension		%	41.9	10.0	"	"
Proteinuria		%	30.6	14.0	"	"
Renal failure		%	8.1	2.0	"	"
Cardiac dysfunction		%	4.8	4.0	"	"

Effect	Short Description	Unit	Treatment Combination LEV+EVE	Control EVE	Uncertainties/ Strength of evidence	References
Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS)		event	1 PRES	0	"	"
Arterial thromboembolisms		%	1.6	6.0	"	"
Venous thromboembolisms		%	6.5	4.0	"	"
Haemorrhage		%	38.7	28	"	"
QTc prolongation		%	- 11(greater than 60 ms) - 6 (greater than 500 ms)	0	"	"
Hypothyroidism		%	24	2	"	"
Hypocalcemia		%	8.1	4.0	"	"
Perforated appendicitis		%	1.6	0	"	"

Abbreviations: HR: hazard ratio, NA: not applicable, Mo: months, LEN: lenvatinib, EVE: everolimus

Notes: Unfavourable effect rates are from the pooled safety dataset (n=62) for the lenvatinib-everolimus combination.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The observed magnitude of the PFS gain and the magnitude of ORR in the combination arm compared to everolimus arm are statistically significant and clinically relevant in the second-line treatment of advanced RCC, a disease with currently evolving unmet medical need. New therapeutic options are needed to improve outcomes, particularly in terms of overall survival, and also PFS. The intended combination showed improvement in PFS compared to standard treatment. Blinded independent imaging review and conducted sensitivity analyses provide reassurance regarding the robustness of data. OS data are supportive and consistent with PFS/ORR data. The magnitude of PFS benefit is of particular value in this clinical setting in patients that have already received prior VEGF-targeted therapy. The overall safety profile of combination observed was consistent with known safety profiles of individual components, was predictable and in general manageable. No new safety signals were identified to date. This observation is reassuring and of importance for a combination therapy in view of unacceptable toxicities observed with other similar combinations.

However, the small safety database represents a limitation in the assessment of the safety profile. There are several post-authorisation studies (study 218, 307, 221, 205) which will further characterise the safety profile of lenvatinib in combination with everolimus.

A full understanding of the safety profile will be investigated in planned or on-going studies.

3.7.2. Balance of benefits and risks

An improvement in PFS benefit with the combination everolimus+lenvatinib treatment compared with everolimus monotherapy was observed in a single, small, open-label study. The benefits of Kisplyx in combination with everolimus outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

The CHMP considers the following measures necessary to address issues related to safety: further studies and collection of real-life data are recommended to further address uncertainties.

3.8. Conclusions

The overall B/R of lenvatinib in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy is considered positive.

The CHMP recommends the approval of lenvatinib in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kisplyx is not similar to Nexavar (sorafenib tosylate) and Torisel (temsirolimus) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See Annex 7.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Kisplyx is positive in the following indication:

Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.