EU Risk Management Plan for Lenvima/Kisplyx (Lenvatinib)

Risk Management Plan (RMP) version number:	18.0
Data lock point for this RMP	15 May 2024
Date of final sign off:	Dec 2024
Summary of significant changes in RMP Version 18.0:	
Part II Modules SVII - Identified and potential risks and Module SVIII – Summary of the safety concerns	Due to the completion of the Study E7080-G000-307 postauthorisation measure, Long-term use is removed as Missing Information.
Part III: Pharmacovigilance plan	Updated milestone date of final report submission for Study E7080-G000-307.
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Removed Study E7080-G000-307 as an additional pharmacovigilance measure for the Identified and Potential Risks. .
Part VI: Summary of the risk management plan	The summary of RMP was updated to reflect changes in Part II and Part III.
Part VII: Annexes	Administrative change (Annex II and Annex III): Moved Study E7080-G000-307 to completed studies with final report date. Administrative change (Annex VIII): Updated the summary of changes to the RMP over time to include the latest approved version.
Other RMP versions under evaluation:	None
Details of the currently approved RMP:	
Version number:	17.0
Approved with procedure:	EMEA/H/C/003727/II/0056
Date of approval (opinion date):	31 Oct 2024
Qualified Person for Pharmacovigilance (QPPV) name:	Angela Schmidt-Mertens
The QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.	

TABLE OF CONTENT

List of Tables

List of Figures

LIST OF ABBREVIATIONS

1L	first-line
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ASMR	age-standardised mortality rate
AST	aspartate aminotransferase
ASIR	age-standardised incidence rate
ATC	Anatomical Therapeutic Chemical or anaplastic thyroid cancer, depending on context
ATE	arterial thromboembolic event
BCLC	Barcelona-Clinic Liver Cancer
BCRP	breast cancer resistance protein
BP	blood pressure
BSEP	bile salt export pump
CHF	congestive heart failure
CrCl	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DLP	data lock point
dMMR	deficiency mismatch repair
DTC	differentiated thyroid cancer
EC	endometrial carcinoma
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EPAR	European Public Assessment Report
FGFR	fibroblast growth factor receptor
GI	gastrointestinal
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
ILD	interstitial lung disease
INR	International Normalized Ratio
KDIGO	Kidney Disease|Improving Global Outcomes

LVEF	left ventricular ejection fraction
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MSI	microsatellite instability
MTC	medullary thyroid cancer
nccRCC	non-clear cell renal cell carcinoma
NO	nitric oxide
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PIP	paediatric investigational plan
PL	Package Leaflet
PND	postnatal day
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PSUR	Periodic Safety Update Report
PTC	papillary thyroid cancer
QD	once daily
QPPV	Qualified Person for Pharmacovigilance
QTc	corrected QT interval
RAI	radioactive iodine
RCC	renal cell carcinoma
RMP	risk management plan
RTK	receptor tyrosine kinase
SAE	serious adverse event
SGQ	sponsor-generated query
SmPC	Summary of Product Characteristics
SMQ	standard MedDRA query
TEAE	treatment-emergent adverse event

TKI	tyrosine kinase inhibitor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VTE(s)	venous thromboembolic event(s)

PART I: PRODUCT OVERVIEW

Active substance (INN or common name)	lenvatinib mesilate
Pharmacotherapeutic group (ATC Code)	L01EX08
Marketing Authorisation <Holder> <Applicant>	Eisai GmbH
Medicinal products to which this RMP refers	2
Invented names in the European Economic Area (EEA)	Lenvima (DTC, HCC, EC); Kisplyx (RCC)
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class: Receptor tyrosine kinase (RTK)
	Summary of mode of action: Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor receptors (VEGFR1 [FLT1], VEGFR2 [KDR], and VEGFR3 [FLT4]), in addition to other proangiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor receptors (FGFR) 1, 2, 3, and 4, the platelet-derived growth factor receptor α (PDGFRα), KIT, and rearranged during transfection (RET). In addition, lenvatinib had selective, direct antiproliferative activity in hepatocellular cell lines dependent on activated FGFR signalling, attributed to the inhibition of FGFR signalling by lenvatinib. The dual VEGF and FGFR inhibition seen with lenvatinib results in potent inhibition of angiogenesis and direct antitumour activity. In syngeneic mouse tumour models, lenvatinib decreased tumour-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumour activity in combination with an anti-programmed cell death protein-1 (PD-1) monoclonal antibody compared to either treatment alone. The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumour activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signalling in vitro

	and tumour volume in mouse xenograft models of human renal cell cancer greater than each drug alone.
	Important information about its composition: N/A
Hyperlink to the Product Information	The Summary of Product Characteristics (SmPC) is included in Module 1.3.1.
Indication(s) in the EEA	Current: **LENVIMA** is indicated for the treatment of adult patients: • as monotherapy in patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI). • as monotherapy in patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy. • in combination with pembrolizumab in patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation. **KISPLYX** is indicated for the treatment of adults with advanced renal cell carcinoma (RCC): • in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy. • in combination with pembrolizumab, as first-line (1L) treatment.
	Proposed: Not applicable.
Dosage in the EEA	Current: **DTC:** The recommended daily dose of lenvatinib is 24 mg (two 10-mg capsules and one 4-mg capsule) taken orally once daily. **RCC:** *In combination with pembrolizumab as 1L treatment:* The recommended dose of lenvatinib is 20 mg (two 10-mg capsules) orally once daily in combination with pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

	In combination with everolimus as second-line treatment: The recommended daily dose of lenvatinib is 18 mg (one 10-mg capsule and two 4-mg capsules) orally once daily in combination with 5 mg of everolimus once daily. **HCC:** The recommended daily dose of lenvatinib is 8 mg (two 4-mg capsules) in patients <60 kg in weight and 12 mg (three 4-mg capsules) in patients ≥60 kg in weight. **EC:** The recommended dose of lenvatinib is 20 mg orally once daily, in combination with pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks, administered as an intravenous infusion over 30 minutes. The daily doses are to be modified as needed according to the dose/toxicity management plan in Section 4.2 of the SmPC.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Hard capsules containing lenvatinib mesilate equivalent to 4 mg or 10 mg lenvatinib.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	**LENVIMA**: No **KISPLYX**: No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

Indication: Radioactive iodine-refractory differentiated thyroid cancer

Brand Name of Concerned Product (with this Indication): Lenvima

For the purpose of this Risk Management Plan (RMP), the generic name lenvatinib is used in accordance with the terminology used in the nonclinical and clinical studies.

Epidemiology of the Disease:

There are 3 main histologic types of thyroid cancer: differentiated thyroid cancer (DTC), arising from follicular epithelial cells (including papillary thyroid cancer [PTC], follicular thyroid cancer, and Hürthle cell thyroid carcinomas), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC). Approximately 90% to 95% of thyroid cancers arise from follicular epithelial cells and, based on histologic appearance, are designated as either papillary (approximately 80%), follicular (approximately 13%), or Hürthle cell (approximately 3%), as subtypes of DTC (Hundahl, et al., 1998). The remaining 5% to 10% of thyroid cancers are either neuroendocrine-derived MTC or ATC.

Incidence:

According to the European Union Cancer Database (EUCAN, 2012), 36,864 new cases of thyroid cancer (6.5 per 100,000) were estimated in the EU in 2012; GLOBOCAN estimated 37,282 new cases in 2012 (including those from Croatia). Incidence rates in individual member states range from 1.9 to 15.5 cases per 100,000 individuals across the EU, with the highest rates (those above 9/100,000) reported in Lithuania, Italy, Austria, Croatia, Luxembourg, Cyprus, and France (Figure 1) (EUCAN, 2012).

Incidence rates for the histologic subtypes of thyroid cancer are available from RARECARE (2014), which estimates rates of 2.05 and 0.57 per 100,000 for the papillary and follicular subtypes, respectively, and a rate of 3.65 per 100,000 for thyroid cancer as a whole. These estimates are for the year 2008 based on cases that occurred in the EU in the period 1995-2002, collated from 70 registries across Europe. RARECARE (2014) population numbers, thus, report DTC to be 87% of the total thyroid cancer population, which is consistent with the proportion of 90% cited by Cancer Research UK (2014).

An escalating incidence of DTC during the last decade has been reported worldwide. NORDCAN (2014) reports an annual increase in incidence over the last decade of +3.4% in men and +3.2% in women. This phenomenon is due mainly to an increase in the micropapillary (<2 cm) histotype, while there has been no substantial change in the incidence of follicular, medullary, and anaplastic cancers according to the European Society of Medical Oncology (Pacini, et al., 2012). Agate, et al. (2012) suggested that this "over-diagnosis" of small cancers that would have previously remained occult has been revealed because of an increased diagnostic scrutiny rather than a real increase of incidence.

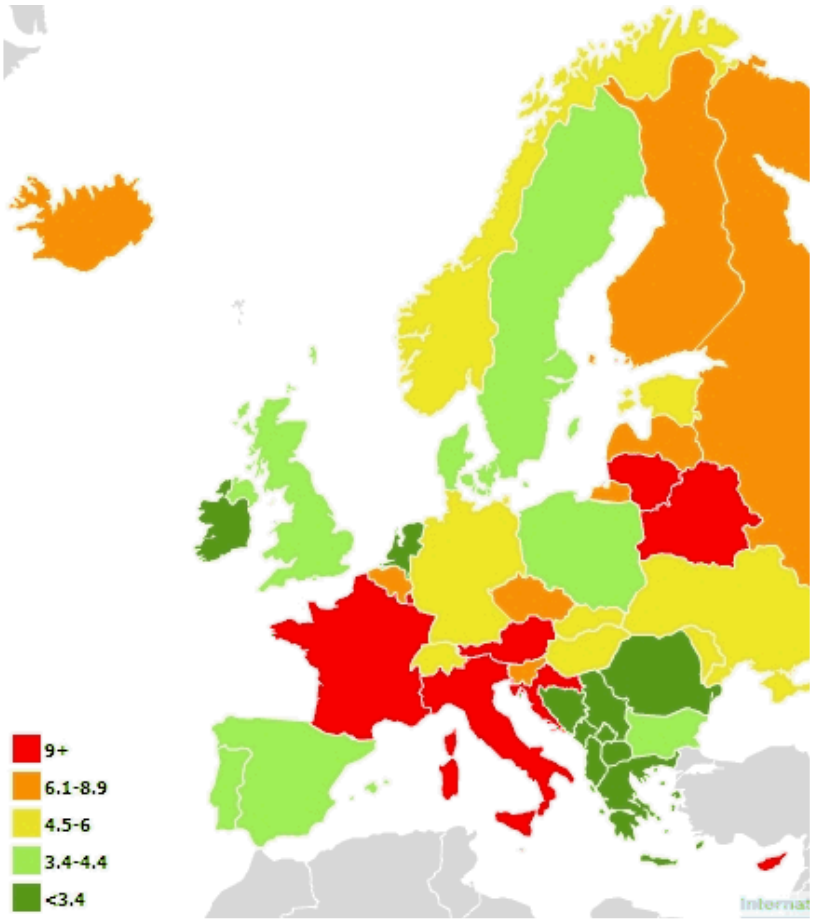

Figure 1 Estimated Incidence of Thyroid Cancer in Both Sexes in the EU, 2012

Key: Age-standardized incidence rate per 100,000.
Source: EUCAN, Thyroid Cancer Fact Sheet, 2012.

Prevalence:

The 5-year prevalence estimate for thyroid cancer as a whole was 149,044 adult individuals (aged greater than 15 years) within the EU in 2012, including 110,661 females and 38,383 males (GLOBOCAN, 2012; EUCAN, 2012). Extrapolation of this figure to 2014, accounting for a decline in female mortality of 2.3% per year (NORDCAN, 2014) and an overall population increase in the EU of 0.4% (Eurostat), results in a 5-year prevalence estimate of 149,638 persons living with thyroid cancer in the EU in 2014.

Neither RARECARE nor GLOBOCAN provide information on the subset of patients with radioactive iodine (RAI)-refractory DTC; hence, an estimate of 5-year prevalence for this subgroup has been calculated based on the following assumptions:

- DTC comprises approximately 90% of cases of thyroid cancer (RARECARE, 2008; Cancer Research UK, 2014).
- The disease recurs within 5 years in approximately 10% of DTC patients (Mazzaferri and Kloos, 2001).

- 28% to 40% of patients with metastatic thyroid cancers lose functional ability to concentrate iodine and for whom radioiodine treatment is no longer appropriate (Schlumberger, et al., 1986; Schlumberger, et al., 1996; Samaan et al., 1985; Durante, et al., 2006).

If these estimates are taken together and applied to the 2014 prevalence estimate for thyroid cancer, then the 5-year prevalence of RAI-refractory DTC was approximately 4938 persons in the EU in 2014.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

No specific demographic data for the RAI-refractory DTC population have been reported; therefore, information in this section is presented for thyroid cancer as a whole (and DTC where available).

The median age of individuals at the time of diagnosis of thyroid cancer (as a whole) is between 45 and 50 years (Agate, et al., 2012; SEER Cancer Statistics Review, 2014). Patients with follicular thyroid cancer tend to be older than those with PTC and to have a more advanced tumour stage at diagnosis (Mazzaferri and Kloos, 2001). Thyroid cancer is rare in individuals <16 years of age, with an annual incidence of between 0.02 and 0.7 cases per 100,000 children and it is exceptional before the age of 10 (Agate, et al., 2012; Holmes, et al., 2012).

Female subjects represent 73% of the thyroid cancer population in Scandinavian countries (including Iceland and Faroe Islands) (NORDCAN, 2014). In the UK, female subjects represent 71% of the population with an incidence of 2.2 and 5.5 per 100,000 in male and female subjects, respectively (UK Office of National Statistics). A higher incidence in female subjects is also observed in the US (SEER Cancer Statistics Review, 2014).

No racial differences in the incidence of thyroid cancer are clearly defined or reported within Europe. In the US, there is evidence of racial differences in the incidence of PTC, which occurs more frequently among Asian female (10.96/100,000) than in black female subjects (4.9/100,000), and is higher in white male (3.58/100,000) than in black male subjects (1.56/100,000) (Pacini, et al., 2012; SEER Cancer Statistics Review, 2014). The incidence of other subtypes does not appear to vary substantially by race or ethnicity (Aschebrook-Kilfoy, et al., 2011). The Asian populations of Europe do not account for sufficient proportions of the population to influence underlying rates.

The only established environmental risk factor for thyroid carcinoma is exposure to ionizing radiation, and the risk, particularly of PTC, is greater in subjects of younger age at exposure (Pacini, et al., 2012).

The main existing treatment options:

Single-agent or combination chemotherapy in RAI-refractory DTC offers patients little to no benefit and is associated with significant toxicity (Shimaoka, et al., 1985; Matuszczyk, et al., 2008). The lack of benefit of chemotherapy, associated with substantial cytotoxicity, is

addressed in consensus guidelines by the European Society of Medical Oncology and the National Comprehensive Cancer Network (NCCN; Tuttle, et al., 2010; Pacini, et al., 2012). These guidelines recommend that patients with RAI-refractory DTC avoid traditional chemotherapy and move directly to treatment with antiangiogenic tyrosine kinase inhibitors (TKIs). Several TKIs are under clinical development and one TKI, sorafenib, was approved for RAI-refractory DTC in the US in November 2013 and in the EU in May 2014. Physicians have begun to expand their use of TKIs as data on the efficacy in patients with RAI-refractory DTC become available.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The prognosis for thyroid cancer at the time of diagnosis is generally good, with a 5-year relative survival rate of 98% (SEER Cancer Statistics Review, 2014) and a 10-year survival rate of 85% (Hundahl, et al., 1998).

Differentiated thyroid cancer is usually asymptomatic for long periods and commonly presents as a solitary thyroid nodule. The current treatment of choice for primary management of DTC is surgery (total thyroidectomy or unilateral lobectomy), commonly followed by ^{131}I ablation and thyroxine therapy (Pacini, et al., 2012; NCCN Practice Guidelines, Version 2.2013). The goal of this treatment is to destroy any residual thyroid tissue and prevent locoregional recurrence. Mazzaferri and Kloos (2001) reported tumour recurrence in 23.5% of DTC patients at the 16.6 year median follow-up time for the study; 16% had local recurrence and 8% had distant metastases (which includes 2% with both local and distant metastases). After a 40-year follow-up, the recurrence rate was approximately 35%, a third of which were distant metastases. Distant metastases are associated with 5-year survival rates of approximately 50% (Schlumberger, et al., 1986; SEER Cancer Statistics Review, 2014), 10-year survival rates of 40% (Schlumberger, et al., 1986), and 15 year survival rates of 30% (Schlumberger, et al., 1986; Schlumberger, et al., 1996).

The main predictors of outcome for patients with distant metastases are age, metastatic site, the ability of the tumour to concentrate ^{131}I, and morphology on a chest radiograph (Schlumberger, et al., 1986). Approximately one-third of metastatic thyroid cancers lose functional ability to concentrate iodine and will no longer be appropriate for RAI treatment (Schlumberger, et al., 1996; Durante, et al., 2006). Once becoming refractory to RAI, DTC exhibits a more aggressive behaviour. The absence or loss of ^{131}I uptake in tumours correlates with a 10-year survival rate of approximately 10% (Schlumberger, et al., 1996; Durante, et al., 2006).

Important co-morbidities:

An observational study revealed that of 29,225 patients with thyroid cancer (90% of whom had DTC), 2.7% died from thyroid cancer, 1.8% from other cancers, and 3.5% from other non-cancer causes (Yang, et al., 2013). The most frequent causes of non-cancer death were heart diseases (33.9%), cerebrovascular diseases (10.4%), and chronic obstructive pulmonary disease and associated conditions (5.7%). The most frequent secondary cancer deaths were

due to cancers of the lung and bronchus (22.6%), colon excluding rectum (6.3%), pancreas (5.9%), and breast (5.2%).

In a population-based study of 378 DTC patients in the Netherlands, hypertension was the most frequent comorbidity (18%) and was twice as high as expected (Kuijpens, et al., 2006) compared with patients with other cancer types in the same region (Janssen-Heijnen, et al., 2005).

In a retrospective cohort study in the Netherlands comparing 524 patients with DTC and 1572 sex and age–matched controls, hypertension and diabetes mellitus were more common in DTC patients than in controls (17.7% versus 11.5%) and (4.2% versus 2.5%), respectively (Klein Hesselink, et al., 2013). This study also showed that the risk of cardiovascular (CV) mortality is increased 3.3-fold in patients with DTC compared with controls, independent of age, sex, and CV risk factors, and that lower thyroid stimulating hormone (TSH) levels were independently associated with an increased risk of CV mortality. The authors suggested that the increased CV risk may be due to long-term exposure to thyroid hormone suppression therapy rather than the underlying disease.

Indication: Renal cell carcinoma

Brand Name of Concerned Product (with this indication): Kisplyx

For the purpose of this RMP, the generic name lenvatinib is used in accordance with the terminology used in the nonclinical and clinical studies.

Incidence:

Worldwide, kidney cancer is the 14th most common cancer, and is the 9th most frequently diagnosed cancer in men and 14th in women (World Cancer Research Fund, 2020). The incidence of renal cell carcinoma (RCC) is increasing and it is estimated that in 2021, 76,080 (48,780 male and 27,300 female) new cases of kidney cancer will be diagnosed in the US. Approximately 13,780 people are expected to die from the disease in the US (American Cancer Society, 2021). In 2020, an estimated 138,611 new cases of kidney cancer were expected to be diagnosed in Europe with approximately 54,054 people expected to die from the disease (GLOBOCAN, 2020).

The age-standardised incidence of kidney cancer (per 100,000) is highest in North America (10.9) and Northern Europe (10.0); rates are lowest in Middle Africa (0.87; Ferlay, et al., 2018). More than one-third of incident cases occur in Europe, with nearly 137,000 incident cases expected in 2018 (Ferlay, et al., 2018). In the US, kidney cancer incidence is 16.1 per 100,000, yielding roughly 74,000 new cases in 2019 (SEER*Stat, 2019).

Prevalence:

The 5-year prevalence of kidney cancer in Europe (Central and Eastern Europe, Northern Europe, Southern Europe and Western Europe) in 2018 was 382,191, while the total population was 922,832,486 individuals (GLOBOCAN, 2020), leading to a prevalence of kidney cancer in Europe of 41.4/100,000. This prevalence is in line with the prevalence for

RCC of 42.0/100,000, as published in the most recent Orphanet Report Series (Orphanet Report Series, 2021).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Renal cell carcinoma (RCC) is a male-predominant disease and in most countries, it is roughly twice as common among males compared to females. Kidney cancer incidence increases with age, and typically presents in the sixth and seventh decades of life (median age about 60 years; Escudier and Kataja, 2010; Ferlay, et al., 2018; SEER*Stat, 2019). Incidences in Europe and the US increase consistently with age, with a plateau reached around ages 70 to 75 years (Ljungberg, et al., 2011). RCC is rare in children, accounting for approximately 0.1% to 0.3% of all neoplasms and from 1.8% to 6.3% of all malignant renal tumours, and has shown significant differences in histology and pathogenesis when compared to RCC in adults (Perlman, 2010; Indolfi, et al., 2003).

Incidence of RCC seems to be substantially lower among Asians, both in most Asian countries and in the US, suggesting a higher risk of RCC among whites compared to Asians. The lowest incidences have been reported from African countries. However, the incidence is highest among African Americans in the US. Racial disparities in incidence may be attributable to differences in frequency of diagnostic imaging, access to health care, genetic background, and prevalence of lifestyle or environmental risk factors (Ljungberg, et al., 2011).

Established risk factors for RCC include obesity, smoking, hypertension, and chronic kidney disease; other probable risk factors include low physical activity, diabetes, occupational chemical exposure, radiation exposure, and analgesic use (Capitanio et al., 2019; Petejova, 2016; Rossi, 2018). However, antihypertensive medications such as diuretics are not independently associated with RCC development. RCC also appears to be more common in patients with end-stage renal failure, acquired renal cystic disease and tuberous sclerosis (Escudier, et al., 2014).

Renal cell cancer generally is not considered an occupational disease, although there is epidemiologic evidence linking trichloroethylene exposure to RCC, with most recent studies reporting increased risk with increased exposure (Chow, et al., 2010).

Approximately 2% to 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 disease (Escudier, et al., 2014).

The main existing treatment options:

Renal cell carcinoma generally resists both traditional chemotherapy and radiation therapy. Surgical resection can be curative for patients presenting with localized disease. Of patients with localised RCC treated with nephrectomy with curative intent, approximately one quarter relapse at distant sites. The prognosis in these cases is poor (Choueiri and Motzer, 2017). However, one third of patients present with regional or distant metastases.

Advances in understanding of the pathogenesis and molecular biology of RCC led to a shift from predominantly cytokine-based treatment options to the use of targeted agents.

Current strategies for optimizing treatment of advanced disease have focused on the development of new therapeutic agents and optimal sequencing of drugs. One challenge is that multiple overlapping and complementary angiogenic and oncogenic signaling pathways can provide tumours with potential evasive resistance mechanisms to targeted therapy. Combinations of agents may overcome the resistance that develops with single-agent therapy hence, novel strategies include new combinations of agents to maximize their impact on clinical outcomes. Since 2017, several immune checkpoint inhibitor combinations have demonstrated a survival advantage in advanced RCC and globally approved 1L therapy has changed to include nivolumab plus ipilimumab (for intermediate or poor risk disease by IMDC risk model), axitinib plus avelumab, axitinib plus pembrolizumab, and cabozantinib plus nivolumab. All the pivotal studies that support these indications included sunitinib as the comparator arm, since sunitinib was standard of care at that time. Despite the increase in active systemic treatments available to advanced RCC patients, most patients with advanced disease will progress or die within 1.5 years (median progression-free survival [PFS] 5.5 to 16.6 months for currently approved 1L therapies). Therefore, more effective therapies in 1L RCC are needed.

Despite significant progress, treatment of advanced RCC after disease progression with anti-PD-1/programmed cell death protein ligand 1 (PD-L1) therapy, remains a challenge given the lack of established treatment options. However, the response rate with initial targeted therapy is approximately 30% and nearly all patients who do respond eventually progress. This is evidenced by the lack of specific guidance available for patients who previously received anti-PD-1/PD-L1 therapy in guidelines, where many regimens include an anti-PD-1/PD-L1 therapy. Data for all second-line regimens after an anti-PD-1/PD-L1 therapy are generally retrospective and have not shown strong efficacy in a well-defined population (NCCN, 2020). Overall, these limitations underscore the high unmet need in advanced RCC patients with progression following anti-PD-1/PD-L1 based regimen.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

RCC originates within the renal cortex from the proximal renal tubular epithelium and is the most common kidney cancer, constituting 80% to 85% of primary renal neoplasms (Motzer, et al., 1996). Most cases of RCC (70% to 80%) are classified as clear-cell tumours.

One-third of patients present with regional or distant metastases and the 5-year survival rate for metastatic disease is approximately 12% (Siegel, et al., 2018).

Worldwide, kidney cancer age-standardised mortality rates (per 100,000) are highest in Central/Eastern Europe (3.6) and Western Europe (3.0); 55,000 deaths occurred in Europe during 2018 (Ferlay, et al., 2018). Prognosis has improved significantly in the US and Europe, due in part to the advent of TKI therapy and immunotherapy (Mangone, 2017; SEER*Stat, 2019). The majority (65%) of kidney cancers diagnosed in the US are localized and 16% of tumours are metastatic (SEER*Stat, 2019). The overall 5-year survival in

Europe and the US is 60% and 75%, respectively (SEER*Stat, 2019; Marcos-Gragera, et al., 2015). Clear cell histology, accounting for the majority of RCC, is associated with a better prognosis than non-clear cell RCC (Rao, 2018).

Important co-morbidities:

Cardiovascular or cerebrovascular diseases, hypertension, chronic obstructive pulmonary disease, diabetes and other prevalent comorbidities among elderly populations are frequently observed in cancer patients (Sarfati, et al., 2016).

Indication: Hepatocellular carcinoma

Brand Name of Concerned Product (with this Indication): Lenvima

For the purpose of this RMP, the generic name lenvatinib is used in accordance with the terminology used in the nonclinical and clinical studies.

Epidemiology of the Disease:

Hepatocellular carcinoma (HCC), a tumour of the parenchymal cells of the liver, is the most common liver cancer, representing 75% to 90% of all tumour histologies (GLOBOCAN, 2020). The second most common histology (approximately 15%) is intrahepatic cholangiocarcinoma (ICC), which arises in the cholangiocytes of the intrahepatic bile duct. Large geographic disparities in incidence and mortality of all types of liver cancer exist (McGlynn, et al., 2015).

It is important to distinguish between primary liver cancer and secondary liver cancer, since the liver is a common site of metastatic spread in other tumour types, and in some countries, mortality can appear to be even higher than incidence as secondary liver cancer can be mistakenly counted as primary liver cancer (McGlynn, et al., 2015).

Incidence:

Primary liver cancer is the fifth most commonly occurring cancer worldwide in men, the ninth most common cancer in women, and the third most common cause of cancer mortality worldwide, estimated to be responsible for 905,677 new cases and nearly 830,180 deaths in 2020 (8.3% of the total deaths) (GLOBOCAN, 2020). The incidence of liver cancer is highly variable on a geographic basis, with the highest incidence rates associated with the less developed regions, where 83% of the total number of cases occurred (50% of cases in China alone).

Rates vary substantially worldwide. Among men, liver cancer incidence rates in 2012 (cases per 100,000) ranged from approximately 4 in Northern Europe and South Central Asia to 32 in South-Eastern Asia. Among women the incidence rates ranged from approximately 2 in Northern Europe and Micronesia to 10 in Eastern Asia (GLOBOCAN, 2012).

The incidence of liver cancer for Europe is specified in Table 1.

Table 1 Estimated Number of Primary Liver Cancer Cases and Deaths, and Age-Standardised Incidence and Mortality per 100,000 Persons in 2020, by European Region

	Population		Incidence				Mortality
Region	Total (thousands)	Percentage of World Total (%)	Number of Cases	Percentage of World Total (%)	ASR	M:F	Number of Deaths
Central-Eastern Europe	293,013	3.8	24,800	2.7	4.3	2.6	23,000
Northern Europe	106,261	1.4	11,900	1.3	5.0	2.1	10,500
Southern Europe	153,423	2.0	24,800	2.7	6.7	3.3	21,200
Western Europe	196,146	2.5	26,100	2.9	5.4	3.3	23,700

ASR = age-standardised rate per 100,000, M:F = male female ASR ratio.
Source: Rumgay et al., 2022.

The age-standardised incidence rates (ASIR) ranged from 2.7 to 9.2 cases per 100,000 individuals across Europe (Figure 2) (GLOBOCAN, 2020).

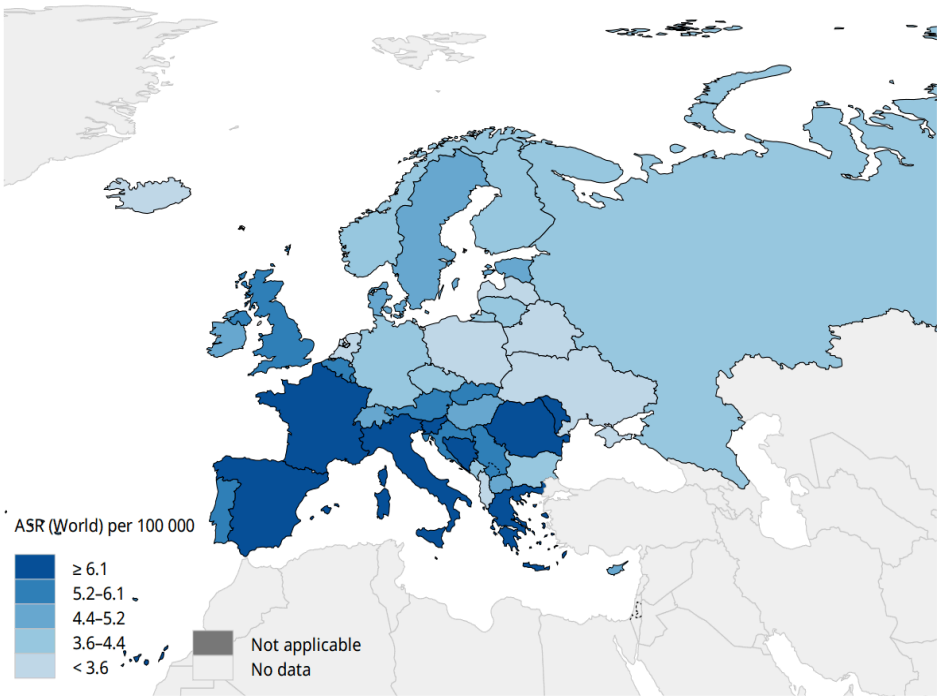

Figure 2 Estimated Age-Standardised Incidence Rates of Liver Cancer in Both Sexes in Europe, 2020

Key: Age-standardised incidence rate per 100,000.
Data source: GLOBOCAN 2020 Map production: IARC (http://gco.iarc.fr/today) World Health Organization.

Prevalence:

Globally, liver cancer is the 14th most prevalent cancer with a 5-year prevalence in 2020 of 994,539 individuals from both sexes.

In Europe, the 5-year prevalence estimate for liver cancer in both sexes in 2020 was 85,119 individuals, 57,816 males and 27,303 females (GLOBOCAN, 2020).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Rates of both incidence and mortality are 2 to 3 times higher among men than women in most regions (GLOBOCAN, 2020). Although the differences in incidence rates by gender are not well understood, it has been hypothesized that differences in sex steroid hormones, immune responses and epigenetics could be related to the higher rates among men (McGlynn, et al., 2015).

In addition to gender differences, racial/ethnic disparity within multiethnic populations is also notable. In the US between 2006 and 2010, Asians/Pacific Islanders had the highest

incidence rate per 100,000 (11.7), followed by Hispanics (9.5), blacks (7.5), and finally, whites (4.2). Rates of liver cancer among persons of the same ethnicity also vary by geographic location. For example, liver cancer rates among Chinese populations outside China are lower than the rates reported by Chinese registries. As with gender differences, racial/ethnic differences are likely due to variability in the prevalence of risk factors between racial/ethnic groups and between geographic locations (McGlynn, et al., 2015).

The risk of developing liver cancer increases with advancing age and is more prevalent in men than women. Approximately 90% of HCCs are associated with a known underlying risk factor. The most frequent risk factors include chronic viral hepatitis. HBV infection is the most common viral risk factor in sub-Saharan Africa and East Asia (Schweitzer, et al., 2015), while HCV is the most common in Western Europe (Roudot-Thoraval, 2021). Worldwide, approximately 54% of cases can be attributed to hepatitis B (HBV) infection (which affects 400 million people globally) while 31% can be attributed to hepatitis C (HCV) infection (which affects 170 million people), leaving approximately 15% associated with other causes (EASL-EORTC, 2012).

Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis, alcohol, inherited metabolic diseases such as hemochromatosis or alpha-1-antitrypsin deficiency, and non-alcoholic fatty liver disease. Obesity, diabetes and fatty liver disease have come to be recognized as a cause of HCC (El-Serag, et al., 2001; Marrero, et al., 2005), although the mechanisms by which these overlapping conditions contribute to cancer development remain elusive. Smoking has also been identified as a clear risk factor for HCC, with heavy smokers having a higher risk than non-smokers (Marrero, et al., 2005).

The main existing treatment options:

Prior to the introduction of antiangiogenic targeted therapies and immunotherapy, outcomes for patients with HCC did not improve for many decades despite scientific advances in the understanding of hepatocarcinogenesis.

Sorafenib was the first TKI approved for the treatment of HCC. On 20 Aug 2018, lenvatinib was approved in the EU as monotherapy for the treatment of adult patients with advanced or unresectable HCC who have received no prior systemic therapy, based on data from the REFLECT trial (Kudo, et al., 2018).

Immune checkpoint inhibitors have demonstrated efficacy in multiple tumour types, and the combination of atezolizumab in combination with bevacizumab is preferred therapy for the 1L treatment of patients with advanced HCC since its approval in the EU on 27 Oct 2020 based on a survival benefit versus sorafenib in the randomised Phase 3 trial IMbrave150 (Finn et al., 2020). Strategies for 1L treatment of advanced HCC now focus on the development of novel combinations of these agents, optimal sequencing, and the assessment of new therapeutic targets. The combination of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) was EMA approved in the EU on 30 Jan 2023 for the 1L treatment of adults with advanced or unresectable HCC (Abou-Alfa et al., 2022). Given the survival benefit observed versus sorafenib for both combinations, 1L treatment has dramatically changed

from monotherapy TKIs to immunotherapy based regimens as standard of care (Abou-Alfa, et al., 2018).

In patients previously treated with systemic therapy, treatment options are limited to single-agent antiangiogenics; sorafenib is approved regardless of prior therapy received, regoraenifb, cabozantinib, and ramucirumab are approved in patients previously treated with sorafenib.

In specific circumstances, radiotherapy can be used to alleviate pain in patients with bone metastasis. Patients with Barcelona-Clinic Liver Cancer (BCLC) classification D (terminal stage) should receive palliative support including management of pain, nutrition and psychological support. In general, they should not be considered for participating in clinical trials (EASL-EORTC, 2012).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In advanced HCC (BCLC Stages B or C), the prognosis in patients with cancer-related symptoms (symptomatic tumours, Eastern Cooperative Oncology Group [ECOG] performance status 1–2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) has dramatically evolved with the introduction of immunotherapy based regimen, with expected median survival times from 6 months in the 2000s (Llovet and Bruix, 2008) to approximately 16 to 19 months in the 2020s (Abou-Alfa, et al., 2022; Cheng, et al., 2022). Patients with end-stage disease (BCLC Stage D) typically have a very poor performance status (ECOG 3–4). Their median survival is 3 to 4 months (Llovet, et al., 1999) or 11% at 1-year (Cabibbo, et al., 2010). Similarly, Child–Pugh C patients with tumours beyond the transplantation threshold also have a very poor prognosis (EASL-EORTC, 2012).

Hepatocellular carcinoma is frequently complicated by the presence of comorbid conditions, which can affect liver function, limit treatment options, and lead to poor outcomes; these include cirrhosis, a major cause of HCC development and is present in 70% to 90% of those who have primary liver cancer (Herbst and Reddy, 2012), and coinfection with HBV or HCV, which varies depending on geographic region. For example, comorbid HBV infection is the most common viral risk factor in sub-Saharan Africa and East Asia (Schweitzer, et al., 2015), while HCV is the most common in Western Europe (Roudot-Thoraval, 2021), and, although most patients (70%-90%) have liver cirrhosis at diagnosis, in Asian populations HCC may develop in individuals at a younger age without cirrhosis (Blum, 2005; Marrero, et al., 2010). Clinically significant portal hypertension is a common comorbidity in HCC, which occurs in 25% to 55% of patients with both HCC and cirrhosis. Portal hypertension correlates with the severity of cirrhosis, and it can complicate HCC treatment by increasing the risk of perioperative haemorrhage and liver failure (Zhong, et al., 2014). Other co-morbidities may include those arising from other risk factors for developing HCC, such as alcoholic liver disease, diabetes, and obesity (Sanyal, et al., 2010).

Indication: Endometrial carcinoma

Brand Name of Concerned Product (with this Indication): Lenvima

For the purpose of this RMP, the generic name lenvatinib is used in accordance with the terminology used in the nonclinical and clinical studies.

Epidemiology of the Disease:

Adenocarcinoma of the endometrium (lining of the uterus) is the most common histologic type of uterine cancer. Endometrial adenocarcinomas are often classified into 2 histologic categories—Type 1 and Type 2. Type 1 tumours are more common and less aggressive, accounting for 70% to 80% of new cases, with endometrioid histology being the most common (Kerr, 2017). In contrast, Type 2 tumours typically have a poorer prognosis and are not clearly associated with oestrogen stimulation (Fleming, 2015; Makker, et al., 2017; Tran and Gehrig, 2017). Type 2 tumours consist of higher-grade adenocarcinomas and often have non-endometrioid histologies (eg, clear cell and serous cell types). In the recurrent setting, high-grade, aggressive tumours like serous and clear cell become more prevalent (Ramondetta, et al., 2001; Slomovitz, et al., 2003; del Carmen, et al., 2012).

A recent finding has been the identification of tumours with shortening or lengthening of small repetitive elements in DNA, a condition called microsatellite instability (MSI; Murali, et al., 2018). Microsatellite instability is a result of the inability of DNA mismatch repair (MMR) proteins to repair random mutations (termed MMR deficiency [dMMR]), leading to tumourigenesis. The MSI/MMR status is a key component in influencing treatment decisions for recurrent endometrial tumours.

Incidence:

Carcinoma of the uterine corpus, often referred as endometrial cancer (EC), is the sixth most common cancer among women worldwide with an estimated 382,069 new cases diagnosed in 2018 (Ferlay, et al., 2018). The incidence rate of EC is generally higher in high-income countries than low- and middle-income countries, with the highest age-standardised incidence rate (ASIR) (per 100,000) found in North America (20.5) and the lowest rate in South-Central Asia (2.5; Ferlay, et al., 2018). The ASIR in the EU (EU-28) is 14.3 per 100,000, yielding roughly 78,900 new cases each year (ECIS, 2018). Incidence rates of EC have been increasing over the past 2 decades in the US with an age-adjusted incidence rate of 27.5 per 100,000, corresponding to approximately 61,900 new cases (3.5% of all new cancers) annually (Howlader, 2019).

Prevalence:

Globally, the 5-year prevalence (per 100,000) is the highest in North America (139.9), followed by Northern Europe (124.8) and Central and Eastern Europe (121.6); and the lowest is in Middle Africa (2.6), Western Africa (3.3), and Eastern Africa (3.5) (Ferlay, et al., 2018). Prevalence (per 100,000) varies by region in Europe from 107.0 in Western Europe to 124.8 in Northern Europe (Ferlay, et al., 2018). In the US, an estimated 772,245 women were living with EC in 2016 (Howlader, 2019). According to a recent meta-analysis of 53

publications including over 12,000 patients, the pooled prevalence of MSI-high (MSI-H) and dMMR EC tumours is 26% and 25%, respectively (Lorenzi, 2018); therefore, the majority of patients will have tumours that are not MSI-H or dMMR.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Endometrial cancer is most frequently diagnosed among women aged 45–74 years with a median age at diagnosis of 63 years (Howlader, et al., 2019). Endometrial cancer incidence rate varies by race/ethnicity with the highest incidence rate in White women (28.1 per 100,000) and the lowest incidence rate in American Indian/Alaska Native women (19.7 per 100,000) (Howlader, 2019). On the other hand, Black women (8.5 per 100,000) have the highest mortality rate, and Asian/Pacific Islander women (3.1 per 100,000) have the lowest mortality rate (Howlader, 2019). The main risk factors for EC are related to endogenous and exogenous oestrogen, including being overweight, abdominal fatness, oestrogen replacement therapy, early age at menarche, late menopause, nulliparity and diabetes (Morice, 2016; Torre, 2017).

The main existing treatment options:

Treatment of EC may vary depending on the histology, grade, stage of the disease, and the MSI/MMR status. Currently, the mainstay of 1L treatment for localized EC is surgery with hysterectomy and bilateral salpingo-oophorectomy, with or without radiotherapy or chemotherapy depending on risk factors (Tran and Gehrig, 2017). Platinum-based chemotherapy is the standard 1L systemic therapy for patients with metastatic, recurrent, or high-risk disease (NCCN, 2020). Some subgroups of patients, based on molecular profiling, may benefit less from chemotherapy as suggested by a retrospective analysis on the PORTEC-3 study including dMMR tumours that demonstrated worse outcomes compared with proficient mismatch repair (pMMR) tumours (polymerase epsilon [POLE] mutated and no specific molecular profile [NSMP]) (Prendergast, et al., 2019).

Cytotoxic therapy remains the de facto second-line treatment, despite limited efficacy and substantial toxicities (Makker, et al., 2017) and being associated with low response rates (≤15%) and short PFS (4 months), resulting in poor overall survival and quality of life (McMeekin, et al., 2015). Therefore, further development of novel therapies or combinations with unequivocal demonstration of rapid disease control, durable clinical benefit and prolonged OS in a clinically meaningful number of participants is needed for the treatment of advanced EC of both endometrioid and nonendometrioid (including clear cell and serous histologies) and regardless of MMR biomarker status.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Endometrial cancer is the fourteenth leading cause of cancer-related death among women worldwide with the age-standardised mortality rate (ASMR) of 1.8 per 100,000, corresponding to an estimated 89,929 deaths in 2018 (Ferlay, et al., 2018). The highest mortality rate (per 100,000) is observed in Central and Eastern Europe (3.9) and the lowest

rate is observed in Northern Africa (0.7) (Ferlay, et al., 2018). Approximately 18,800 patients die each year from EC in Europe (EU-28) (ECIS, 2018); the ASMR is 2.4 per 100,000, with the highest rate in Central/Eastern Europe (3.9) and the lowest rate in Western Europe (2.1) (ECIS, 2018; Ferlay, et al., 2018).

The prognosis for EC is significantly influenced by disease stage. At diagnosis, 67% of patients have localized disease, while 21% have regional disease, and approximately 9% have distant metastases (Howlader, et al., 2019). Patients with localised disease have a 5-year survival rate of 95%, whereas those with regional and distant metastatic disease have 5-year survival rates of 69% and 16.8%, respectively (Howlader, et al., 2019). Despite the favourable outcomes associated with early detection, approximately 20% of EC cases recur with poor outcomes (Suhaimi, et al., 2016). The population of patients with recurrent EC represents a heterogeneous mix of different histological subtypes and grades, stages at initial diagnosis, prior therapy, duration of recurrence-free intervals, and site(s) of recurrence (distant or local; Obel, et al., 2006). In general, the prognosis is dismal for women diagnosed with advanced or recurrent disease, with a median survival of only 12 months (Makker, et al., 2017).

Important co-morbidities:

Co-morbidities are common among patients with cancer, particularly with older adults (Williams, et al., 2016). Most cases of EC occur among adults over age 55 and excess oestrogen exposure is a well-known risk factor of EC, thus, patients with EC often have comorbidities such as hypertension, diabetes, and obesity (Cook, et al., 2013; Nicholas, et al., 2014; Kurnit, et al., 2015).

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage:

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
Single and repeat-dose toxicity	The toxicity of lenvatinib was evaluated in single- and repeated-dose oral toxicity studies (for up to 26, 4, or 39 weeks) in male and female rats, dogs, and monkeys, respectively. Lenvatinib caused toxicologic changes in various organs and tissues in rats, dogs, and monkeys. The majority of the findings were related to the pharmacologic effects of lenvatinib as a VEGFR RTK inhibitor and its antiangiogenic activity in selected tissues. In addition, reversibility of the toxicologic changes was indicated at the conclusion of a 4-week off-dose interval in all animal species investigated.	
	No abnormalities in mean blood pressure (BP) were noted with E7080 administration in dogs and monkeys at doses up to 0.5 and 30 mg/kg, respectively.	Hypertension has been observed in clinical trials.
	Arterial lesions characterised by arterial fibrinoid necrosis, medial degeneration, or haemorrhage were observed in various organs in rats, dogs, and monkeys. The test article-related vascular lesions were histologically characterized by arterial fibrinoid necrosis, medial degeneration, or haemorrhage, and were observed in various organs in rats (spleen, kidney, testis, heart, gastrointestinal (GI) tract, and choroid plexus), monkeys (GI tract, gallbladder, and choroid plexus), and dogs (GI tract, gallbladder, liver, urinary bladder, heart, ovaries, uterus, vagina, adrenals, sciatic nerve, optic nerves, and mammary gland). The vascular lesions in monkeys were less severe compared to those in dogs.	The VEGF/VEGFR signalling pathway has a variety of physiological functions including the maintenance of vascular endothelial cell homeostasis under normal conditions and following injury. Inhibition of this pathway can compromise the integrity of the vascular endothelial cell lining and this can predispose to platelet aggregation, arterial thromboembolic events (ATEs), cardiac failure, and haemorrhage. Such events have been observed in clinical trials.
	Soft stool and watery stool were observed as GI effects in dogs and monkeys and were accompanied with histopathologic changes including haemorrhage, inflammation, erosion/ulcer, submucosal oedema, crypt hyperplasia, and mucosal atrophy. Particularly, bloody and blackish stool were observed in dogs at lethal doses. Both nonrodent species showed anorexia at higher doses and experienced severe morbidity. These signs disappeared gradually after test drug withdrawal.	GI toxicity has been observed with clinical use.

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
	Changes in the pancreas were noted in rats administered 10 mg/kg/day in a 26-week oral toxicity study (pancreatitis, fatty necrosis, and decreased zymogen granules) and in monkeys administered 3 mg/kg/day in a 39-week oral toxicity study (decreased zymogen granules).	Events of pancreatitis were observed in clinical trials but were assessed not to be related to lenvatinib. However, given that pancreatitis is a safety concern for other TKIs, this finding for lenvatinib is deemed to be of unknown significance to human usage.
	Lenvatinib caused bone changes, specifically increased thickness of epiphyseal growth plate and cartilage in rats and monkeys, which were characterised by increased thickening of the cartilage layer in bones. Dysplasia in incisors was also observed in rats.	Bone changes are considered relevant to the paediatric population, in which bone development continues through adolescence. The bone changes in rats are not considered relevant to human adults because unlike human adults, rodents have continuous growth of epiphyseal cartilage in bones throughout life. Therefore, this finding is considered relevant only to the paediatric population and not the targeted (ie, adult) population. The incisor changes in rats are not considered relevant to humans because unlike human teeth, rodent incisors are open-rooted and grow continuously throughout life, making them more sensitive to the pharmacologic effects of lenvatinib. As human teeth do not grow and remodel continuously throughout life, they are not expected to exhibit the same sensitivity to the effects of lenvatinib. Visible changes in rat molars, which do not grow continuously throughout life and therefore may be more representative of human teeth, were not noted in the rat toxicity studies with lenvatinib.
	Ovarian changes characterised by follicular atresia or increased atretic follicles were observed in rats, dogs, and monkeys. Decreased menstruation was observed during long-term studies in monkeys. Effects were observed in nonrodents at exposures below the anticipated clinical exposure (based on area under concentration time curve [AUC]) at the maximum recommended human dose.	Female fertility may be affected.
	Testicular hypocellularity was observed in rats, dogs, and monkeys. Effects were observed in nonrodents at exposures below the anticipated	Male fertility may be affected.

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
	clinical exposure (based on AUC) at the maximum recommended human dose.	
Reproductive and developmental toxicity	Administration of lenvatinib during organogenesis resulted in embryo lethality and teratogenicity in both rats and rabbits at exposures below the clinical exposure (based on AUC) at the maximum recommended human dose. Fetal external and skeletal anomalies were observed at lenvatinib doses ≥0.1 mg/kg in rats, and fetal external, visceral, or skeletal anomalies were noted at 0.1 and 0.5 mg/kg in rabbits.	May be associated with abnormal pregnancy outcome.
	Lenvatinib and its metabolites are excreted in rat milk. Low levels of radioactivity were detected in rat pups after oral administration of ^{14}C-lenvatinib to lactating rats.	May be excreted in human breast milk.
	In a 2-week dose range finding (DRF) study in juvenile rats the toxicity of lenvatinib was more prominent in younger rats (dosing initiated on postnatal day [PND] 7) compared with those with dosing initiated on PND21. Daily oral administration of lenvatinib mesilate (0.4, 2, or 10 mg/kg) to young rats for 8 weeks starting on PND21 resulted in growth retardation (decreased body weight gain and decreased food consumption), secondary delay of physical development, and lesions attributable to pharmacologic effects (incisors, femur, kidneys, adrenals, and duodenum) at doses ≥2 mg/kg (approximately 2 times the systemic exposure [AUC] in patients administered the recommended human dose). Additional findings observed in the rats administered 10 mg/kg/day (approximately 7 to 11 times the systemic exposure [AUC] in patients administered the recommended human dose) included mortality attributed to primary duodenal lesions. The toxicologic profile of lenvatinib in young rats was similar to the profile in adult animals, and toxicities were mostly reversible during the 4-week recovery period. The no observed adverse effect level (NOAEL) was 0.4 mg/kg.	The prominent toxicity observed in very young juvenile rats (dosing initiated on PND7) suggests that administration to paediatric patients under the age of 2 years is not appropriate as many of the target organs (CV system, kidney, and bone) of lenvatinib continue to develop after birth in children. By 2 years of age, development of the CV system and kidney are complete; however, the effects of lenvatinib on bones in juvenile animals suggest an increased risk for bone effects in children, who have an active growth plate.

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
Nephrotoxicity	Lenvatinib caused glomerulopathy, sometimes with proteinuria, in rats, dogs, and monkeys at dose levels of 2 mg/kg (26-week toxicity study), 0.5 mg/kg (4 week toxicity study), and 0.5 mg/kg (39-week toxicity study), respectively. Reversibility of this glomerular change was investigated in rats (15 mg/kg), dogs (0.5 mg/kg), and monkeys (3 and 30 mg/kg) and was confirmed in all species.	Proteinuria has been observed with clinical use.
Hepatotoxicity	In a 26-week oral toxicity study in rats, changes in the liver (Kupffer cell hypertrophy or hyperplasia and pigmentation of periportal hepatocytes) were observed at 10 mg/kg. These were secondary to vascular changes attributed to the pharmacologic effect of the drug and therefore were not a significant nonclinical concern. Elevated transaminase levels were observed in rats, dogs, and monkeys, and were associated with marked toxicity.	Elevated transaminase levels and other signs of hepatotoxicity have been observed with clinical use.
Genotoxicity	In the standard battery of genotoxicity studies, lenvatinib was negative in the Ames assay, mouse lymphoma thymidine kinase (tk) assay, and micronucleus assay in rats.	No risk anticipated.
Carcinogenicity	In accordance with the recommendations of ICH S9, *Nonclinical Evaluation for Anticancer Pharmaceuticals*, no carcinogenicity studies have been conducted.	Not applicable; therefore, this is not carried over as an important nonclinical safety concern.
General safety pharmacology	No significant adverse effects of lenvatinib on the CV, respiratory, and central nervous system were observed in rats and dogs. With the exception of a weak inhibitory effect of lenvatinib on human ether-à-go-go-related gene (hERG) potassium current (IC_{50} = 11.89 µmol/L), no significant adverse effects were observed in the 2 in vitro electrophysiology studies conducted to assess the effect of lenvatinib on hERG potassium current or action potential parameters.	Lenvatinib is anticipated to have a low risk of CV, respiratory and central nervous system adverse effects in humans, although hypertension was observed in subjects in clinical trials.
Mechanisms for drug interactions	Drug metabolising enzyme and transporter inhibition In vitro, lenvatinib exhibited a potent inhibitory effect on cytochrome P450 (CYP) 2C8 (IC_{50}: 10.1 µmol/L), and weakly inhibited CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in human liver microsomes. Virtually no inhibition of CYP2A6 and CYP2E1 was seen. In human liver microsomes, lenvatinib directly inhibited UGT1A1 and UGT1A4. In contrast,	Low risk of interference with the pharmacokinetics (PK) of other drugs co-administered in usual clinical practice.

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
	inhibition of UGT1A6, UGT1A9, UGT2B17, or UGT2B7 by lenvatinib was minimal or not observed. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity. In vitro, lenvatinib did not inhibit P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and OATP1B3, and weakly inhibited OAT1, OAT3, OATP1B1, OCT1, OCT2, and bile salt export pump (BSEP). Time-dependent inhibition of the formation of 1′ hydroxymidazolam from midazolam (CYP3A) by lenvatinib was observed. Drug metabolising enzyme and transporter induction Lenvatinib slightly induced CYP3A4 but had no effects on CYP1A1, CYP1A2, CYP2C9, CYP2B6, or P-gp (MDR1). Lenvatinib did not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 enzyme activities. Substrate potency of transporters Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or BSEP.	
Other toxicity-related information or data	Lenvatinib absorbs light within the range of 290–700 nm, and has an affinity to melanin based on the slow elimination of radioactivity in the melanin-containing tissues; however, the results of the in vitro 3T3 neutral red uptake phototoxicity test were negative.	No phototoxic potential

Conclusions on Nonclinical Data:

Important identified risks and potential risks from the nonclinical safety findings are shown below.

Nonclinical Safety Concerns
Important nonclinical safety findings (confirmed by clinical data) • Arterial lesions (thromboembolic events, cardiac failure, and haemorrhage) • Gastrointestinal toxicity • Proteinuria • Hepatotoxicity
Important nonclinical safety findings (not refuted by clinical data or which are of unknown significance) • Male and female fertility

• Abnormal pregnancy outcome • Excretion of lenvatinib in rat milk • Juvenile toxicity • Bone abnormalities in the paediatric population • Pancreatitis
Missing nonclinical safety information • None

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The pooled safety analyses include subjects from completed studies who received single-agent lenvatinib on a continuous basis, the combination of lenvatinib and pembrolizumab and the combination of lenvatinib and everolimus. Specific safety sets were created to evaluate the safety profile of lenvatinib monotherapy and lenvatinib combination therapy in subjects with the various carcinoma types.

The clinical trial exposure data are summarised by the following analysis sets:

- All DTC, Non-HCC Lenvatinib Monotherapy Safety Set, which is hereafter referred to as "All DTC" – including all subjects with DTC and Non-HCC who were treated with lenvatinib (N=458). This includes data from subjects with DTC from Studies 201 and 208, as well as from Study 303 (including subjects in the randomised lenvatinib arm and the optional open-label portion of the study). The data cutoff date for this safety set is 10 Dec 2014.
- Non-DTC Monotherapy Safety Set – including data from all remaining studies conducted in non-DTC subjects with cancer (including tumour types such as endometrial, glioma, melanoma, MTC) who received lenvatinib as monotherapy at the proposed dosing regimen (N=656). This includes data from subjects in Studies 101, 102 (monotherapy cohort, continuous dosing), 104, 105, 203, 204, and 206, as well as subjects with MTC or ATC in Study 208 and subjects with MTC in Study 201. The data cutoff date for this safety set is 15 Sep 2013.
- Lenvatinib 24 mg Monotherapy Safety Set (N=1119): All subjects with a starting dose level of lenvatinib 24 mg QD which is the approved monotherapy dose for DTC, and was used in studies for all solid tumours except HCC (11 studies):
  E7080-J081-105 (advanced solid tumours; cutoff date 01 Sep 2016),
  E7080-G000-201 (advanced thyroid cancers; cutoff date 01 Sep 2016),
  E7080-G000-203 (malignant glioma; cutoff date 01 Sep 2016),
  E7080-G000-204 (advanced endometrial carcinoma; cutoff date 01 Sep 2016),
  E7080-G000-205 (RCC; hereafter referred to as Study 205; cutoff date 15 Mar 2018),
  E7080-G000-206 (unresectable Stage III or IV melanoma; cutoff date 01 Sep 2016),
  E7080-J081-208 (differentiated thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer; cutoff date 01 Sep 2016),
  E7080-G000-209 (K1F5B RET positive adenocarcinoma of the lung and other confirmed RET translocations; cutoff date 01 Sep 2016),

E7080-G000-303 (differentiated thyroid cancer; cutoff date 01 Sep 2016), E7080-G000-398 (advanced differentiated thyroid cancer; cutoff date 01 Sep 2016), E7080-703 (advanced or metastatic NSCLC; cutoff date 01 Sep 2016).

- All RCC Lenvatinib + Everolimus Safety Set (N=623), which is hereafter referred to as the "RCC Lenvatinib + Everolimus Safety Set"– including all subjects with RCC who were treated with the combination of lenvatinib at the recommended dose of 18 mg and everolimus 5 mg in Study 112 (Phase 1; N=7), Study 205 (Phase 1b and Phase 2; N=62), Arm A (Lenvatinib 18 mg + Everolimus) of Study 218 (Phase 2; N=168), Study 221 (Phase 2; N=31), and Arm A (Lenvatinib 18 mg + Everolimus) of Study 307 (Phase 3; N=355). The data cutoff dates for these safety sets are 07 Jul 2017, 31 Jul 2015, 14 Feb 2020, 17 Jul 2019, and 28 Aug 2020, respectively.
- All RCC Lenvatinib + Pembrolizumab Safety Set (N=497)– including data from all subjects with RCC who received at least 1 dose of lenvatinib 20 mg QD + pembrolizumab 200 mg as the starting dose, regardless of prior anticancer therapy, in Study 307 (N=352) and Study 111(N=145). The data cutoff date for the Study 307 safety set is 28 Aug 2020 and for the Study 111 safety set is 18 Aug 2020.
- HCC Lenvatinib Monotherapy Safety Set, which is hereafter referred to as the "HCC Lenvatinib Safety Set" – including all subjects who received at least 1 dose of lenvatinib in Study E7080-G000-304 (N=476) and subjects in the Phase 2 portion of Study E7080-J081-202 who had a baseline body weight ≥60 kg and received at least 1 dose of lenvatinib (ie, received the planned labelling dose) (N=20).
- All EC Lenvatinib + Pembrolizumab All Participants-as-Treated Population (APaT; N=530), which is hereafter referred to as the "All EC Lenvatinib + Pembrolizumab Safety Set" – including data from all subjects with EC who received at least 1 dose of lenvatinib 20 mg QD + pembrolizumab 200 mg in Study 309 (N=406) and Study 111 (N=124). The data cutoff date for this safety set is 26 Oct 2020 for Study 309 and 18 Aug 2020 for Study 111.

The All DTC Lenvatinib Safety Set had a median treatment duration of 14.7 months, while the Non-DTC, Non-HCC Monotherapy Safety Set had a median duration of 3.5 months. The RCC Lenvatinib + Everolimus Safety Set had a median treatment duration (lenvatinib) of 9.3 months. The All RCC Lenvatinib + Pembrolizumab Safety Set had a median treatment duration (lenvatinib) of 14.8 months. The HCC Lenvatinib Safety Set had a median treatment duration of 5.9 months. The All EC Lenvatinib + Pembrolizumab Safety Set had a median treatment duration of 7.1 months. Pooling of all safety sets could potentially have led to a dilution in incidence of adverse drug reactions (ADRs) in the DTC and RCC populations; hence, the proposed analysis set groupings represent a conservative stance.

The Non-DTC, Non-HCC Monotherapy Safety Set has been further analysed to exclude non-thyroid cancer patients, and this data has been presented under the identified risk section for hypothyroidism (See Section SVII.3).

Table 2 Number of Lenvatinib-Treated Subjects by Development Phase and Indication – Lenvatinib Monotherapy and Lenvatinib Plus Everolimus Safety Analysis Sets

Phase Indication	Safety Analysis Set				
	All DTC Lenvatinib[a]	Non-DTC, Non-HCC Monotherapy[b]	RCC Lenvatinib		HCC Lenvatinib[e]
			18 mg lenvatinib + 5 mg everolimus[c]	All other lenvatinib doses[d]	
Phase 1/1b Studies					
Advanced Solid Tumour	0	156	0	0	0
Renal cell carcinoma	0	0	18	9	0
Clear cell	0	0	17	7	0
Papillary	0	0	1	1	0
Chromophobe	0	0	0	0	0
Other	0	0	0	1	0
Phase 1/1b Subtotal	0	156	18	9	0
Phase 2 and 3 Studies					
Thyroid cancer	458	72	0	0	0
ATC	0	9	0	0	0
DTC	458	0	0	0	0
MTC	0	63	0	0	0
Renal cell carcinoma	0	0	605	52	0
Clear cell	0	0	572	51	0
Non-clear cell	0	0	31	0	0
Papillary	0	0	0	0	0
Chromophobe	0	0	0	1	0
Other	0	0	2	0	0
Hepatocellular carcinoma	0		0	0	496
Other indications	0	428	0	0	0
Endometrial cancer	0	133	0	0	0
Melanoma	0	182	0	0	0
Glioblastoma	0	113	0	0	0
Phases 2 and 3 Subtotal	458	500	605	52[f]	496
Total All Phases	**458**	**656**	**623**	**61**	**496**

Data cutoff date is 10 Dec 2014 for all other studies in subjects with DTC. Data cutoff dates for RCC: 07 Jul 2017 (Study 112), 31 Jul 2015 (Study 205), 14 Feb 2020 (Study 218), 17 Jul 2019 (Study 221), and 28 Aug 2020 (Study 307). Data cutoff date for HCC is 13 Nov 2016.

ATC = anaplastic thyroid cancer, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, ISS = integrated summary of safety, MTC = medullary thyroid cancer, RCC = renal cell carcinoma.

a: All DTC Lenvatinib Safety Set includes subjects with DTC from Studies 201 (N=58) and 208 (N=24), as well as from Study 303 (including subjects in the randomised lenvatinib arm [N=261] and subjects in the OOL portion of the study [N=115]).

b: Non-DTC, Non-HCC Monotherapy Safety Set includes all remaining studies conducted in subjects with non-DTC, Non-HCC cancer who received lenvatinib as monotherapy, which includes Studies 101 (N=82), 102 (monotherapy cohort, continuous dosing [N=59]), 104 (N=6), 105 (N=9), 203 (N=113), 204 (N=133), and 206 (N=182), as well as subjects with MTC or ATC in Study 208 (N=13) and subjects with MTC in Study 201 (N=59).

c: RCC Lenvatinib + Everolimus Safety Set comprise all subjects in Study 112 (Phase 1), Study 205 (Phase 1 and Phase 2), Study 218 (Phase 2), Study 221 (Phase 2), and Study 307 (Phase 3) who received the combination of lenvatinib 18 mg once daily and everolimus 5 mg once daily at the recommended dose (N=623).

d: Includes subjects who were treated with a combination of lenvatinib at doses of 12 mg or 24 mg and everolimus 5 mg once daily.

e: Includes all subjects who received at least 1 dose of lenvatinib in Study E7080-G000-304 and subjects in the Phase 2 portion of Study E7080-G000-202 who had a baseline body weight ≥60 kg and received at least 1 dose of lenvatinib (ie, received planned labelling dose).

Table 2 Number of Lenvatinib-Treated Subjects by Development Phase and Indication – Lenvatinib Monotherapy and Lenvatinib Plus Everolimus Safety Analysis Sets

Phase Indication	Safety Analysis Set				
	All DTC Lenvatinib[a]	Non-DTC, Non-HCC Monotherapy[b]	RCC Lenvatinib		HCC Lenvatinib[e]
			18 mg lenvatinib + 5 mg everolimus[c]	All other lenvatinib doses[d]	

f: Subjects received lenvatinib monotherapy.
Source: DTC ISS Table 1.1; RCC ISS Table 2.2, Study 205 clinical study report (CSR) Phase 1b in-text Table 10, RCC Summary of Clinical Safety Table 2.7.4-11, HCC Summary of Clinical Safety in-text Table 2.7.4.1.

Table 3 Number of Lenvatinib-Treated Subjects by Development Phase and Indication – Lenvatinib + Pembrolizumab Safety Analysis Set

Phase Indication	Safety Analysis Set
	Lenvatinib + Pembrolizumab
Phase 1/1b/2 Studies	
Renal cell carcinoma	6
Endometrial carcinoma	124
Phase 1/1b Subtotal	130
Phase 2/Phase 3 Studies	
Renal cell carcinoma	491
Endometrial carcinoma	406
Phases 2 and 3[a] Subtotal	897
Total All Phases	**1027**

Data cutoff date for Study 111, 307, and 309 is 18 Aug 2020, 28 Aug 2020, and 26 Oct 2020, respectively.
a: Phase 3 Study 307 includes data from Indication Safety Set subjects in Arm B (352 subjects), who received at least 1dose of either lenvatinib or pembrolizumab.
Source: Study 111 clinical study report (CSR); Study 307 CSR; Study 309 CSR.

Table 4 Overall Subjects Exposed and Subject-Years of Exposure to Lenvatinib by Duration of Treatment – Lenvatinib Monotherapy and Lenvatinib Plus Everolimus Safety Analysis Sets

	All DTC Lenvatinib[a]	Non-DTC, Non-HCC Monotherapy[b]	RCC Lenvatinib + Everolimus	HCC Lenvatinib
	Lenvatinib N=458	Lenvatinib N=656	Lenvatinib N=623	Lenvatinib N=496
Subjects Exposed, n (%)				
1 day –<1 week	3 (0.7)	11 (1.7)	3 (0.5)	7 (1.4)
1 week – <3 months	81 (17.7)	318 (48.5)	100 (16.1)	116 (23.4)
3 months – <6 months	58 (12.7)	150 (22.9)	117 (18.8)	126 (25.4)
6 months – <1 year	84 (18.3)	98 (14.9)	150 (24.1)	128 (25.8)
1 year – <2 years	120 (26.2)	55 (8.4)	179 (28.7)	100 (20.2)
≥2 years	112 (24.5)	24 (3.7)	74 (11.9)	19 (3.8)

Table 4 Overall Subjects Exposed and Subject-Years of Exposure to Lenvatinib by Duration of Treatment – Lenvatinib Monotherapy and Lenvatinib Plus Everolimus Safety Analysis Sets

	All DTC Lenvatinib[a]	Non-DTC, Non-HCC Monotherapy[b]	RCC Lenvatinib + Everolimus	HCC Lenvatinib
	Lenvatinib N=458	Lenvatinib N=656	Lenvatinib N=623	Lenvatinib N=496
Total	**458 (100.0)**	**656 (100.0)**	**623 (100.0)**	**496 (100.0)**
Subject-Years of Exposure				
1 day – <1 week	0.0	0.1	0.03	0.1
1 week – <3 months	10.3	37.9	13.42	15.2
3 months – <6 months	21.8	53.6	44.76	45.9
6 months – <1 year	61.6	68.7	108.90	93.9
1 year – <2 years	182.2	75.7	265.88	140.3
≥2 years	273.0	68.9	176.97	44.5
Total SY	**549.0**	**304.9**	**609.95**	**340.0**

Duration of exposure is defined as number of days a subject actually received a dose for the All DTC and Non-DTC, Non-HCC monotherapy sets. Duration (days) of exposure is calculated as (Last dose date – First dose date + 1) for lenvatinib in the Safety Set. For HCC Lenvatinib, duration of exposure is defined as the sum of all years based on treatment duration (date of last dose of study drug – first date of study drug +1).
Subject-year = sum of duration of exposure (in years) for all subjects in each category.
BID = twice daily, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, ISS = integrated summary of safety, OOL = optional open-label, QD = once daily, RCC = renal cell carcinoma, SY = subject-years.
a: The lenvatinib starting dose was 24 mg QD except for 29 subjects (27 subjects from the OOL part of Study 303 had a starting dose of 20 mg QD and 2 subjects from Study 201 were treated with 10 mg BID).
b: The lenvatinib starting dose was <14 mg (93 subjects), ≥14 to <20 mg (12 subjects), ≥20 to <24 mg (12 subjects), 24 mg (508 subjects), and >24 mg (31 subjects).
Source: RCC ISS DTC Table 4.1.2, DTC ISS Table 4.1.3, RCC ISS Table 4.3, Len_EURMP Table 2.2, HCC ISS Table 4.

Table 5 Overall Subjects Exposed and Subject-Years of Exposure to Lenvatinib by Duration of Treatment – All RCC Lenvatinib + Pembrolizumab Safety Analysis Set

	All RCC Lenvatinib + Pembrolizumab
	N=497
Subjects Exposed, n (%)	
1 day –<1 week	4 (0.8)
1 week – <3 months	54 (10.9)
3 months – <6 months	46 (9.3)
6 months – <1 year	103 (20.7)
1 year – <2 years	170 (34.2)
≥2 years	120 (24.1)
Total	**497 (100.0)**
Subject-Years of Exposure	
1 day – <1 week	0.04
1 week – <3 months	7.01
3 months – <6 months	17.18
6 months – <1 year	78.26
1 year – <2 years	246.56
≥2 years	292.73

Table 5 Overall Subjects Exposed and Subject-Years of Exposure to Lenvatinib by Duration of Treatment – All RCC Lenvatinib + Pembrolizumab Safety Analysis Set

	All RCC Lenvatinib + Pembrolizumab
	N=497
Total SY	**641.78**

Each subject is counted once in the applicable duration row category.
Duration (days) of Lenvatinib Exposure is calculated as (Last dose date – First dose date + 1) for lenvatinib in the combination.
Duration (weeks) of Lenvatinib Exposure is calculated as (Duration in days/7) for lenvatinib in the combination.
Duration (months) of Lenvatinib Exposure is calculated as (Duration in days/30.4375) for lenvatinib in the combination.
Duration (years) of Lenvatinib Exposure is calculated as (Duration in days/365.25) for lenvatinib in the combination.
Subject-years is the sum of the durations of lenvatinib exposure (in years) from all subjects within a row category.
RCC = renal cell carcinoma.
Source: Len_EURMP Table 2.1 (for LenPem).

Table 6 Overall Subjects Exposed and Subject-Years of Exposure to Lenvatinib by Duration of Treatment – All EC Lenvatinib + Pembrolizumab Safety Analysis Set

	All EC Lenvatinib + Pembrolizumab N=530
Subjects Exposed, n (%)	
1 day –<1 week	12 (2.3)
1 week – <3 months	123 (23.2)
3 months – <6 months	100 (18.9)
6 months – <1 year	156 (29.4)
1 year – <2 years	111 (20.9)
≥2 years	28 (5.3)
Total	**530 (100.0)**
Subject-Years of Exposure	
1 day – <1 week	0.1
1 week – <3 months	16.2
3 months – <6 months	36.5
6 months – <1 year	116.5
1 year – <2 years	154.3
≥2 years	76.2
Total SY	**399.8**

Each subject is counted once in the applicable duration row category.
Duration (days) of Lenvatinib Exposure is calculated as (Last dose date – First dose date + 1) for lenvatinib in the combination.
Duration (weeks) of Lenvatinib Exposure is calculated as (Duration in days/7) for lenvatinib in the combination.
Duration (years) of Lenvatinib Exposure is calculated as (Duration in days/365.25) for lenvatinib in the combination.
Subject-years is the sum of the durations of lenvatinib exposure (in years) from all subjects within a row category.
EC = endometrial carcinoma.
Source: Table len0exp0dur.

Table 7 Subject Exposure to Lenvatinib by Age Group and Gender – All DTC Lenvatinib Safety Set (N=458)

	Subjects Exposed n (%)		Duration of Exposure (Subject-years)	
Age Subgroup	Male	Female	Male	Female
<65 years	144 (31.4)	120 (26.2)	191.7	158.2
≥65 – <75 years	75 (16.4)	84 (18.3)	79.9	94.7
≥75 years	19 (4.1)	16 (3.5)	11.8	12.6
Total	**238 (52.0)**	**220 (48.0)**	**283.4**	**265.5**

Baselines for all variables use the baselines for randomization phase for subjects in the OOL portion of Study 303.
Duration of exposure is defined as number of days a subject actually received a dose.
Subject-year = sum of duration of exposure (in years) for all subjects in each category.
DTC = differentiated thyroid cancer, ISS = integrated summary of safety, OOL = optional open-label, RCC = renal cell carcinoma.
Source: RCC ISS DTC Tables 4.2.2 and 4.2.2.1.

Table 8 Subject Exposure to Lenvatinib by Age Group and Gender – RCC Lenvatinib + Everolimus Safety Set (N=623)

	Subjects Exposed n (%)		Duration of Exposure (Subject-years)	
Age Subgroup	Male	Female	Male	Female
<65 years	266 (42.7)	91 (14.6)	299.6	79.4
≥65 – <75 years	141 (22.6)	54 (8.7)	129.0	45.2
≥75 years	55 (8.8)	16 (2.6)	44.9	11.8
Total	**462 (74.2)**	**161 (25.8)**	**473.5**	**136.4**

Duration of exposure is defined as number of days a subject actually received a dose.
Subject-year = sum of duration of exposure (in years) for all subjects in each category.
RCC = renal cell carcinoma.
Source: Len_EURMP Table 4.2.

Table 9 Subject Exposure to Lenvatinib by Age Group and Gender – All RCC Lenvatinib + Pembrolizumab Safety Analysis Set (N=497)

	Subjects Exposed n (%)		Duration of Exposure (Subject-years)	
Age Subgroup	Male	Female	Male	Female
<65 years	215 (43.3)	66 (13.3)	303.9	90.9
≥65 – <75 years	112 (22.5)	49 (9.9)	145.6	51.7
≥75 years	38 (7.6)	17 (3.4)	34.3	15.4
Total	**365 (73.4)**	**132 (26.6)**	**483.8**	**158.0**

Duration (days) of Lenvatinib Exposure is calculated as (Last dose date – First dose date + 1) for lenvatinib in the combination.
Subject-years is the sum of the durations (in years) of lenvatinib exposure from all subjects within a category where duration (years) = duration in days/365.25.
RCC = renal cell carcinoma.
Source: Len_EURMP Table 4.1 (for LenPem).

Table 10 Subject Exposure to Lenvatinib by Age Group and Gender – HCC Lenvatinib Safety Set (N=496)

	Subjects Exposed n (%)		Duration of Exposure (Subject-years)	
Age Subgroup	Male	Female	Male	Female
<65 years	249 (58.9)	34 (46.6)	172.7	22.0
≥65 – <75 years	129 (30.5)	26 (35.6)	94.2	14.9
≥75 years	45 (10.6)	13 (17.8)	30.5	5.8
Total	**423 (100.0)**	**73 (100.0)**	**297.4**	**42.6**

Duration of treatment = Date of last dose of study drug - Date of first dose of study drug+1.
Subject-year = sum of duration of exposure (in years) for all subjects in each category.
HCC = hepatocellular carcinoma, ISS = integrated summary of safety.
Source: HCC ISS Table 4.1.2.

Table 11 Subject Exposure to Lenvatinib by Age Group and Gender* – All EC Lenvatinib + Pembrolizumab Safety Analysis Set (N=530)

	Subjects Exposed n (%)	Duration of Exposure (Subject-years)
Age Subgroup		
<65 years	252 (47.5)	210.6
≥65 – <75 years	233 (44.0)	165.5
≥75 years	45 (8.5)	23.7
Total	**530 (100.0)**	**399.8**

Duration of lenvatinib exposure (day) is defined as (last dose date – first dose date + 1) for lenvatinib in the combination.
Subject-year = sum of duration of lenvatinib exposure (in years) for all subjects in each category where duration (year) = duration in days/365.25.
EC = endometrial carcinoma.
* All subjects are females.
Source: Table len0exp0char.

Table 12 Overall Subject Exposure to Lenvatinib by Actual Dose Received – Lenvatinib Monotherapy and Lenvatinib Plus Everolimus Safety Analysis Sets

	Safety Analysis Set			
	All DTC Lenvatinib	**Non-DTC, Non-HCC Monotherapy**	**RCC Lenvatinib + Everolimus**	**HCC Lenvatinib**
QD Dose (mg)[a]	**Lenvatinib N=458**	**Lenvatinib N=656**	**Lenvatinib N=623**	**Lenvatinib N=496**
>24	0.07	7.97	0.04	<0.01
24	155.10	127.42	<0.01	0.01
>20 – <24[b]	–	0.02	–	–
20	114.67	49.19	0.05	–
>18	–	–	<0.1	–
18	–	–	209.05	–
16	0.02	–	–	0.02
>14 – <20[b]	–	13.31	–	–
14	146.06	38.83	147.87	–
12	0.22	–	<0.01	166.22
>10 – <14[b]	–	21.96	–	–
10	96.72	24.91	124.95	–
>8 – <10[b]	–	0.11	–	–
8	26.21	5.40	59.97	128.72
>4 – <8[b]	–	8.85	–	–
4	9.89	0.83	12.42	30.35
<4[b]	–	6.11	–	–
Total SY	**548.96**	**304.91**	**554.36**	**325.33**

Duration of exposure is defined as number of days a subject actually received a dose.
Total subject-year of exposure is calculated as the sum of all exposure for all subjects at each dose level.
DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, ISS = integrated summary of safety, QD = once daily, RCC = renal cell carcinoma, SY = subject-years.
a: All doses denote the actual total daily dose received. Subjects are counted in multiple rows if they received more than 1 dose.
b: Calculated for the Non-DTC, Non-HCC Monotherapy Safety Set only.
Source: RCC ISS DTC Table 4.5.2, DTC ISS Table 4.5.3, RCC ISS Table 3.2, Len_EURMP Table 3.2, HCC ISS Table 3.

Table 13 Overall Subject Exposure to Lenvatinib by Actual Dose Received – All RCC Lenvatinib + Pembrolizumab Safety Analysis Set

	Safety Analysis Set
QD Dose (mg)[a]	All RCC Lenvatinib + Pembrolizumab N=497
>24	0.04
20	231.76
16	<0.01
14	183.26
12	0.01
10	117.57
8	40.11
4	14.43

Table 13 Overall Subject Exposure to Lenvatinib by Actual Dose Received – All RCC Lenvatinib + Pembrolizumab Safety Analysis Set

Total SY	**587.17**

Duration of exposure is defined as number of days a subject actually received a dose.
Total subject-year of exposure is calculated as the sum of all exposure for all subjects at each dose level.
QD = once daily, RCC = renal cell carcinoma, SY = subject-years.
a: All doses denote the actual total daily dose received. Subjects are counted in multiple rows if they received more than 1 dose.
Source: Len_EURMP Table 3.1 (for LenPem).

Table 14 Overall Subject Exposure to Lenvatinib by Actual Dose Received – All EC Lenvatinib + Pembrolizumab Safety Analysis Set

QD Dose (mg)[a]	**All EC Lenvatinib + Pembrolizumab N=530**
40	0.003
20	119.398
16	0.005
14	90.804
10	82.590
8	46.305
4	15.565
Total SY	**354.669**

Duration of exposure is defined as number of days a subject actually received a dose.
Total subject-year of exposure is calculated as the sum of all exposure for all subjects at each dose level.
QD = once daily, EC = endometrial carcinoma, SY = subject-years.
a: All doses denote the actual total daily dose received. Subjects are counted in multiple rows if they received more than 1 dose.
Source: Table len0exp0dose.

Table 15 Subject Exposure to Lenvatinib by Subgroup – All DTC Lenvatinib Safety Set (N=458)

Subgroup	Subjects Exposed n (%)	Duration of Exposure (Subject-years)
Total, n (%)	**458 (100.0)**	**549.0**
Race Group		
White	345 (75.3)	422.8
Asian	97 (21.2)	106.0
Other	16 (3.5)	20.1
Renal Function (Creatinine Clearance)		
<30 mL/min	1 (0.2)	0.3
≥30 – <60 mL/min	48 (10.5)	30.8
≥60 mL/min	409 (89.3)	517.9
Hepatic Function[a]		
Normal	406 (88.6)	490.0
Abnormal liver test	52 (11.4)	59.0
Grade 1	49 (10.7)	56.3
Grade 2	2 (0.4)	2.7
Grade 3	1 (0.2)	0.0
ECOG Performance Status		
0	253 (55.2)	343.3
1	187 (40.8)	194.2
2	17 (3.7)	10.7
3	1 (0.2)	0.7
Baseline Hypertension[b]		
Yes	262 (57.2)	315.5
No	196 (42.8)	233.5
Baseline Diabetes[c]		
Yes	80 (17.5)	100.0
No	378 (82.5)	449.0
Previous VEGF/VEGFR-Targeted Therapy		
Yes	109 (23.8)	129.6
No	349 (76.2)	419.3

Baselines for all variables use the baselines for randomization phase for subjects in the OOL portion of Study 303.
Subject-year = sum of duration of exposure (in years) for all subjects in each category.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, DTC = differentiated thyroid cancer, ECOG = Eastern Cooperative Oncology Group, ISS = integrated summary of safety, OOL = optional open-label, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.
a: Grade is the worst grade among AST, ALT and bilirubin grades.
b: Baseline hypertension status is determined by medical history, concomitant medication, or subject's screening blood pressure.
c: Baseline diabetes is determined by any medical history with diabetes/hyperglycaemia and any prior medications used for diabetes.
Source: RCC ISS DTC Tables 4.3.2 and 2.2.2.

Table 16 Subject Exposure to Lenvatinib by Subgroup – RCC Lenvatinib + Everolimus Safety Set (N=623)

Subgroup	Subjects Exposed n (%)	Duration of Exposure (Subject-years)
Total, n (%)	**623 (100.0)**	**609.95**
Race Group		
White	478 (76.7)	463.41
Asian	112 (18.0)	117.00
Other	16 (2.6)	15.31
Missing	17 (2.7)	14.23
Renal Function (Creatinine Clearance)		
<60 mL/min	176 (28.3)	141.31
≥60 mL/min	423 (67.9)	437.93
Missing	24 (3.9)	30.72
Hepatic Function[b]		
Normal	556 (89.2)	540.68
Abnormal	64 (10.3)	64.43
Grade 1	63 (10.1)	63.20
Grade 2	1 (0.2)	1.23
Grade 3	0	0
Grade 4	0	0
Missing	3 (0.5)	4.84
ECOG[a]		
0	59 (59.0)	61.62
1	41 (41.0)	24.20
Baseline Hypertension[c]		
Yes	365 (58.6)	339.80
No	258 (41.4)	270.15
Baseline Diabetes[d]		
Yes	118 (18.9)	108.83
No	505 (81.1)	501.13

Subject-year = sum of duration of exposure (in years) for all subjects in each category.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, ECOG = Eastern Cooperative Oncology Group, RCC = renal cell carcinoma.
a: Percentages and subject-years are based on subjects from studies with data available: N=523 for baseline KPS from Studies 307 and 218; N=100 for baseline ECOG from Studies 205, 112, and 221.
b: Hepatic Function: Normal: No value of AST, ALT, and Bilirubin has CTCAE Grade ≥1; Abnormal: CTCAE Grade ≥1 AST, ALT or Bilirubin. Grade is the worst grade among AST, ALT, and bilirubin grades.
c: Hypertension = Yes if a subject has an ongoing medical history of hypertension, otherwise, Hypertension = No.
d: Baseline diabetes is determined by any medical history with diabetes/hyperglycemia and any prior medications used for diabetes.
Source: Len_EURMP Table 4.2.

Table 17 Subject Exposure to Lenvatinib by Subgroup – All RCC Lenvatinib + Pembrolizumab Safety Analysis Set (N=497)

Subgroup	Subjects Exposed n (%)	Duration of Exposure (Subject-years)
Total, n (%)	497 (100.0)	641.78
Age Group		
< 65 years	281 (56.5)	394.79
≥65 – <75 years	161 (32.4)	197.25
≥75 years	55 (11.1)	49.74
Other	20 (4.0)	26.30
Race Group		
White	385 (77.5)	504.07
Asian	84 (16.9)	101.64
Other	20 (4.0)	26.30
Missing	8 (1.6)	9.77
Body Weight		
<60 kg	56 (11.3)	61.50
≥60 kg	441 (88.7)	580.28
Renal Function (Creatinine Clearance)		
<60 mL/min	137 (27.6)	142.91
≥60 mL/min	343 (69.0)	474.51
Missing	17 (3.4)	24.36
Hepatic Function		
Normal	466 (93.8)	605.98
Abnormal Liver Test[a]	31 (6.2)	35.80
Grade 1	30 (6.0)	35.48
Grade 2	1 (0.2)	0.32
Grade 3	0 (0.0)	---
Grade 4	0 (0.0)	---
Karnofsky Performance Status		
100	209 (42.1)	295.22
90	181 (36.4)	243.38
80	94 (18.9)	91.21
70	12 (2.4)	10.31
Missing	1 (0.2)	1.65
ECOG Performance Status		
0	74 (51.0)[b]	98.45
1	71 (49.0)[b]	60.81
Baseline Hypertension[c]		
Yes	303 (61.0)	371.03
No	194 (39.0)	270.75

Duration (days) of Lenvatinib Exposure is calculated as (Last dose date – First dose date + 1) for lenvatinib in the combination.
Subject-years is the sum of the durations (in years) of lenvatinib exposure from all subjects within a category where duration (years) = duration in days/365.25.
CTCAE = Common Terminology Criteria for Adverse Events, RCC = renal cell carcinoma.
a: Hepatic Function: Normal: No value of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin has CTCAE Grade ≥1; Abnormal: CTCAE Grade ≥1 AST, ALT or bilirubin. Grade is the worst grade among AST, ALT, and bilirubin grades.
b: Percentages are based on subjects from studies with data available: N=145 for baseline Eastern Cooperative Oncology Group (ECOG) from Studies 111/KN146.
c: Hypertension = Yes if a subject has an ongoing medical history of hypertension, otherwise, Hypertension = No.
Source: Len_EURMP Table 4.1 (for LenPem)

Table 18 Subject Exposure to Lenvatinib by Subgroup – HCC Lenvatinib Safety Set (N=496)

Subgroup	Subjects Exposed n (%)	Duration of Exposure (Subject-years)
Total, n (%)	**496**	**340.0**
Age Group		
<65 years	283 (57.1)	194.6
≥65 – <75 years	155 (31.3)	109.1
≥75 years	58 (11.7)	36.3
Sex		
Male	423 (85.3)	297.4
Female	73 (14.7)	42.6
Region		
Asia-Pacific	341 (68.8)	236.4
Western regions	155 (31.2)	103.6
Race		
White	134 (27.0)	92.1
Black or African American	7 (1.4)	2.5
Asian	353 (71.2)	244.5
American Indian or Alaska Native	1 (0.2)	0.6
Other	1 (0.2)	0.3
ECOG Performance Status		
0	320 (64.5)	223.7
≥1	176 (35.5)	116.3

Subject-year = sum of duration of treatment (in years) for all subjects in each category.
ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, ISS = integrated summary of safety.
Source: HCC ISS Table 4.1.1, Table 4.1.2.

Table 19 Subject Exposure to Lenvatinib by Subgroup – All EC Lenvatinib + Pembrolizumab Safety Analysis Set (N=530)

Subgroup	Subjects Exposed n (%)	Duration of Exposure (Subject-years)
Total, n (%)	**530 (100.0)**	**399.8**
Age Group		
<65 years	252 (47.5)	210.6
≥65 – <75 years	233 (44.0)	165.5
≥75 years	45 (8.5)	23.7
Race Group		
White	364 (68.7)	286.4
Asian	90 (17.0)	60.6
Other	40 (7.5)	26.3
Missing	36 (6.8)	26.5
Region		
EU	137 (25.8)	94.4
Ex-EU	393 (74.2)	305.4
ECOG Performance Status		
0	306 (57.7)	229.5
1	224 (42.3)	170.2
Renal Function (Creatinine Clearance)		
<60 mL/min	94 (17.7)	51.4
≥60 mL/min	434 (81.9)	347.7
Missing	2 (0.4)	0.6
Hepatic Function[a]		
Normal	457 (86.2)	345.8
Abnormal	73 (13.8)	54.0

Duration (days) of Lenvatinib Exposure is calculated as (Last dose date – First dose date + 1) for lenvatinib in the combination.
Subject-years is the sum of the durations (in years) of lenvatinib exposure from all subjects within a category where duration (years) = duration in days/365.25.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, ECOG = Eastern Cooperative Oncology Group.
a: Hepatic Function: Normal: No value of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin has CTCAE Grade ≥1; Abnormal: CTCAE Grade ≥1 AST, ALT, or bilirubin. Grade is the worst grade among AST, ALT and bilirubin grades.
Source: Table len0exp0char.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Important exclusion criteria in pivotal clinical studies within the development programme

Table 20 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
Subjects without adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1.	Known class effect	No	Hypertension is an important identified risk.
Proteinuria: urine protein ≥1 g/24 h.	Nonclinical safety concern and known class effect	No	Proteinuria is an important identified risk.
Significant CV impairment: history of congestive heart failure (CHF) greater than New York Heart association (NYHA) Class II, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment (12 months for RCC Study 307 and EC Study 309).	Known class effect	No	Cardiac failure is an important identified risk.
Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, requiring therapeutic International Normalized Ratio (INR) monitoring. Active haemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks (Study 309 within 2 weeks) prior to the first dose of study drug. HCC Study 304: Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin and factor X	Haemorrhage is a nonclinical risk and known class effect. At the time of initiation of the studies, the extent of interaction of lenvatinib with warfarin was unknown.	No	Haemorrhagic events are an important identified risk.

Table 20 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
inhibitors that do not require INR monitoring was permitted. Antiplatelet agents were prohibited throughout the study. Adequate blood coagulation function, defined as INR ≤2.3. Gastrointestinal bleeding event or active haemoptysis (bright red blood of at least 0.5 teaspoon) within 28 days prior to randomisation. Gastric or oesophageal varices that require active treatment (prophylactic therapy: both interventional and pharmacological was permitted). Patients receiving treatment for active bleeding or requiring surgical intervention to prevent bleeding were excluded.			
Brain metastases unless previously treated and clinically stable for at least 1 month prior to screening. HCC Study 304: Any history of or current brain or subdural metastases. RCC Study 307: Subjects with CNS metastases were not eligible unless completed local therapy and discontinued use of corticosteroids for the indication for at least 4 weeks before starting study treatment. CNS metastases must be stable for at least 4 weeks prior to starting study treatment.	Haemorrhage is a nonclinical risk and known class effect.	No	Haemorrhagic events are an important identified risk.
Recent major surgery, or subjects who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting treatment (Study 307).	Known class effect	No	Impaired wound healing is an important potential risk.

Table 20 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
Prolongation of QTcF interval to >480 ms (Studies 303, 304, 208, 205, 307, 309) or ≥500 ms (Study 201).	Standard exclusion criterion in clinical trials and QTc prolongation has been observed with other agents in class.	No	QTc prolongation is an important identified risk.
Adequate renal function (defined as calculated creatinine clearance (CrCl) ≥30 mL/min per the Cockcroft and Gault formula). HCC Study 304: Adequate renal function defined as CrCl >40 mL/min calculated per the Cockcroft and Gault formula. RCC Study 307: Adequate renal function defined as creatinine ≤1.5 × upper limit of normal (ULN); or for subjects with creatinine >1.5 × ULN, the calculated creatinine clearance ≥30 mL/min (per the Cockcroft-Gault formula) is acceptable.	Standard exclusion criterion in clinical trials.	No	Summary of product characteristics address these risks, and no additional pharmacovigilance is planned to further characterise risks.
Adequate liver function a. Bilirubin ≤1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome. b. Alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (≤5 × ULN if subject has liver metastases). RCC Study 307: Additional criteria to the above is that subjects with alkaline phosphatase values >3 × ULN and known to have bone metastases can be included. HCC Study 304: a. Albumin ≥2.8 g/dL b. Bilirubin ≤3.0 mg/dL c. Alkaline phosphatase, ALT, and AST ≤5 × ULN. d. Child-Pugh Score A.	Lenvatinib is hepatically metabolised.	No	Summary of product characteristics address these risks, and no additional pharmacovigilance is planned to further characterise risks

Table 20 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
Females who are pregnant.	Nonclinical safety concern and standard practice to exclude pregnant women from clinical trials.	No	Abnormal pregnancy outcome is an important potential risk.
Additional exclusion criteria (pertaining to pembrolizumab treatment): • Known history of or any evidence of interstitial lung disease. • History of non-infectious pneumonitis requiring steroids or current pneumonitis. • Subjects with a diagnosis of immunodeficiency or receiving chronic systemic steroid therapy or immunosuppressive therapy within 7 days prior to study treatment. • Active autoimmune disease (except psoriasis) requiring systemic treatment in past 2 years with disease modifying agents, corticosteroids or immunosuppressive drugs.	Standard exclusionary requirements in pembrolizumab clinical studies.	No	No such exclusionary criteria in lenvatinib monotherapy clinical studies.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect rare ADRs. A total of 2597 subjects have been exposed to a regimen of single-agent lenvatinib on a continuous basis per the latest Development Safety Update Report (DSUR) (Data Lock point [DLP] of 12 Feb 2022). ADRs with a frequency greater than 1 in 150 could be detected in the DTC population, and ADRs with a frequency greater than 1 in 160 could be detected in the HCC population. ADRs with a frequency greater than 1 in 200 could be detected in the Lenvatinib + Everolimus RCC population at the recommended combination regimen. Adverse drug reactions with a frequency greater than 1 in 160 could be detected in the All RCC Lenvatinib + Pembrolizumab Safety Set at the recommended combination regimen and ADRs with a

frequency greater than 1 in 170 could be detected in the All EC Lenvatinib + Pembrolizumab Safety Set at the recommended combination regimen.

More than two thirds (69.0%) of the 458 subjects with DTC received lenvatinib for over 6 months, and 50.7% received it for over 1 year. A total of 24.5% of subjects were treated for more than 2 years, and this population represents 49.7% (273.0/549.0 subject-years) of the total exposure in the All DTC Lenvatinib Safety Set.

Of the subjects with RCC in the Lenvatinib + Everolimus Safety Set, 64.7% had received lenvatinib for 6 months or more, and 40.6% had received lenvatinib for more than 1 year. A total of 11.9% of subjects were treated with lenvatinib for more than 2 years, and this population represents 29.0% (176.97/609.95 subject-years) of the total exposure in the RCC Lenvatinib + Everolimus Safety Set.

Of the subjects with RCC in the All RCC Lenvatinib + Pembrolizumab Safety Set, 79.0% had received lenvatinib for 6 months or more, 58.3% had received lenvatinib for more than 1 year and 24.1% had received lenvatinib for more than 2 years and represents 45.6% (292.73/641.78 subject-years) of the total exposure in this safety set.

Approximately half (49.8%) of the subjects with HCC received lenvatinib for 6 months or more, and 24.0% received it for more than a year. A total of 10.5% of subjects received lenvatinib for at least 18 months.

Of the subjects with EC in the All EC Lenvatinib + Pembrolizumab Safety Set, 55.6% had received lenvatinib for 6 months or more, 26.2% had received lenvatinib for more than 1 year, and 5.3% had received lenvatinib for more than 2 years representing 19.1% (76.2/399.8 subject-years) of the total exposure in this safety set.

The safety database should contain sufficient information to detect common AEs that are likely to occur after prolonged exposure to lenvatinib.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with hepatic impairment	DTC: No subjects with severe hepatic impairment were included. The inclusion and exclusion criteria required subjects to have adequate hepatic function as defined by bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	levels. The majority of subjects in the All DTC Lenvatinib Safety Set had normal hepatic function; 52 subjects (11.4%) had abnormal function and contributed 59.0 subject-years of exposure. RCC Lenvatinib + Everolimus Combination: No subjects with severe hepatic impairment were included. In the RCC Lenvatinib + Everolimus Safety Set, 89.2% of subjects had normal hepatic function at baseline and 10.3% had abnormal hepatic function at baseline (CTCAE Grade 1 in 10.1% and Grade 2 in 0.2%). RCC Lenvatinib + Pembrolizumab Combination: In the All RCC Lenvatinib + Pembrolizumab Safety Set, 93.8% of subjects had normal hepatic function at baseline and 6.2% had an abnormal liver test at baseline (CTCAE Grade 1 in 6.0% and Grade 2 in 0.2%). HCC: The inclusion and exclusion criteria required subjects to have adequate hepatic function as defined by albumin, bilirubin, alanine aminotransferase, aspartate aminotransferase levels and a Child-Pugh score of A. In the HCC Lenvatinib Safety Set, 38.9% of subjects had normal hepatic function, and 61.1% of subjects had an abnormal liver test at baseline (CTCAE Grade 1 in 51.4%, Grade 2 in 9.1%, and Grade 3 in 0.6% of subjects). EC Lenvatinib + Pembrolizumab Combination: No subjects with severe hepatic dysfunction were included. In the All EC Lenvatinib + Pembrolizumab Safety Set, 86.2% of subjects had normal hepatic function at baseline and 13.8% had abnormal hepatic function at baseline.
Patients with renal impairment	DTC: The inclusion and exclusion criteria required subjects to have adequate renal function as defined by a calculated CrCl ≥30 mL/min per the Cockcroft and Gault formula; 48 (10.5%) subjects had moderate impairment (CrCl ≥30 to <60 mL/min) and one subject had severe impairment (CrCl <30 mL/min). Subjects with moderate impairment contributed 30.8 person-years of exposure. RCC Lenvatinib + Everolimus Combination: No subjects with severe renal impairment (CrCl <30 mL/min) were included in Study 205 and Study 307.In the All RCC Lenvatinib + Everolimus Safety Set, 176 subjects (28.3%) with a baseline CrCl rate of <60 mL/min contributed 141.31 subject-years of exposure, and 423 subjects (67.9%) with a baseline

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	CrCl rate of ≥60 mL/min contributed 437.93 subject-years of exposure. RCC Lenvatinib + Pembrolizumab Combination: In the All RCC Lenvatinib + Pembrolizumab Safety Set, 137 subjects (27.6%) with a baseline CrCl rate of <60 mL/min contributed 142.91 subject-years of exposure, and 343 subjects (69.0%) with a baseline CrCl rate of ≥60 mL/min contributed 474.51 subject-years of exposure. No subjects with severe renal impairment (CrCl <30 mL/min) were included in Study 307. HCC: The inclusion criteria for subjects with HCC participating in Study 202 and Study 304 required all subjects to have adequate renal function, defined as CrCl >40 mL/min as calculated per the Cockcroft and Gault formula (or serum creatinine ≤2.0 mg/dL in Study 202). In the HCC Lenvatinib Safety Set, 87.3% of subjects had normal renal function (CrCl ≥60 mL/min) and 12.7% of subjects had mild-to-moderate renal impairment (CrCl ≥30 - <60 mL/min). There were no subjects with severe renal impairment (CrCl <30 mL/min). EC Lenvatinib + Pembrolizumab Combination: No subjects with severe renal impairment were included. Most subjects (81.9%) had normal renal function, defined as CrCl ≥60 mL/min; 17.7% of subjects had impaired renal function (defined as CrCl <60 mL/min) and contributed 51.4 subject-years of exposure.
Patients with CV impairment	Patients with significant CV impairment were not included in the clinical development program.
Immunocompromised patients	Immunocompromised patients were not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	DTC: Subjects enrolled in the pivotal study for DTC must have had progressing disease within 12 months of study entry. Lenvatinib has not been studied in RAI-refractory DTC patients with lesions smaller than the minimum dimensions required for accurate measurement. Nor has it been studied in RAI-refractory DTC subjects with ECOG performance status scores of greater than 2. RCC Lenvatinib + Everolimus Combination: Subjects enrolled in the Phase 3 Lenvatinib + Everolimus study for RCC (Study 307) must have had histological or cytological conformation of RCC with

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	a clear-cell component and documented evidence of advanced RCC. Subjects with previous systemic anticancer therapy for RCC were excluded. Lenvatinib has not been studied in RCC subjects with severe renal impairment (<30 mL/min) or subjects with Karnofsky Performance Status of <70. RCC Lenvatinib + Pembrolizumab Combination: Subjects enrolled in the pivotal Phase 3 Lenvatinib + Pembrolizumab study for RCC (Study 307) must have had histological or cytological confirmation of RCC with a clear-cell component and documented evidence of advanced RCC. Subjects with previous systemic anticancer therapy for RCC, including anti-VEGF therapy, or any systemic investigational anticancer agent were excluded. Lenvatinib has not been studied in RCC subjects with severe renal impairment (<30 mL/min) or subjects with Karnofsky Performance Status of <70. HCC: Subjects enrolled in the pivotal Phase 3 study for HCC (Study 304) were excluded if imaging findings for HCC corresponded to any of the following: HCC with ≥50% liver occupation, clear invasion into the bile duct, portal vein invasion at the main portal branch (Vp4). Subjects also must have had at least 1 measurable target lesion according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) with at least one dimension as ≥1.0 cm in the longest diameter or ≥2.0 cm in the short axis. Lenvatinib has not been studied in subjects with smaller target lesions. Lenvatinib has also not been studied in subjects with Child-Pugh B or C (moderate or severe) hepatic impairment (since only subjects with Child-Pugh A were allowed to participate in Study 304), and in subjects with severe renal impairment (<30 mL/min) or ECOG PS of greater than 1. EC Lenvatinib + Pembrolizumab Combination: Subjects enrolled in the pivotal study for EC must have had documented evidence of advanced, recurrent or metastatic EC and radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen. Subjects also must have had at least 1 measurable target lesion according to RECIST 1.1 and confirmed by blinded independent central review (BICR) with the following criteria: non-nodal lesion that measured ≥1.0 cm in the longest diameter; lymph node lesion that measured as ≥1.5 cm in the short axis and suitable for repeat measurement

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	using computed tomography/magnetic resonance imaging (CT/MRI).
Population with relevant different racial and/or ethnic origin	DTC: The European geographic region was well represented in the All DTC Lenvatinib Safety Set with 208 (45.4%) subjects, followed by North America (including Australia) with 146 (31.9%) subjects. The remaining countries (Thailand, Japan, Republic of Korea, Argentina, Chile, Brazil, and the Russian Federation) contributed 104 (22.7%) subjects. The majority of subjects in the All DTC Lenvatinib Safety Set were white (345, 75.3%), 97 (21.2%) subjects were Asian, and 16 (3.5%) belonged to other races including Black and Native Hawaiian or other Pacific Islander. Subjects of Asian origin contributed proportionally less exposure to the safety database. The Asian subpopulation largely comprised Japanese subjects (65/97 [67%]) who tended to have a longer duration of treatment (median of 17.7 vs. 13.8 months), and a higher occurrence of dose reduction (95.4% vs. 75.1%) compared with non-Japanese subjects. RCC Lenvatinib + Everolimus Combination: In the RCC Lenvatinib + Everolimus Safety Set, the highest proportion of subjects were from Western Europe and North America (62.4%), followed by the Rest of World (37.6%). Nearly all subjects were white (76.7%); 112 subjects (18.0%) were Asian, 16 subjects (2.6%) were of other race groups, and for 17 subjects (2.7%), information was missing for race. Exposure relative to the numbers of subjects was similar for the white and Asian populations. RCC Lenvatinib + Pembrolizumab Combination: In the All RCC Lenvatinib + Pembrolizumab Safety Set, 385 subjects (77.5%) were white and contributed 504.07 subject-years of exposure, 84 subjects (16.9%) were Asian and contributed 101.64 subject-years of exposure, and 20 subjects (4.0%) were of other racial groups. Exposure relative to the numbers of subjects was similar for the white and Asian populations. HCC: In the HCC Lenvatinib Safety Set, the majority of subjects (68.8%) were located in the Asia Pacific Region (China, Japan, Taiwan, South Korea), and all other subjects (31.2%) were from Western regions (EU, Canada, Israel, and North America). Subjects from other global regions were not represented. The highest proportion of subjects was Asian (71.2%),

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	followed by white (27.0%). Of the remaining subjects, 1.4% were Black or African American, and there was 1 subject each (0.2%) of American Indian or Alaska Native, and Other Race. EC Lenvatinib + Pembrolizumab Combination: In the All EC Lenvatinib plus Pembrolizumab Safety Set, most subjects were from outside of the EU region (74.2%); 25.8% of subjects were located in EU. The highest proportion of subjects was white (68.7%), followed by Asian (17.0%). Of the remaining subjects, 7.5% were Other Race and for 6.8% of subjects, information was missing for race.
Elderly patients	DTC: In the All DTC Lenvatinib Safety Set, a total of 35 subjects (7.6%) of 75 years and above were included and contributed 24.4 subject-years (11.8 subject-years [male]; 12.6 subject-years [female]) to the overall exposure. RCC Lenvatinib + Everolimus Combination: In the RCC Lenvatinib + Everolimus Safety Set, there were 71 subjects (11.4%) aged 75 years or more that contributed 56.75 subject-years. There were 195 subjects (31.3%) aged ≥65 to <75 years that contributed 174.21 subject-years, and 357 subjects (57.3%) aged <65 years that contributed 378.99 subject-years of exposure. RCC Lenvatinib + Pembrolizumab Combination: In the All RCC Lenvatinib + Pembrolizumab Safety Set, 55 subjects (11.1%) aged 75 years or more contributed 49.74 subject-years of exposure and 161 subjects (32.4%) aged ≥65 to <75 years contributed 197.25 subject-years of exposure. HCC: In the HCC Lenvatinib Safety Set, subjects aged ≥65 to <75 years contributed 32.1% of the total duration of exposure (109.1/340.0 subject-years). In the oldest age group, subjects ≥75 years contributed 10.7% (36.3/340.0 subject-years) of the total duration of exposure. EC Lenvatinib + Pembrolizumab Combination: In the All EC Lenvatinib plus Pembrolizumab Safety Set, 45 subjects (8.5%) were 75 years and above and contributed 23.7 subject-years of exposure. A total of 44.0% were subjects aged 65 and above but less than 75 years and contributed 165.5 subject-years of exposure.

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Children	Lenvatinib is not licensed for use in children. A paediatric investigational plan (PIP; EMEA-001119-PIP02-12-M08) is in place for the treatment of follicular thyroid cancer, papillary thyroid cancer, or refractory/relapsed osteosarcoma in subjects from 2 years to less than 18 years of age (≤25 years for osteosarcoma), with a waiver for the paediatric population from birth to less than 2 years of age. The 2 clinical studies included in this PIP are as follows: Study E7080-G000-207 (hereafter referred to as Study 207) and Study E7080-G000-230 (hereafter referred to as Study 230). Study 207 evaluated the activity of lenvatinib or lenvatinib in combination with ifosfamide and etoposide in paediatric subjects with solid tumor malignancies and young adults with osteosarcoma. Study 230 compared the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide to ifosfamide and etoposide in paediatric and young adult subjects with relapsed/refractory osteosarcoma. The observed safety profile of lenvatinib as monotherapy or in combination with ifosfamide and etoposide was overall consistent with the known safety profile of lenvatinib in adults and children, and the established safety profiles of ifosfamide and etoposide. Although signals of activity were observed for lenvatinib as a single agent or in combination with ifosfamide and etoposide, the safety and efficacy of lenvatinib in children aged 2 to <18 years have not been established and the results of these studies do not support an indication for lenvatinib in paediatric patients with relapsed or refractory DTC or osteosarcoma. A paediatric investigational plan (PIP; EMEA-001119-PIP03-19-M03) is in place for the treatment of relapsed or refractory solid malignancies in subjects from 2 years to < 18 years of age, with a waiver for the paediatric population from birth to less than 2 years of age. The 2 clinical studies included in this PIP are as follows: Study E7080-A001-216 (hereafter referred to as Study 216) and Study E7080-G000-231 (hereafter referred to as Study 231). Study 216 evaluated the antitumor activity of lenvatinib in combination with everolimus in paediatric subjects with relapsed or refractory solid malignancies, including central nervous system tumors. Study 231 is an ongoing study to evaluate the antitumor activity and safety of lenvatinib as a single agent in children,

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	adolescents, and young adults with relapsed or refractory solid malignancies. The safety profile of lenvatinib as a single agent or in combination with everolimus in paediatric subjects is overall consistent with the known safety profile of these agents in the adult population. The efficacy results from Studies 216 and 231 do not support an indication for lenvatinib as a single agent or in combination with targeted therapy (everolimus) in paediatric subjects with relapsed or refractory solid malignancies.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The method used to calculate exposure utilises the wholesale data on the number of lenvatinib tablets sold, providing an estimate of the total quantity (mg) of lenvatinib; this is then converted into patient days exposure, assuming an average daily dose of 16.1 mg for lenvatinib (based on data from the E7080-G000-303 study). The estimate of exposure is likely to be lower than the actual exposure as the HCC indication is now approved in a number of countries. The recommended starting dose of lenvatinib in HCC is 8 mg or 12 mg daily and the estimated number of patients treated for HCC is now higher than for DTC and RCC; it is not currently possible to determine what the proportion of use has been in HCC or what the average daily dose is in clinical practice.

SV.1.2 Exposure

Up to 12 Feb 2022 (DLP of most recent periodic safety updated report [PSUR]), it is estimated that there have been approximately 61,900 patient-years of exposure since the international birth date (IBD).

Post-marketing data are not generally available by age group, gender, or indication, but based on available data within the most recent PSUR it is estimated that approximately 31,385 patients with DTC, 9,357 with RCC (lenvatinib and everolimus; lenvatinib and pembrolizumab), 11,463 with EC (lenvatinib and pembrolizumab) and 191,397 with HCC have been exposed.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes:

There have been no psychoactive effects reported with the use of lenvatinib. Therefore, there is no perceived potential for lenvatinib to be used for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

The summary of safety concerns in the approved initial RMP for lenvatinib is presented in Table 22.

Table 22 Summary of Safety Concerns After Approval of Initial RMP (Version 6.0)

Summary of safety concerns	
Important identified risks	• Hypertension • Proteinuria • Renal failure or impairment • Hypokalaemia • Cardiac failure • Posterior reversible encephalopathy syndrome (PRES) • Hepatotoxicity • Haemorrhagic events • Arterial thromboembolic events (ATEs) • QTc prolongation • Hypocalcaemia
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
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

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable as this is not the initial RMP for the product.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable as this is not the initial RMP for the product.

For completeness, the summary of safety concerns in the current approved RMP (Version 15.2) is presented in Table 23.

Table 23 Summary of Safety Concerns in Current Approved RMP (Version 17.0)

Summary of safety concerns	
Important identified risks	• Proteinuria and nephrotic syndrome • Renal failure or impairment • Cardiac failure • Posterior reversible encephalopathy syndrome (PRES) • Hepatotoxicity • Haemorrhagic events • Arterial thromboembolic events (ATEs) • QTc prolongation • Hypothyroidism • Gastrointestinal perforation and fistula formation • Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax
Important potential risks	• Venous thromboembolic events (VTEs) • Abnormal pregnancy outcome, excretion of lenvatinib in breast milk • Male and female fertility • Bone and teeth abnormalities in the paediatric population • Impaired wound healing • Interstitial lung disease (ILD)-like conditions • Overdose (concomitant everolimus) (RCC)
Missing information	• Long-term use

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

None. Long-term use previously classified as Missing Information, is removed from the list of safety concerns due to the additional pharmacovigilance measure MEA/FSR 009.4 for Study 307 being completed.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Identified Risk: Proteinuria and Nephrotic Syndrome	
Potential mechanisms:	The mechanism of proteinuria in response to kinase inhibition has been postulated to be due to alteration in the normal biological activity of VEGF by podocytes. In nonclinical models, an abnormally low secretion of VEGF-A by podocytes or the inhibition of its activity interferes with normal kidney function and results in multiple alterations including proteinuria. Other possible mechanisms are the concomitant occurrence of hypertension as a consequence of reduced production of nitric oxide (NO) and glomerular thrombotic microangiopathy (Horsley, et al., 2012). The essential pathological process in nephrotic syndrome of any aetiology is due to an increased glomerular permeability to large molecules, mostly albumin but including other plasma proteins. Proteinuria causes a fall in serum albumin and if the liver fails to fully compensate for urinary protein losses by increased albumin synthesis, plasma albumin concentrations decline, leading to oedema formation. (Hull and Goldsmith, 2008).
Evidence source(s) and strength of evidence:	Evidence from randomised clinical studies. In randomised clinical trials, proteinuria was reported in more patients treated with lenvatinib than placebo. There was only 1 nephrotic syndrome event on the active arm compared to none in the placebo arm. Nephrotic syndrome was identified from post-marketing surveillance.
Characterisation of the risk:	• Frequency All DTC Lenvatinib Safety Set (N=458): Proteinuria (per standard Medical Dictionary for Regulatory Activities [MedDRA] query [SMQ]) was reported in 38.9% of subjects and included TEAEs of proteinuria (38.9%) and protein urine present (0.4%). Nephrotic syndrome was reported in 1 subject (0.2%). RCC Lenvatinib + Everolimus Safety Set (N=623): Proteinuria (per SMQ) was reported in 34.8% of subjects and included TEAEs of proteinuria (34.2%), and protein in urine present (0.5%). Urine protein/creatinine ratio increased and microalbuminuria were reported in 1 subject (0.2%) each. No events of nephrotic syndrome were reported in this cohort. HCC Lenvatinib Safety Set (N=496): Proteinuria (per SMQ) was reported in 27.4% of subjects. No events of nephrotic syndrome were reported in this cohort. All RCC Lenvatinib + Pembrolizumab (N=497): Proteinuria (per SMQ) was reported in 33.0% of subjects. Nephrotic syndrome was reported in 1 subject (0.2%). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Proteinuria (per SMQ) was reported in 29.4% of subjects. No events of nephrotic syndrome were reported in this cohort. Post-authorisation events of proteinuria have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes All DTC Lenvatinib Safety Set (N=458): The TEAE of proteinuria was considered to be serious in only 2 subjects (0.4%). In both cases the proteinuria was Grade 3 in severity and both subjects were hospitalised. Lenvatinib treatment was discontinued in 1 subject and the event resolved. Lenvatinib treatment was interrupted in the other

subject but the event did not resolve. The sole serious event of nephrotic syndrome (Grade 2) was considered medically important by the investigator.

RCC Lenvatinib + Everolimus Safety Set (N=623): Four subjects (0.6%) had SAEs of proteinuria.

HCC Lenvatinib Safety Set (N=496): Proteinuria was reported as an SAE in 3 subjects (0.6%). All subjects were hospitalized, and in all cases the proteinuria was Grade 2 in severity. Lenvatinib treatment was interrupted in all 3 subjects and the proteinuria resolved or was resolving in all subjects. Lenvatinib therapy was restarted at a reduced dose in 1 subject and the 2 other subjects withdrew from the study.

All RCC Lenvatinib + Pembrolizumab (N=497): Proteinuria was reported as an SAE in 1 subject (0.2%) and was Grade 2 in severity. Treatment was interrupted and the event was resolving.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): 1 subject (0.2%) had an SAE of proteinuria, which was Grade 3 in severity. No action was taken regarding lenvatinib and the event of proteinuria resolved.

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458): Proteinuria was Grade 1 or 2 for the majority of subjects. Grade 3 events for proteinuria were reported in 10.5% of subjects. There were no Grade 4 or 5 TEAEs for proteinuria. Dose interruptions and reductions for proteinuria were reported in 16.2% and 10.9% of subjects, respectively. However, proteinuria led to treatment discontinuation in only 1.3% of subjects (n=6). The majority of cases had an outcome of recovered or resolved following dose interruption or reduction.

RCC Lenvatinib + Everolimus Safety Set (N=623): The majority of TEAEs of proteinuria (16.4%) were Grade 2. Grade 3 proteinuria was reported in 8.8% of subjects. There was one Grade 4 and no Grade 5 TEAEs for proteinuria. Dose interruptions and reductions for proteinuria were reported in 9.8% and 9.6% of subjects, respectively. Proteinuria led to treatment discontinuation in 2.1% of subjects. The majority of cases had an outcome of recovered or resolved following dose interruption or reduction.

HCC Lenvatinib Safety Set (N=496): The majority of TEAEs of proteinuria were Grade 2 (11.1%). Grade 3 proteinuria was reported in 6.7% of subjects. Dose interruptions and reductions for proteinuria were reported in 6.9% and 3.0% of subjects, respectively. However, proteinuria led to treatment discontinuation in only 1.2% of subjects (n=6).

All RCC Lenvatinib + Pembrolizumab (N=497): Proteinuria was Grade 1 or 2 for the majority of subjects. Grade 3 events for proteinuria were reported in 8.0% of subjects. There were no Grade 4 or 5 TEAEs for proteinuria events. Dose interruptions and reductions for proteinuria were reported in 9.3% and 10.1% of subjects, respectively. Proteinuria led to treatment discontinuation in 1.8% of subjects (n=9). The majority of events had an outcome of 'resolved' or 'resolving.'

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Proteinuria was Grade 1 or Grade 2 for the majority of subjects. Grade 3 proteinuria was reported in 4.9% of subjects and Grade 4 was reported in 0.2% of subjects. Lenvatinib dose interruptions and reductions for proteinuria were reported in 7.4% and 7.7% of subjects, respectively. Proteinuria led to lenvatinib discontinuation in 1.3% of subjects (n=7).

Overview of Proteinuria (SMQ)			
For Proteinuria-SMQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458**	**RCC Lenvatinib + Everolimus Safety Set N=623**	**HCC Lenvatinib Safety Set**

	SY[a]=608.1	SY[a]=654.6	N=496 SY[a]=340.0
TEAE, n (%)	178 (38.9)	217 (34.8)	136 (27.4)
TEAE, no. of episodes (episodes/SY)	314 (0.52)	N/A	192 (0.56)
TEAE with maximum CTCAE Grade of [b], n (%)			
1	46 (10.0)	59 (9.5)	48 (9.7)
2	84 (18.3)	102 (16.4)	55 (11.1)
3	48 (10.5)	55 (8.8)	33 (6.7)
4	0	1 (0.2)	0
5	0	0	0
SAE	2 (0.4)	4 (0.6)	3 (0.6)
TEAE leading to treatment discontinuation, n (%)	6 (1.3)	11 (2.1)[d]	6 (1.2)
TEAE leading to study drug modification [c], n (%)			
Reduction	50 (10.9)	51 (9.6)[d]	15 (3.0)
Interruption	74 (16.2)	52 (9.8)[d]	34 (6.9)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, N/A = not applicable, RCC = renal cell carcinoma, SMQ = standard MedDRA query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

Overview of Proteinuria (SMQ)		
For Proteinuria-SMQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**All RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	156 (29.4)	164 (33.0)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	41 (7.7)	50 (10.1)
2	88 (16.6)	74 (14.9)
3	26 (4.9)	40 (8.0)
4	1 (0.2)	0
5	0 (0.0)	0
SAE	1 (0.2)	1 (0.2)
TEAE leading to lenvatinib discontinuation, n (%)	7 (1.3)	9 (1.8)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	41 (7.7)	50 (10.1)
Lenvatinib drug interruption	39 (7.4)	46 (9.3)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell

	carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event. a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions). b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade. c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
Risk factors and risk groups:	DTC The presence of hypertension during lenvatinib treatment appeared to be correlated with the development of proteinuria. The incidence of proteinuria was higher in females, Asians, elderly subjects (≥75 years of age), diabetic subjects, and subjects with baseline renal function impairment. RCC (Lenvatinib + Everolimus): The incidence of proteinuria increased with increasing age and was higher in the Asian population and subjects with baseline diabetes. In subjects aged <65 years, the incidence of proteinuria was 31.1%, and in subjects aged ≥65 to <75 and ≥75 years, the incidences were 38.5% and 43.7%, respectively. Asian subjects had a higher incidence of proteinuria (52.7%) than white subjects (31.0%) with a higher incidence of Grade 3 TEAEs (17.9% vs 7.3%). Subjects with baseline diabetes were also more likely to experience proteinuria events than those without (50.0% vs 31.3%), although the differences in Grade 3 events were smaller in magnitude (11.0% vs 8.5%). The presence of baseline hypertension was associated with a modest increase in the incidence of proteinuria (38.9%) compared with subjects without baseline hypertension (29.1%). RCC (Lenvatinib + Pembrolizumab): The incidence of proteinuria was increased with increasing age, was higher in Asians, and subjects with baseline hypertension. The incidence of proteinuria and severe (Grade 3 or more) TEAEs increased with advancing age. In subjects aged <65 years, the incidence of proteinuria was 29.5% (Grade≥ 3 :6.4%), and in subjects aged ≥65 to <75 and ≥75 years, the incidences were 36.0% and 41.8% (Grade ≥3: 9.3%, 12.7%) respectively. Asian subjects had a higher incidence of proteinuria (56.0%) than White subjects (28.8%) with a corresponding higher incidence of Grade 3 TEAEs (19.0% vs 6.0%). Subjects with baseline hypertension were also more likely to experience proteinuria events than those without (38.6% vs 24.2%), although the differences in Grade 3 events were smaller in magnitude. (9.6% vs 5.7%). HCC: The incidence of proteinuria increased with advancing age. The overall incidence of TEAEs and the incidence of severe (Grade 3) TEAEs for proteinuria tended to be higher in the 2 older age groups compared with the youngest subjects. In subjects aged <65 years the incidence of proteinuria was 21.2%, and in subjects ≥65 to <75, and ≥75 years, the incidences were 34.2% and 39.7%, respectively. In addition, subjects from the Asia-Pacific region had a notably higher incidence of proteinuria (31.7%) compared with subjects from Western Regions (18.1%). Asian subjects had a higher incidence of proteinuria (30.9%) than white subjects (20.1%). In addition, the incidences of severe (Grade 3) TEAEs in Asian subjects were higher than those in White subjects and the incidences in subjects from the Asia-Pacific region were higher than those for subjects from the Western regions. Of note, the incidence of proteinuria in subjects with an ECOG PS of ≥1 was lower (21.0%) compared with subjects with an ECOG PS of 0 (30.9%), however the number of subjects with a Baseline ECOG PS of ≥1 was small (n=37). Events of nephrotic syndrome were rare in the clinical trial cohorts, but theoretically the risks for nephrotic syndrome are similar to those for proteinuria.
Preventability	Proteinuria can be controlled with routine monitoring and dose modifications. Urine protein should be monitored regularly in all subjects receiving lenvatinib. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary based on individual safety and tolerability.

	Because no interventional study has been performed with regard to proteinuria induced by VEGF/VEGFR-targeted agents, and because the mechanisms underlying its development are not well understood, evidence-based recommendations cannot be made and most treatments are nonspecific, but may include angiotensin-converting enzyme (ACE) inhibitors. The risk of nephrotic syndrome is mitigated by urinary protein monitoring and dose modifications as nephrotic syndrome follows severe or untreated proteinuria.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures have been implemented, and proteinuria and nephrotic syndrome are not expected to impact the risk-benefit balance of lenvatinib.
Public health impact:	No public health impact identified.

Identified Risk: Renal Failure or Impairment	
Potential mechanisms:	Renal events are well known AEs associated with treatment with TKIs (Chen and Cleck, 2009). VEGF plays a role in maintaining mucosal homeostasis and mucosal epithelialization after mucosal damage, and it has been proposed that VEGF inhibition can result in mucosal damage leading to cutaneous toxicity, and upper or lower digestive tract mucositis with pain, vomiting, or diarrhea. This can then lead to lower intake and GI uptake of fluids resulting in dehydration and subsequent renal injury. The important identified risk of proteinuria, as discussed above, is also a direct toxic effect on the kidney. Although most subjects who developed renal failure or impairment had 1 or more contributory factors, some subjects did not have relevant comorbidities or prior relevant medical history. Therefore, causality secondary to the administration of lenvatinib cannot be excluded due to its known class antiangiogenic effects on the kidney.
Evidence source(s) and strength of evidence:	Evidence from randomised clinical studies. In randomised clinical trials, renal failure and impairment was reported in more patients treated with lenvatinib than placebo.
Characterisation of the risk:	• Frequency All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs for renal events (SMQ) were reported in 12.9% of subjects (n=59). The most frequently reported renal events were blood creatinine increased (6.6%; n=30) and blood urea increased (3.3%; n=15). Renal failure acute and renal failure were reported in 2.4% (n=11) and 1.1% (n=5) of subjects, respectively, and renal impairment in 1.1% of subjects (n=5). RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs for renal events were reported in 17.2% of subjects (n=107). The most frequently reported renal events were blood creatinine increased (11.4%, n=71), acute kidney injury (5.3%, n=33), blood urea increased (1.3%, n=8), and renal failure (1.3%, n=8). HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs for renal events (SMQ) were reported in 7.1% of subjects (n=35). The most frequently reported renal events were blood creatinine increased (2.2%, n=11), acute kidney injury (1.8%, n=9), blood urea increased (1.2%, n=6), and renal impairment (1.0%, n=5).

	All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for renal events (SMQ) were reported in 22.5% of subjects (n=112). The most frequently reported renal events were blood creatinine increased (14.9%; n=74) and acute kidney injury (4.4%; n=22). Renal failure and renal impairment events (all grades) were reported in 2.6% (n=13) and 0.4% (n=2) of subjects, respectively. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs for renal events (SMQ) were reported in 17.0% of subjects (n=90). The most frequently reported renal events were blood creatinine increased (10.8%; n=57), acute kidney injury (4.5%; n=24) and renal failure (1.1%, n=6). Post-authorisation events of renal failure or impairment have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes All DTC Lenvatinib Safety Set (N=458): Serious AEs for renal events were reported in 2.6% of subjects (n=12) with 1 fatal outcome (death due to acute renal failure related to disease progression). The most frequently reported SAEs for renal events were renal failure acute (n=6) and renal failure (n=2). Other SAEs for renal events included acute prerenal failure (n=1), blood creatinine increased (n=1), renal impairment (n=1), and renal tubular necrosis (n=1). The majority of renal events reported were reversible and resolved with hydration and lenvatinib dose interruption or reduction. RCC Lenvatinib + Everolimus Safety Set (N=623): Serious AEs for renal events were reported in 5.1% of subjects (n=32). The most frequently reported SAEs were acute kidney injury (n=22), blood creatinine increased (n=5), and renal failure (n=3). One subject died due to a renal event (acute kidney injury). HCC Lenvatinib Safety Set (N=496): Serious AEs for renal events were reported in 1.4% of subjects (n=7). One subject died due to a renal event (renal impairment/renal function aggravated). All RCC Lenvatinib + Pembrolizumab (N=497): SAEs for renal events were reported in 4.4% of subjects (n=22) with 2 fatal outcomes (1 death due to blood creatinine increase, which occurred with ongoing pembrolizumab treatment 267 days after lenvatinib treatment was withdrawn and another due to nephritis, which was associated with SAEs of myocarditis, pneumonitis and hepatitis). The most frequently reported SAEs for renal events were acute kidney injury (n=13) and renal failure (n=5). Other SAEs for renal events included nephritis (n=3) and blood creatinine increased (n=2). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): SAEs for renal events (SMQ) were reported in 2.6% of subjects (n=14). The most frequently reported SAEs for renal events were acute kidney injury (n=9) and renal failure (n=3). • Severity and nature of risk All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs of Grade 3 or higher for renal events occurred in 2.6% of subjects (n=12). Most TEAEs were Grade 1 or 2 and led to discontinuation of treatment in only 0.4% of subjects (n=2). Three subjects in the Non DTC Monotherapy Safety Set experienced Grade 4 TEAEs for renal events. This included 2 subjects with renal failure and 1 subject with azotemia. RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs of Grade 3 or higher for renal events were reported in 4.3% of subjects (n=27). TEAEs leading to study drug dose reduction or interruption occurred in 2.3% and 4.0% of subjects, respectively. Treatment-emergent AEs leading to study drug discontinuation occurred in 1.9% of subjects.

HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs of Grade 3 or higher for renal events were reported in 2.0% of subjects (n=10). There was 1 Grade 4 event and 1 Grade 5 event. TEAEs leading to study drug discontinuation or interruption occurred in 0.4%, and 1.0% of subjects, respectively.

All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for Grade 3 or higher renal events occurred in 4.8% of subjects (n=24). Most TEAEs were Grade 1 or 2. Three subjects experienced Grade 4 TEAEs for renal events; 2 subjects had renal failure and 1 had acute kidney injury. TEAEs leading to study drug dose reduction or interruption occurred in 1.0% and 4.8% of subjects, respectively. Treatment was discontinued in 1.2% of subjects (n=6).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs of Grade 3 or higher renal events (SMQ) were reported in 4.0% of subjects (n=21). There was 1 Grade 5 event of acute kidney injury. TEAEs leading to lenvatinib reduction or interruption occurred in 1.7% and 3.2% of subjects, respectively. Lenvatinib was discontinued in 1.1% of subjects (n=6).

Overview of Renal Events (SMQ)

For Renal Events-SMQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set (N=623) SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	59 (12.9)	107 (17.2)	35 (7.1)
TEAE, no. of episodes (episodes/SY)	83 (0.14)	N/A	48 (0.14)
TEAE with maximum CTCAE Grade of [b], n (%)			
1	29 (6.3)	37 (5.9)	12 (2.4)
2	18 (3.9)	43 (6.9)	13 (2.6)
3	11 (2.4)	20 (3.2)	8 (1.6)
4	0	6 (1.0)	1 (0.2)
5	1 (0.2)	1 (0.2)	1 (0.2)
SAE	12 (2.6)	32 (5.1)	7 (1.4)
TEAE leading to treatment discontinuation, n (%)	2 (0.4)	10 (1.9)[d]	2 (0.4)
TEAE leading to study drug modification [c], n (%)			
Reduction	5 (1.1)	12 (2.3)[d]	0
Interruption	12 (2.6)	21 (4.0)[d]	5 (1.0)

For each row category, a subject with 2 or more adverse events in that category is counted only once.

AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, N/A = not applicable, RCC = renal cell carcinoma, SMQ = standard MedDRA query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

	Overview of Renal Events (SMQ)

For Renal Events-SMQ, Subjects With At Least 1:	All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8	All RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8
TEAE, n (%)	90 (17.0)	112 (22.5)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	42 (7.9)	51 (10.3)
2	27 (5.1)	37 (7.4)
3	20 (3.8)	19 (3.8)
4	0 (0.0)	3 (0.6)
5	1 (0.2)	2 (0.4)
SAE	14 (2.6)	22 (4.4)
TEAE leading to lenvatinib discontinuation, n (%)	6 (1.1)	6 (1.2)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	9 (1.7)	5 (1.0)
Lenvatinib drug interruption	17 (3.2)	24 (4.8)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Risk factors and risk groups:	Risk factors associated with renal impairment or failure in patients receiving lenvatinib include dehydration and/or hypovolemia, underlying chronic renal impairment, adrenal mass, and sepsis. Almost all subjects who developed renal failure or impairment had 1 or more contributory factors, such as hypertension, diabetes, poor oral intake, GI toxicity (such as diarrhea and or vomiting) leading to dehydration, malnutrition, rhabdomyolysis (due to treatment with a statin), infection, urinary retention, progressive metastatic disease with cancer-related cachexia, or prior history of chronic renal failure and adrenal mass. The primary risk factor identified was dehydration and/or hypovolemia due to GI toxicity or sepsis. GI toxicity was more pronounced in the RCC Lenvatinib Everolimus Safety Set and included diarrhoea (69.0% overall), which was Grade ≥3 in 13.8% of subjects. For most subjects, there was no correlation between the incidence of observed diarrhoea events and the incidence of renal failure events across treatment groups in the RCC Lenvatinib + Everolimus Safety Set. Despite the differences between frequency of diarrhoea in the Lenvatinib + Everolimus RCC Combination Group (69.0%) compared with lenvatinib monotherapy (34.0%), the difference in incidences of renal events was 17.2% versus 10.0%, respectively.
Preventability	Gastrointestinal disorders such as abdominal pain, diarrhea, nausea, and vomiting are very commonly reported in subjects treated with lenvatinib and can result in serious consequences such as dehydration and acute renal failure. Supportive care and close monitoring should be promptly initiated. Gastrointestinal toxicity resulting in dehydration should be actively managed with intravenous fluid therapy in order to reduce the risk of development of renal

	impairment or renal failure. Dose interruptions, adjustments, or treatment discontinuation may be necessary.
Impact on the risk-benefit balance of the product:	Renal impairment is not expected to impact the risk-benefit balance of lenvatinib with routine monitoring unless the event develops into renal failure.
Public health impact:	If renal failure develops then there may be a significant impact on public health resources as the patient would require hospitalization and renal support.

Identified Risk: Cardiac Failure	
Potential mechanisms:	The potential risk of cardiomyopathy with VEGF/VEGFR-targeted therapy is suggested in cardiomyocyte-specific VEGF knockout mouse models, which present with dilated cardio myopathy. In the developed heart, VEGF is important for maintaining cardiomyocyte well-being in response to stress and injury. Additional molecular pathways targeted by TKIs may also play a role. For example, PDGFR, a target of sunitinib and sorafenib, is expressed on cardiac myocytes and is a potent stimulus of normal cardio myocyte growth under hypertensive stress (Chen and Cleck, 2009). Cardiomyopathy and CHF have been reported with the use of VEGF/VEGFR-targeted therapies including sunitinib, in which a decrease in left ventricular ejection fraction (LVEF) below the normal range was observed in 20% of subjects treated, and 8% developed clinical CHF (Di Lorenzo, et al., 2009; Richards, et al., 2011).
Evidence source(s) and strength of evidence:	Evidence from randomised clinical studies. In randomised clinical trials, decreased ejection fraction/cardiac failure was reported in more patients treated with lenvatinib than placebo.
Characterisation of the risk:	• Frequency All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs for decreased ejection fraction/cardiac failure (sponsor generated query [SGQ]) were reported in 7% of subjects and included events of cardiac failure (1.1%; n=5), cardiac failure congestive (0.4%; n=2), ejection fraction decreased (4.8%; n=22), cardiac failure chronic (0.2%; n=1), echocardiogram abnormal (0.2%; n=1), and pulmonary oedema (0.4%; n=2). RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs for decreased ejection fraction/cardiac failure (SGQ) were reported in 3.5% of subjects (n=22) and consisted of events of cardiac failure (1.0% of subjects, n=6), cardiomyopathy (0.3% of subjects, n=2), and cardiac failure acute, cardiogenic shock, congestive cardiomyopathy, and ejection fraction decreased (0.2% of subjects, n=1 for each event). HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs for cardiac dysfunction were reported in 0.6% of subjects (n=3) and consisted of events of cardiac failure congestive, cardiogenic shock, and cardiopulmonary failure (0.2%, n=1 for each event). All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for cardiac dysfunction were reported in 3.0% of subjects (n=15) and consisted of events of ejection fraction decreased (0.8% of subjects, n=4), cardiomyopathy (0.6% of subjects, n=3), left ventricular dysfunction (0.4% of subjects, n=2), cardiac failure (0.4% of subjects, n=2), cardiac failure acute (0.2% of subjects, n=1), and cardiac failure congestive, left ventricular failure, right ventricular dysfunction and stress cardiomyopathy (0.2%, n=1 for each event).

	All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs for cardiac dysfunction SMQ were reported in 2.1% of subjects (n=11) and included events of ejection faction decreased (0.6%, n=3), cardiac failure congestive and cardiac failure (0.4%, n=2 for each event). Post-authorisation events of cardiac failure have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes All DTC Lenvatinib Safety Set (N=458): No deaths were reported. There were SAEs in 0.9% of subjects (n=4). These included the PTs of cardiac failure (0.4%, n=2), cardiac failure chronic (0.2%, n=1), and cardiac failure congestive (0.2%, n=1). RCC Lenvatinib + Everolimus Safety Set (N=623): There were 2 deaths (0.3%) due to cardiac failure. There were SAEs in 1.6% of subjects (n=10). HCC Lenvatinib Safety Set (N=496): There was 1 SAE (Cardiopulmonary failure) reported in 1 subject (0.2%). All RCC Lenvatinib + Pembrolizumab (N=497): Serious AEs for cardiac dysfunction events were reported in 1.2% of subjects (n=6) with 1 fatal outcome due to cardiac failure. These SAEs included the events of cardiac failure, cardiac failure acute, cardiac failure congestive, cardiomyopathy, stress cardiomyopathy and pulmonary oedema (0.2%, n=1 for each event). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): SAEs for cardiac dysfunction SMQ were reported in 0.9% of subjects (n=5) and consisted of events of cardiac failure congestive (0.4%, n=2), and cardiac failure, right ventricular dysfunction, and stress cardiomyopathy, (0.2%, n=1 for each event). • Severity and nature of risk In the All DTC Lenvatinib Safety Set, 15 subjects had a reduction in LVEF of greater than 20% from baseline, and 11 subjects had a decrease in LVEF to less than 40%. All events of decreased ejection fraction were Grade 1 to 3 in severity and only 1 led to permanent discontinuation of treatment. Two Grade 1 and 3 Grade 3 events of cardiac failure, 1 Grade 3 event of cardiac failure congestive, and 1 Grade 1 and 1 Grade 3 event of pulmonary edema were reported. Two subjects who had a decrease in LVEF to less than 40% also had the TEAE of cardiac failure; both events were managed through dose interruption and reduction. RCC Lenvatinib + Everolimus Safety Set (N=623): Seven subjects experienced cardiac failure and 3 subjects had a reduction in ejection fraction. Six of the 7 events of cardiac failure and 1 of the 3 events of ejection fraction decreased were reported as SAEs. HCC Lenvatinib Safety Set (N=496): Of the TEAEs of cardiac dysfunction, there was 1 Grade 2 event and 1 Grade 3 event. One subject died following a Grade 5 event of cardiopulmonary failure secondary to disease progression, and was considered to be unrelated to study drug by the investigator. All RCC Lenvatinib + Pembrolizumab (N=497): Four subjects (0.8%) had decreased ejection fraction Grade 2. Two Grade 1 and 1 Grade 3 events of cardiomyopathy, 1 Grade 1 event and 1 Grade 3 event of left ventricular dysfunction, 1 Grade 2 event of left ventricular failure, 1 Grade 2 event of right ventricular dysfunction, 1 Grade 3 and 1 Grade 5 events of cardiac failure, 1 Grade 3 event of acute cardiac failure, 1 Grade 3 event of congestive cardiac failure, 1 Grade 3 event of stress cardiomyopathy, and 1 Grade 2 and 1 Grade 3 event of pulmonary edema were reported. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Of the TEAEs of cardiac dysfunction SMQ, there were 3 Grade 3 events. One subject died following a

Grade 5 event of right ventricular dysfunction which was considered to be related to study drug by the investigator.

Overview of Decreased Ejection Fraction/Cardiac Failure per SGQ Analysis			
For Decreased EF/Cardiac Failure-SGQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	32 (7.0)	22 (3.5)	3 (0.6)
TEAE, no. of episodes (episodes/SY)	36 (0.06)	N/A	3 (0.01)
TEAE with maximum CTCAE Grade of [b], n (%)			
1	5 (1.1)	5 (0.8)	0
2	14 (3.1)	6 (1.0)	1 (0.2)
3	13 (2.8)	11 (1.8)	1 (0.2)
4	0	0	0
5	0	2 (0.3)	1 (0.2)
SAE	4 (0.9)	10 (1.6)	1 (0.2)
TEAE leading to treatment discontinuation, n (%)	1 (0.2)	3 (0.6)[d]	0
TEAE leading to study drug modification [c], n (%)			
Reduction	5 (1.1)	2 (0.4)[d]	0
Interruption	7 (1.5)	4 (0.8)[d]	0

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, EF = ejection fraction, HCC = hepatocellular carcinoma, N/A = not applicable, RCC = renal cell carcinoma, SGQ = sponsor-generated query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

Overview of Cardiac Dysfunction		
For Cardiac Dysfunction - SMQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**All RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	11 (2.1)	15 (3.0)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	2 (0.4)	0 (0.0)
2	5 (0.9)	7 (1.4)
3	3 (0.6)	7 (1.4)
4	0 (0.0)	0 (0.0)
5	1 (0.2)	1 (0.2)
SAE	5 (0.9)	6 (1.2)

	<table><tr><td>TEAE leading to lenvatinib discontinuation, n (%)</td><td>1 (0.2)</td><td>4 (0.8)</td></tr><tr><td colspan="3">TEAE leading to study drug modification [c], n (%)</td></tr><tr><td>Lenvatinib dose reduction</td><td>5 (0.9)</td><td>2 (0.4)</td></tr><tr><td>Lenvatinib drug interruption</td><td>1 (0.2)</td><td>3 (0.6)</td></tr></table> For each row category, a subject with 2 or more adverse events in that category is counted only once. CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event. a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions). b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade. c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
Risk factors and risk groups:	DTC Most subjects had individual risk factors that could have predisposed to decreased EF, including hypertension, chronic obstructive pulmonary disease, diabetes mellitus, obesity, preexisting heart disease, and prior anthracycline use. Refractory CHF with fatal outcome has rarely been reported. In most subjects, ventricular dysfunction improved after discontinuation of the VEGF/VEGFR–targeted therapy, although it is unclear whether this is true reversibility of the adverse effect, or due to efficacy of cardiac medications, or both. Importantly, evaluation of the changes in echocardiographic parameters in Study 204 has demonstrated that the observed changes in LVEF were small and the results did not suggest a direct cardiotoxic effect of lenvatinib. RCC Subjects with RCC were predominantly older, overweight males with underlying risk factors of hypercholesterolemia, dyslipidaemia, hypertension and diabetes mellitus, all of which are known risk factors associated with cardiovascular disease and subsequent complications of cardiac dysfunction. Additionally, RCC subjects are at a higher risk of developing chronic kidney disease, which is independently associated with increased cardiovascular risk due to dysregulation of lipid metabolism (Chang et al., 2014; Ferro et al., 2018). HCC Portal hypertension is a common comorbidity in subjects with HCC, a risk factor that could have predisposed to cardiac failure events. Ascites and gastrooesophageal varices are the most frequent manifestations of clinically significant portal hypertension. Extrahepatic changes are known to occur in the presence of portal hypertension, in addition to disease progression. These include the development of hypovolaemia which results in hyperkinetic syndrome that causes portal venous blood flow increase. Further increases in portal hypertension can impair cardiac function and the consequences may be life-threatening (La Mura, et al., 2015).
Preventability	Cardiovascular risk assessment for risk groups such as adults with chronic kidney disease and/or diabetes is available and involves evaluation and management of lipid profile, blood pressure and other cardiovascular risk factors through therapeutic lifestyle changes or medication (Kidney Disease|Improving Global Outcomes [KDIGO], 2012; KDIGO, 2013; KDIGO, 2020). Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or permanent discontinuation may be necessary.

Impact on the risk-benefit balance of the product:	Routine risk minimisation measures have been put in place.
Public health impact:	The potential public health impact could be significant; however, the risk should be manageable with the recommended monitoring and dose adjustment.

Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES)	
Potential mechanisms:	Legriel, et al. (2011) reported that the pathophysiology of PRES remains controversial. The 2 main hypotheses contradict each other. One involves impaired cerebral autoregulation responsible for an increase in cerebral blood flow, whereas the other involves endothelial dysfunction with cerebral hypoperfusion. This hypoperfusion hypothesis may be most relevant to cases of PRES associated with cytotoxic therapy. Under both hypotheses, the result of the cerebral blood perfusion abnormalities is blood-brain barrier dysfunction with cerebral vasogenic edema. When mean arterial pressure (MAP) is within the range of 60 to 120 mmHg, cerebral autoregulation via variations in vasoconstriction and vasodilatation keeps the cerebral blood flow at about 50 mL/100 g/min in healthy individuals. To overcome this autoregulation mechanism, MAP must exceed 170 mmHg (systolic BP/diastolic BP of 220/110 mmHg). However, a smaller MAP increase of only 50 mmHg (systolic BP/diastolic BP of 160/100 mmHg) in a patient with de novo hypertension is sufficient to trigger severe vasoconstriction. Cerebral hyperperfusion leads to the release of the vasodilators nitric oxide (NO) and prostacyclin under the influence of endothelial agonists such as acetylcholine, norepinephrine, and substance P. The net result leads to direct cytotoxic effects on the blood vessel wall. This damage to the vascular endothelium causes blood-brain barrier dysfunction and cerebral vasogenic edema. Not all patients with PRES have hypertension. In patients with PRES and normal BP, cytotoxicity has been hypothesised to be the mechanism underlying the brain edema. Causes of PRES without hypertension include eclampsia/ preeclampsia, cyclosporine toxicity, and infection/sepsis/septic shock. The potential mechanisms vary with the cause. Immune system (T-cell) activation leads to endothelial cell activation with the release of various mediators such as histamine, free radicals, NO, bradykinin, and arachidonic acid. This ultimately results in vascular instability with vasoconstriction and downstream hypoperfusion. Blood-brain barrier dysfunction occurs, leading to vasogenic cerebral edema. Certain toxic agents are well known to be associated with PRES and these include antiangiogenic agents.
Evidence source(s) and strength of evidence:	Evidence from randomised clinical trials. A small number of events of PRES were reported in patients treated with lenvatinib and PRES is a known effect associated with other antiangiogenic agents.
Characterisation of the risk:	• Frequency All DTC Lenvatinib Safety Set (N=458): One TEAE for PRES per SGQ (0.2%) was reported. RCC Lenvatinib + Everolimus Safety Set (N=623): One TEAE of PRES was reported for 1 subject treated with the combination of lenvatinib and everolimus. HCC Lenvatinib Safety Set (N=496): One TEAE for PRES per SGQ (0.2%) was reported.

	In addition, 2 TEAEs for PRES were reported in the Non-DTC, Non-HCC Monotherapy Safety Set (N=656). All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for PRES (SMQ) events were reported in 0.6% of subjects (n=2). All EC Lenvatinib + Pembrolizumab (N=530): Treatment-emergent AEs for PRES (SMQ) events were reported in 0.4% of subjects (n=2). Post-authorisation events of PRES have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes All events of PRES in the Lenvatinib Monotherapy Safety Sets (All DTC, non-DTC, Non-HCC and HCC) were considered SAEs. In the lenvatinib monotherapy safety sets, all SAEs of PRES were nonfatal, 2 were life threatening (1 each in the All DTC and the Non-DTC, Non-HCC Monotherapy Safety Sets), 3 required hospitalization, and all recovered or resolved with treatment and dose interruption (1 event in All DTC Lenvatinib Safety Set) or dose interruption alone (1 event each in the Non-DTC, Non-HCC Monotherapy Safety Set and in the HCC Lenvatinib Safety Set), or after permanent treatment discontinuation (1 event each in Non-DTC, Non-HCC Monotherapy and RCC Monotherapy Safety Sets). All RCC Lenvatinib + Everolimus (N=623): The event of PRES was not serious. All RCC Lenvatinib + Pembrolizumab (N=497): Both events of PRES were nonfatal and were considered SAEs. All EC Lenvatinib + Pembrolizumab (N=530): Both events of PRES were nonfatal and resolved with dose interruption (lenvatinib) or after permanent treatment discontinuation. One TEAE of PRES was an SAE. • Severity and nature of risk One event of PRES reported in the All DTC Lenvatinib Safety Set was of Grade 2 and led to dose reduction. Of the 2 PRES events in the Non-DTC, Non-HCC Monotherapy Safety Set, 1 was of Grade 3 and 1 was of Grade 4. One event led to treatment discontinuation and 1 led to dose interruption. The event of PRES in the RCC lenvatinib monotherapy arm was Grade 3 and led to study drug discontinuation. All RCC Lenvatinib + Everolimus (N=623): One event of PRES reported was of Grade 2 and did not lead to any dose modification or discontinuation. The 1 event of PRES in the HCC Lenvatinib Safety Set was Grade 2 and resulted in study drug interruption. All RCC Lenvatinib + Pembrolizumab (N=497): One SAE of PRES was Grade 3 and resulted in lenvatinib dose reduction; the second SAE was Grade 4 and resulted in permanent treatment discontinuation of lenvatinib. All EC Lenvatinib + Pembrolizumab (N=530): One event of PRES was Grade 1 and resulted in dose interruption (lenvatinib); the second event was Grade 3 and resulted in permanent treatment discontinuation.
<u>Risk factors and risk groups:</u>	PRES is a known uncommon TEAE (affecting <1% of subjects) associated with VEGF/VEGFR-targeted agents. Blood pressure is elevated from baseline in most, but not all, patients (Chen and Cleck, 2009). Systemic hypertension is a major risk factor (Le and Loghin, 2014). There are multiple well defined conditions that can cause PRES in cancer patients, including hypertension and renal dysfunction, as can immunosuppressants, chemotherapeutic drugs, bone marrow/stem cell transplants, corticosteroids, and growth factors (Le and Loghin, 2014).

	Targeted therapies such as bevacizumab, sunitinib, sorafenib, and temsirolimus have been implicated as well, given their role in VEGF inhibition, causing disruption of angiogenesis and vasoconstriction, resulting in thrombotic events and systemic hypertension (Le and Loghin, 2014).
Preventability	PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control BP. In patients with signs or symptoms of PRES, dose interruptions, adjustments, or permanent discontinuation may be necessary. For patients with hypertension, BP should be adequately controlled prior to initiation of lenvatinib treatment. Regular monitoring of BP is required for patients whilst on treatment.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures have been put in place. PRES is a rare but well characterised risk and with monitoring of the primary risk factor (hypertension) PRES is not expected to impact the risk-benefit balance of lenvatinib.
Public health impact:	No public health impact identified.

Identified Risk: Hepatotoxicity

Potential mechanisms:	Liver events are known to be associated with treatment with TKIs (Caprelsa [vandetanib] European Public Assessment Report [EPAR], Inlyta [axitinib] EPAR, and Nexavar [sorafenib] EPAR). The potential mechanisms are not clear. Likely mechanisms include oxidative stress from reactive metabolites, immune injury, and disruption of hepatic bile acid transport and resulting mitochondrial dysfunction (Spraggs, et al., 2013).
Evidence source(s) and strength of evidence:	Evidence from randomised clinical trials. In randomised clinical trials liver-related reactions were reported in more patients treated with lenvatinib than placebo.
Characterisation of the risk:	• Frequency The following TEAEs for liver events were reported in 2 or more subjects in any of the safety sets:

MedDRA Preferred Term[a]	Safety Sets, n (%)		
	All DTC N=458	RCC Len+Eve N=623	HCC N=496
Hypoalbuminaemia	38 (8.3)	23 (3.7)	47 (9.5)
Alanine aminotransferase increased	37 (8.1)	74 (11.9)	55 (11.1)
Aspartate aminotransferase increased	33 (7.2)	71 (11.4)	68 (13.7)
Blood alkaline phosphatase increased	25 (5.5)	34 (5.5)	32 (6.5)
Blood bilirubin increased	11 (2.4)	9 (1.4)	71 (14.3)
Hepatic function abnormal	10 (2.2)	8 (1.3)	12 (2.4)
Gamma-glutamyltransferase increased	6 (1.3)	17 (2.7)	38 (7.7)
Transaminases increased	5 (1.1)	8 (1.3)	1 (0.2)
Hepatic enzyme increased	3 (0.7)	1 (0.2)	1 (0.2)
Ascites	1 (0.2)	4 (0.6)	71 (14.3)
Hepatic failure	1 (0.2)	1 (0.2)	15 (3.0)
Hyperbilirubinaemia	1 (0.2)	2 (0.3)	11 (2.2)

Jaundice	1 (0.2)	3 (0.5)	6 (1.2)
Asterixis	1 (0.2)	0	2 (0.4)
Hepatic pain	1 (0.2)	3 (0.5)	8 (1.6)
Liver function test increased	0	6 (1.0)	0
Hepatocellular injury	0	4 (0.6)	0
Hypertransaminasaemia	0	3 (0.5)	0
Metabolic encephalopathy	0	2 (0.3)	0
Hepatotoxicity	0	2 (0.3)	0
International normalised ratio increased	0	2 (0.3)	0
Bilirubin conjugated increased	0	2 (0.3)	2 (0.4)
Hepatic encephalopathy	0	1 (0.2)	41 (8.3)
Jaundice cholestatic	0	1 (0.2)	8 (1.8)
Hyperammonaemia	0	0	10 (2.0)
Urine bilirubin increased	0	0	5 (1.0)
Hepatic cirrhosis	0	0	4 (0.8)
Varices oesophageal	0	0	4 (0.8)
Coma hepatic	0	0	3 (0.6)
Oedema due to hepatic disease	0	0	3 (0.6)
Hepatopulmonary syndrome	0	0	2 (0.4)
Liver abscess	0	0	2 (0.4)

DTC = differentiated thyroid cancer, EVE = everolimus, HCC = hepatocellular carcinoma, LEN = Lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.

a: Adverse event terms for the All DTC Safety Set and RCC Lenvatinib + Everolimus Safety Set were coded using MedDRA Version 23.0. Adverse event terms for the HCC Lenvatinib Safety Set were coded using MedDRA Version 19.1.

MedDRA Preferred Term[a]	**Safety Set, n (%)**	
	All EC Lenvatinib + Pembrolizumab N=530	**All RCC Lenvatinib + Pembrolizumab N=497**
Alanine aminotransferase increased	103 (19.4)	59 (11.9)
Aspartate aminotransferase increased	95 (17.9)	55 (11.1)
Blood bilirubin increased	32 (6.0)	20 (4.0)
Gamma-glutamyltransferase increased	21 (4.0)	14 (2.8)
Ascites	10 (1.9)	3 (0.6)
Hepatic function abnormal	8 (1.5)	8 (1.6)
Liver function test increased	-	6 (1.2)
Hepatotoxicity	5 (0.9)	-
Immune-mediated hepatitis	5 (0.9)	5 (1.0)
Transaminases increased	5 (0.9)	10 (2.0)
International normalised ratio increased	-	5 (1.0)
Bilirubin conjugated increased	4 (0.8)	-
Hyperbilirubinaemia	4 (0.8)	2 (0.4)
Encephalopathy	3 (0.6)	3 (0.6)
Hepatitis	3 (0.6)	-
Hepatocellular injury	3 (0.6)	-
Hypertransaminasaemia	3 (0.6)	4 (0.8)
Blood bilirubin unconjugated increased	2 (0.4)	-
Hepatic enzyme increased	2 (0.4)	-
Jaundice	2 (0.4)	-
Liver disorder	2 (0.4)	-
Metabolic encephalopathy	2 (0.4)	-
Drug-induced liver injury	-	2 (0.4)

Hepatic failure	-	2 (0.4)

EC = endometrial carcinoma, RCC = renal cell carcinoma.
a: Adverse event terms were coded using MedDRA Version 23.0.

All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs for liver events (SGQ) were reported in 24.0% of subjects (n=110). The most frequently reported TEAEs for liver events were hypoalbuminemia (8.3%) and elevations of liver enzyme levels.

RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs for liver events (SGQ) were reported in 20.9% of subjects (n=130). The most frequently reported TEAEs for liver events were alanine aminotransferase increased (11.9%) and aspartate aminotransferase (11.4%).

HCC Lenvatinib Safety Set (N=496) Treatment-emergent AEs for liver events (SGQ) were reported in 47.6% of subjects (n=236). The most frequently reported TEAEs for liver events were blood bilirubin increased and ascites (both 14.3%), aspartate aminotransferase increased (13.7%), and alanine aminotransferase increased (11.1%).

All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for hepatotoxicity (SGQ) were reported in 26.0% of subjects (n=129). The most frequently reported TEAEs for hepatotoxicity were elevations of liver enzyme levels.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs for hepatotoxicity were reported in 31.7% of subjects (n=168). The most frequently reported TEAEs for liver events were alanine aminotransferase increased (19.4%), aspartate aminotransferase increased (17.9%), and blood bilirubin increased (6.0%).

Post-authorisation liver events have been in accordance with the safety profile of lenvatinib in clinical trials.

- Seriousness/outcomes

All DTC Lenvatinib Safety Set (N=458): Serious AEs for liver events were reported in only 1.3% of subjects (n=6) with 1 fatal outcome (death due to hepatic failure related to disease progression). No SAEs for liver events occurred in more than 2 subjects. Serious AEs included alanine aminotransferase increased (n=2), aspartate aminotransferase increased (n=2), blood alkaline phosphatase increased (n=1), hepatic failure (n=1), hepatic function abnormal (n=1), hepatocellular injury (n=1), and liver injury (n=1).

The majority of liver events reported were reversible and resolved with dose interruption or reduction.

RCC Lenvatinib + Everolimus Safety Set (N=623): There were 7 SAEs due to liver events, one of which was Grade 5 in severity. No SAEs occurred in more than 2 subjects.

HCC Lenvatinib Safety Set (N=496): There were 73 SAEs due to liver events, the most frequently reported were hepatic encephalopathy (n=23, 4.6%), hepatic failure (n=14, 2.8%) and ascites (n=12, 2.4%), and 17 subjects experienced TEAEs with fatal outcome. The most common fatal TEAEs were hepatic failure (n=13, 2.6%) and portal vein thrombosis (n=2, 0.4%).

All RCC Lenvatinib + Pembrolizumab (N=497): Serious AEs for hepatotoxicity were reported in 3.0% of subjects (n=15) with 2 fatal outcomes (1 death due to autoimmune hepatitis and another due to hepatic failure). Serious AEs for hepatotoxicity events which occurred in more than 2 subjects were immune-mediated hepatitis (n=5, 1.0%) and encephalopathy (n=3, 0.6%). Other SAEs included alanine aminotransferase increased (n=1), aspartate aminotransferase increased (n=1), autoimmune hepatitis (n=1), blood bilirubin increased (n=1),

drug-induced liver injury (n=1), hepatic function abnormal (n=1), transaminases increased (n=1), ascites (n=1) and hepatic failure (n=1).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There were 21 subjects with reported SAEs of hepatotoxicity; the most frequently reported were encephalopathy and ascites (0.6%, n=3 for each event), and hepatitis, hepatic function abnormal, immune-mediated hepatitis and liver disorder (0.4%, n=2 for each event). One subject (0.2%) had a fatal event of metabolic encephalopathy.

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458): Most TEAEs for liver events were of Grade 1 or 2 and only 1 led to permanent discontinuation of treatment. Liver events of Grade 3 or higher occurred in 5.2% of subjects.

RCC Lenvatinib + Everolimus Safety Set (N=623): Most TEAEs for liver events were of Grade 1 or 2, and 5 led to permanent discontinuation of treatment. Liver events of Grade 3 or higher occurred in 6.1% of subjects.

HCC Lenvatinib Safety Set (N=496): The majority of hepatotoxicity events were Grade 3 (18.5%, n=92). A total of 18 subjects (3.6%) had Grade 4 hepatotoxicity and 17 subjects (3.4%) had Grade 5 hepatotoxicity.

All RCC Lenvatinib + Pembrolizumab (N=497): Most TEAEs for hepatotoxicity events were of Grade 1 or 2. Hepatotoxicity events of Grade 3 or higher occurred in 8.0% of subjects. Treatment was permanently discontinued in 4 subjects (0.8%) due to hepatotoxicity events.

A number of immune-mediated hepatitis events including autoimmune hepatitis (6 subjects; all Grade ≥3 events) were reported in the All RCC Lenvatinib + Pembrolizumab Safety Set whereas none were reported in the Lenvatinib Monotherapy Safety Set (N=1119).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): The majority of hepatotoxicity events were Grade 1 (12.1%, n=64). A total of 58 subjects (10.9%) had Grade 3 events of hepatotoxicity; 6 subjects (1.1%) had Grade 4 hepatotoxicity and 1 subject (0.2%) had Grade 5 hepatotoxicity.

Overview of Liver Events

For Liver Events-SGQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	110 (24.0)	130 (20.9)	236 (47.6)
TEAE, no. of episodes (episodes/SY)	234 (0.38)	N/A	659 (1.94)
TEAE with maximum CTCAE Grade of [b], n (%)			
1	40 (8.7)	58 (9.3)	47 (9.5)
2	45 (9.8)	34 (5.5)	62 (12.5)
3	24 (5.2)	36 (5.8)	92 (18.5)
4	0	1 (0.2)	18 (3.6)
5	1 (0.2)	1 (0.2)	17 (3.4)
SAE	6 (1.3)	7 (1.1)	73 (14.7)
TEAE leading to treatment discontinuation, n (%)	1 (0.2)	5 (0.9)[d]	27 (5.4)
TEAE leading to study drug modification [c], n (%)			
Reduction	13 (2.8)	15 (2.8)[d]	36 (7.3)
Interruption	19 (4.1)	22 (4.2)[d]	58 (11.7)

For each row category, a subject with 2 or more adverse events in that category is counted only once.

CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, N/A = not applicable, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma, SGQ = sponsor-generated query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

Overview of Liver Events		
For Liver Events-SGQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**All RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	168 (31.7)	129 (26.0)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	64 (12.1)	47 (9.5)
2	39 (7.4)	42 (8.5)
3	58 (10.9)	32 (6.4)
4	6 (1.1)	6 (1.2)
5	1 (0.2)	2 (0.4)
SAE	21 (4.0)	15 (3.0)
TEAE leading to lenvatinib discontinuation, n (%)	9 (1.7)	4 (0.8)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	16 (3.0)	19 (3.8)
Lenvatinib drug interruption	29 (5.5)	35 (7.0)

For each row category, a subject with 2 or more adverse events in that category is counted only once.

CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, RCC = renal cell carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Risk factors and risk groups:

Because of the high prevalence of cirrhosis in HCC, this patient group is predisposed to higher incidences of hepatotoxic events compared with other indications.

In other indications, multiple confounding factors were observed in subjects in the clinical trial program, such as the presence of liver metastases or progression of preexisting liver metastases, concurrent medications, and contributing comorbidities. However, there were a few cases without any confounding factors, that occurred shortly after the start of treatment with lenvatinib and that resolved upon discontinuation of lenvatinib. Therefore, causality secondary to the administration of lenvatinib cannot be ruled out.

Combination with Pembrolizumab

	Pembrolizumab is a humanised monoclonal antibody which may trigger immune-related reactions. Hepatitis events including those of autoimmune hepatitis, immune-mediated hepatitis, drug induced liver injury and acute hepatitis are ADRs of pembrolizumab (Keytruda SmPC).
Preventability	Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures have been put in place.
Public health impact:	If hepatic failure occurred, it could have a significant impact on an individual patient, however, with the proposed monitoring and dose adjustment schedule the risk of this event is low in the setting of DTC and RCC; however, the risk is higher in HCC due to the high prevalence of liver cirrhosis.

Identified Risk: Haemorrhagic Events

Potential mechanisms:

VEGF/VEGFR-targeted antiangiogenesis agents can be associated with bleeding and haemorrhage including tumour bleeding (Chen and Cleck, 2009). Two distinctive types of bleeding have been described: mild spontaneous mucocutaneous bleeding and serious tumour-related bleeding.

Inhibition of VEGF could diminish the regenerative capacity of endothelial cells and cause defects that expose pro-coagulant phospholipids on the luminal plasma membrane or underlying matrix, leading to haemorrhage or thrombosis (Kilickap, et al., 2003). VEGF increases production of NO and prostacyclin (PGI2, prostaglandin I2), suppresses pathways involved in endothelial cell activation, apoptosis, and pro-coagulant changes, and inhibits proliferation of vascular smooth muscle cells (Zachary, 2001). However, endothelial cell defects alone are unlikely to explain life-threatening haemorrhage in patients on VEGF/VEGFR-targeted therapy for squamous cell lung cancer and certain other solid tumours. Rather, weakening of the wall of major vessels by tumour erosion, necrosis, cavitation, or other concurrent pathological conditions are likely to play a central role (Kamba and McDonald, 2007).

Evidence source(s) and strength of evidence:

Evidence from randomised clinical trials. In randomised clinical trials, haemorrhage was reported in more patients treated with lenvatinib than placebo.

Characterisation of the risk:

- Frequency

Events reported in 2 or more subjects in any of the safety sets were as follows:

MedDRA Preferred Term[a]	Safety Sets, n (%)		
	All DTC N=458	RCC Len+Eve N=623	HCC N=496
Epistaxis	75 (16.4)	121 (19.4)	38 (7.7)
Haemoptysis	33 (7.2)	10 (1.6)	9 (1.8)
Haematuria	29 (6.3)	26 (4.2)	26 (5.2)
Contusion	14 (3.1)	11 (1.8)	3 (0.6)
Haematochezia	9 (2.0)	6 (1.0)	2 (0.4)
Gingival bleeding	7 (1.5)	7 (1.1)	20 (4.0)
Rectal haemorrhage	7 (1.5)	4 (0.6)	5 (1.0)
Petechiae	6 (1.3)	2 (0.3)	2 (0.4)

Pulmonary haemorrhage	6 (1.3)	2 (0.3)	0
Blood urine present	5 (1.1)	0	4 (0.8)
Haematoma	5 (1.1)	6 (1.0)	0
Vaginal haemorrhage	5 (1.1)	3 (0.5)	0
Conjunctival haemorrhage	3 (0.7)	0	1 (0.2)
Haemorrhoidal haemorrhage	3 (0.7)	2 (0.3)	6 (1.2)
Intracranial tumour haemorrhage	3 (0.7)	0	1 (0.2)
Laryngeal haemorrhage	3 (0.7)	0	0
Purpura	3 (0.7)	3 (0.5)	2 (0.4)
Ecchymosis	2 (0.4)	2 (0.3)	1 (0.2)
Increased tendency to bruise	2 (0.4)	0	0
Skin haemorrhage	2 (0.4)	1 (0.2)	0
Gastric haemorrhage	1 (0.2)	2 (0.3)	1 (0.2)
Upper gastrointestinal haemorrhage	0	3 (0.5)	5 (1.0)
Anal haemorrhage	0	2 (0.3)	0
Disseminated intravascular coagulation	0	2 (0.3)	0
Oesophageal varices haemorrhage	0	0	8 (1.6)
Mouth haemorrhage	0	2 (0.3)	5 (1.0)
Petechiae	0	2 (0.3)	0
Eye contusion	0	2 (0.3)	0
Gastric haemorrhage	0	2 (0.3)	0
Cerebral haemorrhage	0	1 (0.2)	3 (0.6)
Duodenal ulcer haemorrhage	0	0	3 (0.6)
Tumour haemorrhage	0	0	3 (0.6)
Haematemesis	0	0	2 (0.4)

DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, Len + Eve = lenvatinib + everolimus, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma

a: Adverse event terms for the All DTC Safety Set and RCC Lenvatinib + Everolimus Safety Set were coded using MedDRA Version 23.0. Adverse event terms for the HCC Lenvatinib Safety Set were coded using MedDRA Version 19.1.

MedDRA Preferred Term[a]	**Safety Set, n (%)**	
	All EC Lenvatinib + Pembrolizumab N=530	**All RCC Lenvatinib + Pembrolizumab N=497**
Epistaxis	46 (8.7)	46 (9.3)
Vaginal haemorrhage	27 (5.1)	-
Haematuria	22 (4.2)	29 (5.8)
Gingival bleeding	8 (1.5)	16 (3.2)
Metrorrhagia	7 (1.3)	-
Contusion	6 (1.1)	23 (4.6)
Rectal haemorrhage	6 (1.1)	12 (2.4)
Ecchymosis	-	6 (1.2)
Uterine haemorrhage	5 (0.9)	
Haematochezia	4 (0.8)	6 (1.2)
Gastrointestinal haemorrhage	3 (0.6)	-
Haemorrhage intracranial	3 (0.6)	-
Lower gastrointestinal haemorrhage	3 (0.6)	-
Mouth haemorrhage	3 (0.6)	-
Petechiae	3 (0.6)	4 (0.8)

Anal haemorrhage	-	3 (0.6)
Haemorrhoidal haemorrhage	-	3 (0.6)
Cerebral haemorrhage	2 (0.4)	-
Conjunctival haemorrhage	2 (0.4)	-
Haematoma	2 (0.4)	4 (0.8)
Haemoptysis	2 (0.4)	9 (1.8)
Haemorrhage urinary tract	2 (0.4)	-
Injection site haemorrhage	2 (0.4)	-
Purpura	2 (0.4)	-
Upper gastrointestinal haemorrhage	2 (0.4)	2 (0.4)
Gastric haemorrhage	-	2 (0.4)
Haematemesis	-	2 (0.4)
Renal haemorrhage	-	2 (0.4)
Tumour haemorrhage	-	2 (0.4)
Increased tendency to bruise	-	2 (0.4)
Small intestinal haemorrhage	-	2 (0.4)
Subarachnoid haemorrhage	-	2 (0.4)

EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.
a: Adverse event terms were coded using MedDRA Version 23.0.

All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs for haemorrhage (SMQ) occurred in 40.4% of subjects.

RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs for haemorrhage (SMQ) were reported in 28.6% of subjects (n=178).

HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs for haemorrhage (SMQ) were reported in 25.6% of subjects (n=127).

In all safety sets the most commonly reported TEAE related to haemorrhage was epistaxis (16.4%, 19.4%, 7.7% and 8.7% in the All DTC Lenvatinib Safety Set, RCC Lenvatinib + Everolimus Safety Set, HCC Lenvatinib Safety Set, and All EC Lenvatinib + Pembrolizumab Safety Set, respectively).

All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for haemorrhage (SMQ) occurred in 29.4% of subjects. The most commonly reported TEAE related to haemorrhage was epistaxis (9.3%).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs for haemorrhage (SMQ) were reported in 26.0% of subjects (n=138).

Post-authorisation events of haemorrhage have been in accordance with the safety profile of lenvatinib in clinical trials.

- Seriousness/outcomes

All DTC Lenvatinib Safety Set (N=458): Three deaths were reported for haemorrhage (arterial haemorrhage, haemorrhagic stroke, and intracranial tumour haemorrhage). There was no evidence of progressive disease and lenvatinib was stopped in all 3 cases. The majority of intracranial haemorrhagic events were associated with tumour bleeding.

Serious AEs for haemorrhage were reported in 4.4% of subjects (n=20), and the majority of haemorrhagic SAEs occurred in 1 subject each. The most frequently reported SAE was intracranial tumour haemorrhage (3 subjects).

Across the pooled analysis of safety data from clinical trials with lenvatinib (including 458 patients with RAI-refractory DTC and 656 patients with other tumour types), 3 patients (0.3%) had a Grade 4 haemorrhage (1 event of pulmonary haemorrhage and 2 events of subarachnoid haemorrhage), and 5 patients (0.4%) had a Grade 5 event including the 3 RAI-refractory DTC patients

discussed above, and 2 patients with other forms of cancer who experienced haemoptysis and tumour haemorrhage.

RCC Lenvatinib + Everolimus Safety Set: Serious AEs were reported in 3.2% of subjects (n=20). There were 4 fatal events due to pulmonary haemorrhage, haemorrhage intracranial, cerebral haemorrhage, and upper gastrointestinal haemorrhage.

HCC Lenvatinib Safety Set (N=496): Serious AEs for haemorrhage were reported in 5.0% of subjects (n=25) and the most common SAEs were oesophageal varices haemorrhage (1.4%, n=7) and upper gastrointestinal haemorrhage (1.0%, n=5). Seven subjects died due to haemorrhagic events, most commonly cerebral haemorrhage (n=3).

All RCC Lenvatinib + Pembrolizumab (N=497): Four deaths were reported due to ruptured aneurysm, subarachnoid haemorrhage, intracranial tumour haemorrhage and upper gastrointestinal haemorrhage. Serious AEs for haemorrhage were reported in 4.6% of subjects (n=23), and the majority of haemorrhagic SAEs occurred in 1 subject each. The most frequently reported SAEs were haematemesis, tumour haemorrhage, small intestinal haemorrhage, subarachnoid haemorrhage and upper gastrointestinal haemorrhage (n=2 subjects for each event).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): SAEs for haemorrhage SMQ were reported in 4.2 % of subjects (n=22) with the most common SAEs were epistaxis, gastrointestinal haemorrhage, vaginal haemorrhage and haemorrhage intracranial (0.6%, n=3 for each event). Three subjects died due to vaginal haemorrhage, lower gastrointestinal haemorrhage and haemorrhage intracranial (0.2%, n=1 for each event).

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458): The majority of the events for haemorrhage were mild (Grade 1). However, 2 subjects had Grade 4 haemorrhage and 3 subjects had a Grade 5 event. Lenvatinib treatment was discontinued due to haemorrhage for 7 subjects.

RCC Lenvatinib + Everolimus Safety Set (N=623): The majority of TEAEs for haemorrhage were Grade 1. There were no Grade 4 events and 4 Grade 5 events. Lenvatinib treatment was discontinued due to haemorrhage in 3 subjects.

HCC Lenvatinib Safety Set (N=496): The majority of TEAEs for haemorrhage were Grade 1. There was 1 Grade 4 event and 7 Grade 5 events. Lenvatinib treatment was discontinued in 8 subjects.

All RCC Lenvatinib + Pembrolizumab (N=497): The majority of the events for haemorrhage were mild (Grade 1). No Grade 4 events were reported; however, 4 subjects had a Grade 5 event. Treatment was discontinued in 6 subjects due to haemorrhage.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): The majority of TEAEs for haemorrhage SMQ were Grade 1 (17.9%, n=95). There were 3 Grade 4 events (0.6%) and 3 Grade 5 events (0.6%). Lenvatinib treatment was discontinued in 12 subjects due to any event of haemorrhage SMQ.

For Haemorrhage-SMQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	185 (40.4)	178 (28.6)	127 (25.6)
TEAE, no. of episodes (episodes/SY)	320 (0.53)	N/A	189 (0.56)

TEAE with maximum CTCAE Grade of [b], n (%)			
1	143 (31.2)	131 (21.0)	80 (16.1)
2	29 (6.3)	26 (4.2)	23 (4.6)
3	8 (1.7)	16 (2.6)	16 (3.2)
4	2 (0.4)	0	1 (0.2)
5	3 (0.7)	4 (0.6)	7 (1.4)
SAE	20 (4.4)	20 (3.2)	25 (5.0)
TEAE leading to treatment discontinuation, n (%)	7 (1.5)	3 (0.6)[d]	8 (1.6)
TEAE leading to study drug modification [c], n (%)			
Reduction	2 (0.4)	4 (0.8)[d]	4 (0.8)
Interruption	19 (4.1)	22 (4.2)[d]	16 (3.2)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, N/A = not applicable, RCC = renal cell carcinoma, SMQ = standard MedDRA query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

Overview of Haemorrhage Events		
For Haemorrhage-SMQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**ALL RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	138 (26.0)	146 (29.4)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	95 (17.9)	110 (22.1)
2	25 (4.7)	13 (2.6)
3	12 (2.3)	19 (3.8)
4	3 (0.6)	0 (0.0)
5	3 (0.6)	4 (0.8)
SAE	22 (4.2)	23 (4.6)
TEAE leading to lenvatinib discontinuation, n (%)	12 (2.3)	6 (1.2)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	6 (1.1)	2 (0.4)
Lenvatinib drug interruption	15 (2.8)	15 (3.0)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

	b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade. c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
Risk factors and risk groups:	The incidence of haemorrhagic events with TKIs varies significantly among patients with different types of tumours. The highest relative risks (RRs) of all grade haemorrhagic events were observed in patients with gastrointestinal stromal tumour (RR, 14.71; 95% CI: 0.89 – 244.21), although the increased risk was not statistically significant, while the lowest RRs were found in patients with small-cell lung cancer (RR, 0.51; 95% CI: 0.10 – 2.66). Additionally, a significantly increased risk of all-grade haemorrhagic events was observed in metastatic breast cancer (RR, 4.04; 95% CI: 2.62 – 6.20), RCC (RR, 2.45; 95% CI: 1.35 – 4.45) and primitive neuroectodermal tumour (RR, 4.20, 95% CI: 1.48 – 11.95). As for high-grade haemorrhagic events, the highest RRs were observed in patients with melanoma (RR, 6.73; 95% CI: 0.83 – 54.5), while the lowest RRs were observed in patients with non-small-cell lung carcinoma (RR, 0.51; 95% CI: 0.24 – 1.09) (Qi, et al., 2013a). In patients with chronic liver disease, the risk of post-procedure bleeding for so-called minimally invasive procedures is approximately 20% (Caldwell, 2014). The majority of intracranial haemorrhagic events in the lenvatinib clinical database were associated with the presence of tumour in the area of the bleed. These events were also often associated with the confounding factor of hypertension. Fatal intracranial haemorrhagic events were observed in subjects with or without brain metastasis..
Preventability	In the case of bleeding, dose interruptions, adjustments, or permanent discontinuation may be necessary.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures have been put in place. The impact of haemorrhage on the individual patient would depend on the site and severity of bleeding.
Public health impact:	Not identified

Identified Risk: Arterial Thromboembolic Events (ATEs)	
Potential mechanisms:	Arterial thromboembolic events are well known side effects associated with treatment with TKIs (Chen and Cleck, 2009). Accelerated atherogenesis and thrombogenesis is purported to be triggered by drug-induced endothelial damage, which leads to cellular apoptosis and the formation of atherosclerotic plaques, which shifts the endothelium to have procoagulant properties by exposing subendothelial factors and Von Willebrand factor, which activated the coagulation cascade (Conti, et al., 2013). Inhibition of VEGF could diminish the regenerative capacity of endothelial cells and cause defects that expose pro-coagulant phospholipids on the luminal plasma membrane or underlying matrix, leading to thrombosis (Kilickap, et al., 2003). Reduction in NO and PGI2 after inhibition of VEGF signaling may predispose to thromboembolic events. VEGF inhibition may also increase risk of thrombosis by increasing hematocrit and blood viscosity via overproduction of erythropoietin (Spivak, 2002; Tam, et al., 2006).
Evidence source(s) and strength of evidence:	Evidence from randomised clinical trials. In randomised clinical trials ATEs were reported in more patients treated with lenvatinib than placebo.
Characterisation of the	• Frequency

risk:	All DTC Lenvatinib Safety Set (N=458): treatment-emergent AEs for ATEs (SGQ) were reported in 25 subjects (5.5%) and included events of cerebrovascular accident (1.1%), monoparesis (0.9%), transient ischemic attack (0.9%), acute myocardial infarction (0.4%), coronary artery occlusion (0.4%), hemiplegia (0.4%), intracardiac thrombus (0.4%), myocardial infarction (0.4%), splenic infarction (0.4%), cerebral ischemia (0.2%), hemiparesis (0.2%), intracardiac thrombus (0.2%), ischemic stroke (0.2%), mesenteric artery thrombosis (0.2%), monoplegia (0.2%), and peripheral arterial occlusive disease (0.2%). RCC Lenvatinib + Everolimus Safety Set (N=623). Treatment –emergent AEs for ATEs (SGQ) were reported in 17 subjects (2.7%) and included events of myocardial infarction (1.0%), transient ischemic attack (0.3%), cerebrovascular accident (0.3%), acute myocardial infarction (0.3%), and intracardiac thrombus, ischaemic stroke, paraparesis, paraplegia, postinfarction angina, aortic thrombosis, and coronary artery occlusion (0.2%, n=1 for each event). HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs for ATEs (SGQ) were reported in 11 subjects (2.2%) and included events of myocardial infarction (0.8%), cerebral infarction (0.6%), cerebrovascular accident (0.4%), diplegia, renal infarct, and transient ischaemic attack (0.2% each). All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for ATEs SGQ were reported in 27 subjects (5.4%) and included events of myocardial infarction (2.0%), acute myocardial infarction (1.2%), transient ischemic attack (0.6%), cerebrovascular accident (0.4%), and carotid artery occlusion, cerebral ischemia, hemiplegia, arterial embolism, intracardiac thrombus and mesenteric artery thrombosis (0.2%, n=1 for each event). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs for ATEs (SGQ) were reported in 21 subjects (4.0%) and included events of transient ischaemic attack (0.8%, n=4), and acute myocardial infarction, cerebral infarction, and cerebrovascular accident (0.6%, n=3 for each event). Post-authorisation ATEs have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes All DTC Lenvatinib Safety Set (N=458): There was 1 death due to TEAEs for ATEs (myocardial infarction). There were also 3 deaths (2 cerebrovascular accidents and 1 myocardial infarction) in the Non DTC Monotherapy Safety Set. Serious AEs for ATEs were reported in 3.9% of subjects (18/458). The SAEs for ATEs reported in more than 1 subject included cerebrovascular accident (n=5), transient ischemic attack (n=3), acute myocardial infarction (n=2), coronary artery occlusion (n=2), monoparesis (n=2), and myocardial infarction (n=2). RCC Lenvatinib + Everolimus Safety Set: Serious AEs for ATEs were reported in 15 subjects (2.4%). The SAEs reported in more than 1 subject included myocardial infarction (n=6), transient ischaemic attack (n=2), cerebrovascular accident (n=2), and acute myocardial infarction (n=2). There were 2 fatal events of ATEs; 1 subject had a fatal event of myocardial infarction and another subject had a fatal event of cerebrovascular accident. HCC Lenvatinib Safety Set (N=496): Serious AEs for ATEs were reported in 10 subjects (2.0%). The SAEs for ATEs reported in more than 1 subject included myocardial infarction (n=4), cerebral infarction (n=2), and cerebrovascular accident (n=2). All RCC Lenvatinib + Pembrolizumab (N=497): There were no deaths due to ATEs SGQ. Serious AEs for ATEs were reported in 4.0% of subjects (n=20). The SAEs for ATEs reported in more than 1 subject included myocardial infarction (n=9), acute myocardial infarction (n=5), cerebrovascular accident

(n=2) and transient ischaemic attack (n=2).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): SAEs for ATEs SGQ were reported in 14 subjects (2.6%). The SAEs reported in more than 1 subject included transient ischaemic attack (n=3), acute myocardial infarction (n=3), myocardiac infarction (n=2) and cerebrovascular accident (n=2). There were 2 fatal events of ATEs; 1 subject had a fatal event of acute myocardial infarction and another subject had a fatal event of cerebrovascular accident.

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs of Grade 3 or higher for ATEs occurred in 3.1% of subjects. There was 1 Grade 4 event of acute myocardial infarction and 1 Grade 5 event of myocardial infarction. One subject (0.2%) had a TEAE for ATE that led to dose reduction and in 5 subjects (1.1%) lenvatinib treatment had to be discontinued.

RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs were reported in 17 subjects (2.7%). There were 2 deaths, 8 treatment discontinuations, and 3 dose interruptions due to ATEs.

HCC Lenvatinib Safety Set (N=496): A total of 7 subjects discontinued study drug, 2 subjects had dose reduction, and 4 subjects had dose interruption due to ATE. Treatment-emergent AEs of Grade 3 or higher for ATEs occurred in 1.8% of subjects (n=9) of which three subjects died.

All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs of Grade 3 or higher for ATEs occurred in 3.8% of subjects. Five subjects had Grade 4 events (myocardial infarction in 3 subjects and acute myocardial infarction in 2 subjects). Two subjects (0.4%) had TEAEs for ATEs SGQ that led to dose reduction and 5 subjects (1.0%) had TEAEs for ATEs that led to dose interruption. Treatment was discontinued in 14 subjects (2.8%).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): TEAEs of Grade 3 or higher for ATEs occurred in 2.3% of subjects (n=12). Two subjects (0.4%) had Grade 4 events of acute myocardial infarction and cerebral infarction and 2 subjects had Grade 5 events of acute myocardial infarction and cerebrovascular accident. One subject (0.2%) had a TEAE for ATE SGQ that led to lenvatinib dose reduction and 3 subjects (0.6%) had TEAEs that led to lenvatinib interruption. Lenvatinib treatment was discontinued in 8 subjects (1.5%).

Overview of ATEs (SGQ)

For ATEs-SGQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	25 (5.5)	17 (2.7)	11 (2.2)
TEAE, no. of episodes (SY)	33 (0.05)	N/A	12 (0.04)
TEAE with maximum CTCAE Grade of[b], n (%)			
1	5 (1.1)	1 (0.2)	1 (0.2)
2	6 (1.3)	2 (0.3)	1 (0.2)
3	12 (2.6)	11 (1.8)	5 (1.0)
4	1 (0.2)	1 (0.2)	1 (0.2)
5	1 (0.2)	2 (0.3)	3 (0.6)
SAE	18 (3.9)	15 (2.4)	10 (2.0)
TEAE leading to treatment discontinuation, n (%)	5 (1.1)	8 (1.5)[d]	7 (1.4)
TEAE leading to study drug modification[c], n (%)			
Reduction	1 (0.2)	0[d]	2 (0.4)

Interruption	10 (2.2)	3 (0.6)[d]	4 (0.8)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, ATE = arterial thromboembolic event, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, N/A = not applicable, RCC = renal cell carcinoma, SGQ = sponsor-generated query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

Overview of ATEs (SGQ)

For ATEs-SGQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**ALL RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	21 (4.0)	27 (5.4)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	6 (1.1)	1 (0.2)
2	3 (0.6)	7 (1.4)
3	8 (1.5)	14 (2.8)
4	2 (0.4)	5 (1.0)
5	2 (0.4)	0 (0.0)
SAE	14 (2.6)	20 (4.0)
TEAE leading to lenvatinib discontinuation, n (%)	8 (1.5)	14 (2.8)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	1 (0.2)	2 (0.4)
Lenvatinib drug interruption	3 (0.6)	5 (1.0)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
ATE = arterial thromboembolic event, CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor generated query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatments-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Risk factors and risk groups:

Risk factors associated with thromboembolic events in addition to the underlying malignant disease include age ≥65 years, smoking, hypertension, diabetes mellitus, obesity, atrial fibrillation, hyperlipidemia, and prior thromboembolic disease. Lenvatinib has not been studied in patients who have had an ATE within the previous 6 months.

Although there are cases with prior medical history of hypertension, obesity, hypercholesterolemia, and smoking that could predispose them to ATEs, and

	some cases were assessed as not related to lenvatinib, a causal relationship to lenvatinib may exist. This is consistent with the reported side effect profile of the VEGF/VEGFR-targeted agents (Chen and Cleck, 2009). RCC Subjects with RCC are predominantly older, overweight males with underlying risk factors of hypercholesterolemia, dyslipidaemia, hypertension and diabetes mellitus, all of which are known risk factors associated with thromboembolic events. Additionally, RCC subjects are at a higher risk of developing chronic kidney disease, which is independently associated with increased cardiovascular risk due to dysregulation of lipid metabolism and contribution to atherosclerosis. (Chang et al., 2014; Ferro et al., 2018).
Preventability	There are no established data on prevention to date, except for vigilance by review and collection of patient history, CV risk profile, and scores, and measuring and monitoring cardiac ischemia blood markers (Conti, et al., 2013). Risk factors associated with thromboembolic events include age ≥65 years, smoking, hypertension, diabetes mellitus, obesity, atrial fibrillation, hyperlipidemia, and prior thromboembolic disease. Lenvatinib has not been studied in patients who have had an ATE within the previous 6 months.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures in place.
Public health impact:	This event could have a significant impact on the individual patient's quality of life; however, with the proposed monitoring and dose adjustment schedule the risk of this event is low.

Identified Risk: QTc Prolongation	
Potential mechanisms:	QTc prolongation has been observed with other VEGF/VEGFR-targeted therapies (Chen and Cleck, 2009). Although other mitigating factors may have contributed to the QTc prolongation per SMQ, including prior history (eg, hypertension, hyperglycemia, and thyroid disease) and electrolyte alterations, there does appear to be an association of QTc prolongation and the administration of lenvatinib.
Evidence source(s) and strength of evidence:	Evidence from randomised clinical trials. In randomised clinical trials, QT/QTC prolongation was reported in more patients treated with lenvatinib than placebo.
Characterisation of the risk:	• Frequency All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs for QTc prolongation per SMQ analysis were reported in 12.2% of subjects (n=56). RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs for QTc prolongation per SMQ analysis were reported in 3.5% of subjects (n=22). HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs for QTc prolongation per SMQ analysis were reported in 6.7% of subjects (n=33). All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for QTc prolongation were reported in 5.6% of subjects (n=26). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs for QTc prolongation per SMQ analysis were reported in 4.5% of subjects (n=24). Post-authorisation events of QTc prolongation have been in accordance with the

safety profile of lenvatinib in clinical trials.

- Seriousness/outcomes

All DTC Lenvatinib Safety Set (N=458): Grade 3 QTc prolongation events occurred in 3.3% of subjects (n=15) and Grade 4 events were reported in 0.2% of subjects (n=1). TEAEs of QTc prolongation with fatal outcome were recorded in 0.9% of subjects (n=4; cardiac arrest [1 subject], cardio-respiratory arrest [2 subjects], and sudden death [1 subject]). A total of 8 subjects (1.7%) had SAEs of QTc prolongation.

RCC Lenvatinib + Everolimus Safety Set (N=623): No serious events or deaths associated with QTc prolongation were reported.

HCC Lenvatinib Safety Set (N=496): There were no SAEs or deaths recorded due to QTc prolongation events.

All RCC Lenvatinib + Pembrolizumab (N=497): There were no SAEs or deaths recorded due to QTc prolongation events. Grade 3 QTc prolongation events occurred in 2.6% of subjects (n=13).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There was 1 SAE (0.2%) of QTc prolongation (electrocardiogram QT prolonged) reported which was considered related to study treatment.

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458):

Grade 4 occurrences of QTc prolongation were reported in 1 subject (0.2%). A higher percentage of subjects had TEAEs reported for QTc prolongation per SMQ that led to dose interruption (3.1%) than to dose reduction (0.4%). Three subjects (0.7%) discontinued treatment due to QTc prolongation.

Most events for QTc prolongation per SMQ were sporadic and resolved; there was no recurrence when the lenvatinib dose was reduced and no other intervention was required. Moreover, there were no reports of ventricular tachycardia or torsades de pointes in the lenvatinib clinical studies.

RCC Lenvatinib + Everolimus Safety Set (N=623):

No Grade 4 or 5 occurrences of QTc prolongation were reported, and no subjects discontinued treatment. Four subjects (0.8%) had TEAEs reported for QTc prolongation that led to dose interruption.

HCC Lenvatinib Safety Set (N=496):

Grade 3 QTc prolongation events occurred in 5 subjects (1.0%). No Grade 4 or Grade 5 events were recorded, and no subjects discontinued treatment. One subject required a dose reduction due to a QTc prolongation event.

All RCC Lenvatinib + Pembrolizumab (N=497): No Grade 4 or 5 occurrences of QTc prolongation were reported. One subject (0.2%) had TEAEs reported for QTc prolongation that led to dose reduction and 2 subjects (0.4%) had TEAEs reported for QTc prolongation that led to dose interruption. Treatment was discontinued in 1 subject (0.2%) due to QTc prolongation.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): No Grade 4 or Grade 5 events were reported and no subject discontinued lenvatinib treatment. Three subjects required a dose reduction and 3 subjects required a dose interruption due to a QTc prolongation event.

Overview of QTc Prolongation per SMQ Analysis			
For QTc Prolongation-SMQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**

TEAE, n (%)	56 (12.2)	22 (3.5)	33 (6.7)
TEAE, no. of episodes (episodes/SY)	83 (0.14)	N/A	45 (0.13)
TEAE with maximum CTCAE Grade of[b], n (%)			
1	23 (5.0)	11 (1.8)	23 (4.6)
2	13 (2.8)	5 (0.8)	5 (1.0)
3	15 (3.3)	6 (1.0)	5 (1.0)
4	1 (0.2)	0	0
5	4 (0.9)	0	0
SAE	8 (1.7)	0	0
TEAE leading to treatment discontinuation, n (%)	3 (0.7)	0[d]	
TEAE leading to study drug modification[c], n (%)			
Reduction	2 (0.4)	0[d]	1 (0.2)
Interruption	14 (3.1)	4 (0.8)[d]	0

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, N/A = not applicable, RCC = renal cell carcinoma, SMQ = standard MedDRA query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

Overview of QTc Prolongation per SMQ		
For QTc Prolongation-SMQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**ALL RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	24 (4.5)	28 (5.6)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	9 (1.7)	6 (1.2)
2	11 (2.1)	9 (1.8)
3	4 (0.8)	13 (2.6)
4	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)
SAE	1 (0.2)	0 (0.0)
TEAE leading to lenvatinib discontinuation, n (%)	0 (0.0)	1 (0.2)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	3 (0.6)	2 (0.4)
Lenvatinib drug interruption	3 (0.6)	1 (0.2)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell

	carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event. a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions). b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade. c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
Risk factors and risk groups:	Many subjects with QTc prolongation had prior identified risk factors such as hypocalcaemia, hypothyroidism, arterial hypertension, and obesity. Many subjects had electrolyte alterations (eg, hypocalcaemia, hypomagnesemia, and hypokalemia) or concurrent cardiovascular disease (eg, myocarditis, cardiomyopathy and acute cardiac failure) at the time of the QTc prolongation event. All occurrences of maximum QTc prolongation >500 ms and >60 ms increases in QTcF from baseline were single, isolated episodes. Moreover, a thorough QT study concluded that lenvatinib does not exert a clinically relevant effect on QTcF.
Preventability	Electrocardiograms (ECGs) should be monitored in patients with congenital long QT syndrome, CHF, or bradyarrhythmias, as well as in those receiving drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Electrolyte abnormalities should be monitored and corrected in all patients.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures in place.
Public health impact:	Not identified

Identified Risk: Hypothyroidism	
Potential mechanisms:	The precise mechanism of action of TKI-mediated thyroid dysfunction has not been fully elucidated. Many mechanisms have been proposed including their induction of thyroiditis, capillary regression in the thyroid gland, antithyroid peroxidase antibody production, and their ability to decrease iodine uptake by the thyroid gland (Ahmadieh and Salti, 2013). RCC/HCC Thyroid dysfunction is a known class effect of TKIs (Ahmadieh and Salti, 2013). Of note, subjects in the RCC Safety Set and HCC Safety Set had intact thyroids and the majority of subjects were not receiving thyroid replacement therapy; therefore, it appeared that lenvatinib had a direct effect on the thyroid gland. DTC Lenvatinib impairs TSH suppression in patients receiving exogenous thyroid hormone supplementation. In a study of the side effects of broad-acting TKIs, one mechanism to explain worsening TSH elevation in postthyroidectomy patients would be an indirect effect of TKI (sunitinib) on the metabolism of thyroid hormone, or with thyroid hormone action at the pituitary level. It is plausible that the different types of TKIs have more than one mechanism affecting thyroid functions, but it remains more likely that there is a universal drug class effect of these medications that has yet to be clarified (Lodish and Stratakis, 2010).

<table>
<tr><td>Evidence source(s) and strength of evidence:</td><td>Randomised clinical trials. In randomised clinical trials events of blood thyroid stimulating hormone increased were reported in more patients treated with lenvatinib than placebo and there were reports of hypothyroidism in patients treated with lenvatinib.</td></tr>
<tr><td>Characterisation of the risk:</td><td>

- Frequency

All-DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs related to hypothyroidism (SMQ) were reported in 11.4% of subjects (n=52). Events were reported as follows:

<table>
<tr><th rowspan="2">MedDRA Preferred Term[a]</th><th colspan="4">n (%)</th></tr>
<tr><th>All DTC

N=458</th><th>RCC Len+Eve
N=623</th><th>Non-Thyroid
N=584</th><th>HCC

N=496</th></tr>
<tr><td>Blood thyroid stimulating hormone increased</td><td>28 (6.1)</td><td>35 (5.6)</td><td>41 (7.0)</td><td>31 (6.3)</td></tr>
<tr><td>Hypothyroidism</td><td>24 (5.2)</td><td>150 (24.1)</td><td>104 (17.8)</td><td>79 (15.9)</td></tr>
<tr><td>Blood thyroid stimulating hormone abnormal</td><td>0</td><td>0</td><td>1 (0.2)</td><td>0</td></tr>
</table>

DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.

a: Adverse event terms for the All DTC Safety Set and RCC Lenvatinib + Everolimus Safety Set were coded using MedDRA Version 23.0. Adverse event terms for the HCC Lenvatinib Safety Set were coded using MedDRA Version 19.1.

Non-Thyroid Monotherapy Safety Set (N=584): Treatment-emergent AEs related to hypothyroidism (SMQ) were reported in 24.1% of subjects (n=141).

RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs related to hypothyroidism (SMQ) were reported in 29.1% of subjects (n=181).

HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs related to hypothyroidism (SMQ) were reported in 22.0% of subjects (n=109).

All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for hypothyroidism were reported in 268 subjects (53.9%). These included hypothyroidism in 45.1% of subjects (n=224) and increased blood thyroid stimulating hormone in 10.5% of subjects (n=52).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs related to hypothyroidism (SMQ) were reported in 64.3% of subjects (n=341).

Post-authorisation events of hypothyroidism have been in accordance with the safety profile of lenvatinib in clinical trials.

- Seriousness/outcomes

All DTC Lenvatinib Safety Set (N=458): There were no SAEs reported and no subjects required study drug dose modification or discontinuation.

Non-Thyroid Monotherapy Safety Set (N=584): SAEs were reported in 0.7% of subjects (n=4).

RCC Lenvatinib + Everolimus Safety Set (N=623): Serious AEs were reported in 2 subjects (0.3%), and no subjects discontinued study drug. However, 5 subjects (0.9%) required dose interruption and 2 subjects (0.4%) required dose reduction due to hypothyroidism events.

HCC Lenvatinib Safety Set (N=496): There were no SAEs reported and no subjects discontinued study drug; however, 1 subject (0.2%) required dose interruption due to hypothyroidism.

All RCC Lenvatinib + Pembrolizumab (N=497): There were no SAEs or deaths reported due to hypothyroidism events. Grade 3 hypothyroidism events occurred in

</td></tr>
</table>

1.0% of subjects (n=5).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There were SAEs of hypothyroidism SMQ reported in 3 subjects (0.6%); no subjects discontinued lenvatinib treatment. However, 11 subjects (2.1%) required lenvatinib interruption and 4 subjects (0.8) required lenvatinib dose reduction due to hypothyroidism events.

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs of hypothyroidism were all Grade 1 or Grade 2.

Non-Thyroid Monotherapy Safety Set (N=584): Treatment-emergent AEs related to Hypothyroidism (SMQ) were mainly Grade 1 or Grade 2. Grade 3 Hypothyroidism was reported in 1.4% of subjects (n=8).

RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs related to hypothyroidism (SMQ) were mostly Grade 1 or Grade 2. Grade 3 hypothyroidism was reported in 0.5% of subjects (n=3).

HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs related to hypothyroidism (SMQ) were all Grade 1 or Grade 2.

All RCC Lenvatinib + Pembrolizumab (N=497): No Grade 4 or 5 occurrences of hypothyroidism were reported. Five subjects (1.0%) had TEAEs reported for hypothyroidism events that led to dose reduction and 6 subjects (1.2%) had TEAEs reported for hypothyroidism events that led to dose interruption. Treatment was discontinued in 1 subject (0.2%) due to hypothyroidism.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs of hypothyroidism (SMQ) were mainly Grade 1 or Grade 2. Grade 3 events of hypothyroidism were reported in 0.9% of subjects (n=5) and Grade 4 events were reported in 0.2% of subjects (n=1).

Overview of Hypothyroidism

For (SMQ Analysis/Term), subjects with at least 1:	**Safety Sets**			
	All DTC Lenvatinib	**Non-Thyroid Monotherapy Lenvatinib**	**RCC Lenvatinib + Everolimus**	**HCC Lenvatinib**
	Lenvatinib N=458 SY[a]=608.1	Lenvatinib N=584 SY[a]=252.1	Lenvatinib N=623 SY[a]=654.6	Lenvatinib N=496 SY[a]=340.0
TEAE, n(%)	52 (11.4)	141 (24.1)	181 (29.1)	109 (22.0)
TEAE no. of episodes (episodes S/Y)	62 (0.1)	172 (0.68)	N/A	114 (0.34)
TEAE with maximum CTCAE Grade of[b], n(%)				
1	30 (6.6)	65 (11.1)	58 (9.3)	56 (11.3)
2	22 (4.8)	68 (11.6)	120 (19.3)	53 (10.7)
3	0	8 (1.4)	3 (0.5)	0
4	0	0	0	0
5	0	0	0	0
SAE	0	4 (0.7)	2 (0.3)	0
TEAE leading to treatment discontinuation, n(%)	0	N/A	0[d]	0
TEAE leading to study drug modification[c], n(%)				
Reduction	0	N/A	2 (0.4)[d]	0
Interruption	0	N/A	5 (0.9)[d]	1 (0.2)

For each row category, a subject with 2 or more adverse events in that category is counted only once.

AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, RCC = renal cell carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, N/A – not available, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject-year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

d: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

Overview of Hypothyroidism		
For Hypothyroidism-SMQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**ALL RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	341 (64.3)	268 (53.9)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	112 (21.1)	73 (14.7)
2	223 (42.1)	190 (38.2)
3	5 (0.9)	5 (1.0)
4	1 (0.2)	0 (0.0)
5	0 (0.0)	0 (0.0)
SAE	3 (0.6)	3 (0.6)
TEAE leading to lenvatinib discontinuation, n (%)	0 (0.0)	1 (0.2)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	4 (0.8)	5 (1.0)
Lenvatinib drug interruption	11 (2.1)	6 (1.2)

For each row category, a subject with 2 or more adverse events in that category is counted only once.

CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Risk factors and risk groups:

Subjects with DTC who have undergone thyroidectomy and are receiving thyroid replacement therapy could develop low TSH due to thyroxin substitution. It is possible that treatment with lenvatinib may exacerbate thyroid dysfunction due to a direct effect on TSH levels.

Combination with Pembrolizumab

Pembrolizumab is a humanised monoclonal antibody which may trigger immune-related reactions. Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab (Keytruda SmPC). In the lenvatinib and pembrolizumab combination safety sets, the incidence of hypothyroidism events was significantly increased although the vast

	majority were low grade and readily manageable with thyroid hormone replacement or dose modification, if appropriate, and are therefore, of limited clinical significance. RCC (Lenvatinib + Pembrolizumab) Asian subjects had a higher incidence of hypothyroidism (67.9%) than White subjects (52.7%). Combination with everolimus RCC (lenvatinib + everolimus) Asian subjects had a higher incidence of hypothyroidism (50.0%) than white subjects (24.5%).
Preventability	Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures in place.
Public health impact:	Patients may require exogenous thyroid supplementation and thyroid function testing with consequent use of health service resources.

Identified Risk: Gastrointestinal (GI) Perforation and Fistula Formation

Potential mechanisms:	Gastrointestinal perforation and fistula formation are well known AEs associated with treatment with TKIs (Chen and Cleck, 2009). A number of effects on local tissues by VEGF blockage, including hypoxia and impaired wound healing, could increase the risk of bowel perforation and fistula formation in the setting of tumour involvement or bowel inflammation.
Evidence source(s) and strength of evidence:	Evidence from randomized clinical trials. In randomized clinical trials events of gastrointestinal perforation or fistula were reported in more patients treated with lenvatinib than placebo.
Characterisation of the risk:	• Frequency The following events were reported for the All DTC Lenvatinib Safety Set, the RCC Lenvatinib + Everolimus Safety Set, and the HCC Lenvatinib Safety Set:

MedDRA Preferred Term[a]	n (%)		
	All DTC N=458	RCC Len+Eve N=623	HCC N=496
GI Perforation Events			
Perineal abscess	2 (0.4)	2 (0.3)	0
Abscess intestinal	2 (0.4)	0	0
Colonic abscess	1 (0.2)	0	0
Oesophageal perforation	1 (0.2)	0	0
Appendicitis perforated	1 (0.2)	2 (0.3)	1 (0.2)
Oesophageal perforation	1 (0.2)	0	0
Rectal abscess	1 (0.2)	3 (0.5)	0
Diverticular perforation	1 (0.2)	2 (0.3)	0
Anal abscess	1 (0.2)	2 (0.3)	1 (0.2)
Intestinal perforation	0	2 (0.3)	0
Peritonitis bacterial	0	1 (0.2)	6 (1.2)
Retroperitoneal abscess	0	1 (0.2)	0

Appendiceal abscess	0	1 (0.2)	0
Gastric ulcer perforation	0	1 (0.2)	0
Perirectal abscess	0	1 (0.2)	0
Peritonitis	0	2 (0.3)	0
Large intestine perforation	0	4 (0.6)	0
Small intestinal perforation	0	1 (0.2)	0

DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, Len + Eve = lenvatinib + everolimus, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.

a: Adverse event terms for the All DTC Safety Set and RCC Lenvatinib + Everolimus Safety Set were coded using MedDRA Version 23.0. Adverse event terms for the HCC Lenvatinib Safety Set were coded using MedDRA Version 19.1.

The following events were reported for the Lenvatinib + Pembrolizumab Safety Sets:

MedDRA Preferred Term[a]	**Safety Set, n (%)**	
	All EC Lenvatinib + Pembrolizumab N=530	**All RCC Lenvatinib + Pembrolizumab N=497**
GI Perforation Events		
Peritonitis	4 (0.8)	1 (0.2)
Gastrointestinal perforation	3 (0.6)	-
Intestinal perforation	3 (0.6)	-
Anal abscess	2 (0.5)	1 (0.2)
Gastric perforation	2 (0.5)	-
Large intestine perforation	2 (0.5)	1 (0.2)
Rectal perforation	2 (0.5)	-
Abdominal abscess	1 (0.2)	-
Appendiceal abscess	1 (0.2)	-
Appendicitis perforated	1 (0.2)	-
Colonic abscess	1 (0.2)	1 (0.2)
Diverticular perforation	1 (0.2)	-
Duodenal ulcer perforation	-	1 (0.2)
Intestinal ulcer perforation	1 (0.2)	-
Lower gastrointestinal perforation	1 (0.2)	-
Perforated ulcer	1 (0.2)	-
Perineal abscess	1 (0.2)	1 (0.2)
Pneumoperitoneum	-	1 (0.2)
Rectal abscess	-	1 (0.2)
Small intestinal perforation	1 (0.2)	-
Fistula Formation Events		
Female genital tract fistula	7 (1.3)	-
Anal fistula	2 (0.4)	2 (0.4)
Intestinal fistula	2 (0.4)	-
Oroantral fistula	-	1 (0.2)
Urogenital fistula	2 (0.4)	-
Fistula	1 (0.2)	-
Gastrointestinal fistula	1 (0.2)	-
Infected fistula	1 (0.2)	-

EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.

a: Adverse event terms were coded using MedDRA Version 23.0.

	All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs for GI perforation and fistula formation (SGQ) were reported in 2.4% of subjects (n=11). The only TEAE for GI perforation and fistula formation that occurred in more than 2 subjects was anal fistula, which occurred in 5 subjects (1.1%). RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs for GI perforation were reported in 3.7% of subjects (n=23). The only TEAEs for GI perforation that occurred in more than 2 subjects were large intestine perforation (0.6%, n=4), rectal abscess (0.5%, n=3), and diverticular perforation, anal abscess, and intestinal perforation (0.3%, n=2 for each event). Treatment-emergent AEs for fistula formation (SGQ) were reported in 6 subjects (1.0%). The only TEAE for fistula formation that occurred in more than 1 subject was anal fistula, which occurred in 4 subjects (0.6%). HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs for GI perforation and fistula formation (SGQ) were reported in 1.8% of subjects (n=9). The only TEAE for GI perforation and fistula formation that occurred in more than 1 subject was peritonitis bacterial, which occurred in 6 subjects (1.2%). All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for GI perforation SGQ were reported in 1.6% of subjects (n=8) and for fistula formation SGQ were reported in 0.6% of subjects (n=3). No TEAEs for GI perforation and fistula formation occurred in more than 2 subjects. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Treatment-emergent AEs for GI perforation were reported in 4.0% of subjects (n=21) and for fistula formation in 2.8% of subjects (n=15). The only TEAEs for GI perforation that occurred in more than 2 subjects were peritonitis (0.8%, n=4) and intestinal perforation and gastrointestinal perforation (0.6%, n=3 for each event). The only TEAE for fistula formation that occurred in more than 2 subjects was female genital tract fistula in 7 subjects (n=1.3%). Post-authorisation events of GI perforation and fistula formation have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes All DTC Lenvatinib Safety Set (N=458): There were no deaths due to AEs for GI perforation and fistula formation. Eight subjects (1.7%) had SAEs. Two SAEs (anal fistula and perineal abscess) each occurred in 2 subjects. RCC Lenvatinib + Everolimus Safety Set (N=623): There were 2 deaths due to TEAEs for GI perforation SMQ. Sixteen subjects (2.6%) had SAEs of GI perforation. The SAEs of GI perforation reported in more than 1 subject were large intestine perforation (0.6%, n=4) intestinal perforation (0.3%, n=2), and appendicitis perforated (0.3%, n=2). There was 1 death due to a TEAE of fistula formation SMQ. Two subjects (0.3%) had SAEs of fistula formation (colonic fistula and anal fistula; n=1 for each). HCC Lenvatinib Safety Set (N=496): There were 3 SAEs of GI perforation and fistula formation (2 subjects with peritonitis bacterial and 1 subject with appendiceal abscess). One of the SAEs of bacterial peritonitis was fatal. All RCC Lenvatinib + Pembrolizumab (N=497): There were no deaths due to TEAEs for GI perforation and fistula formation SGQ. Seven subjects (1.4%) had SAEs of GI perforation (anal abscess, colonic abscess, duodenal ulcer perforation, peritonitis, large intestine perforation, pneumoperitoneum and rectal abscess; n=1 for each) and 1 subject (0.2%) had an SAE of fistula formation (anal fistula). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Seventeen subjects (3.2%) had SAEs of GI perforation SGQ; the only SAEs of GI perforation that occurred in more than 2 subjects were intestinal perforation, gastrointestinal

perforation and peritonitis (0.6%, n=3 for each event). Four subjects (0.8%) experienced fatal events of GI perforation SGQ. There were 8 subjects (1.5%) with SAEs of fistula formation SGQ; the only SAE of fistula formation reported in more than 1 subject was female genital tract fistula (0.8%, n=4). There were no fatal events of fistula formation SGQ.

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458): All TEAEs for GI perforation and fistula formation were Grade 2 or 3 in severity. Events led to treatment discontinuation in 2 subjects, and to dose reduction in 1 subject.

RCC Lenvatinib + Everolimus Safety Set (N=623): The majority of TEAEs for GI perforation SMQ were Grade 3 or higher in severity (2.9%, n=18). There were 13 Grade 3, 3 Grade 4, and 2 Grade 5 events. GI perforation events led to dose interruption and dose reduction in 8 and 3 subjects, respectively. Treatment was discontinued in 6 subjects (1.1%) due to GI perforation. The majority of TEAEs for fistula formation SMQ were for Grade 2 (0.5%, n=3). There were 2 Grade 3 events and 1 Grade 5 event. Fistula formation led to dose interruption in 4 subjects (0.8%). Treatment was discontinued in 2 subjects (0.4%) due to fistula formation.

HCC Lenvatinib Safety Set (N=496): Four TEAEs for GI perforation and fistula formation were recorded for Grade 1 or Grade 2, and for Grade 3. There was 1 Grade 5 event (bacterial peritonitis).

All RCC Lenvatinib + Pembrolizumab (N=497): The majority of TEAEs for GI perforation were Grade 3 or higher in severity (5 subjects (1.0%) with Grade 3 TEAEs and 2 subjects (0.4%) with Grade 4). For fistula formation, there were 2 Grade 1 and 1 Grade 3 events. GI perforation events led to lenvatinib dose reduction in 2 subjects and dose interruption in 7 subjects. Fistula formation events led to lenvatinib dose interruption in 1 subject. Lenvatinib treatment was discontinued in 1 subject due to GI perforation.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Most events of GI perforation SGQ were Grade 2 and Grade 3 (1.1%, n=6 for each Grade). Lenvatinib dose was interrupted in 2 subjects (0.4%) and discontinued in 15 subjects (2.8%) due to GI perforation events. Most events of fistula formation SGQ were Grade 3 (2.1%, n=11). Lenvatinib dose was interrupted in 1 subject (0.2%) and discontinued in 5 subjects (0.9%) due to fistula formation events.

For GI Perforation and Fistula Formation-SGQ, subjects with at least 1:	**GI Perforation RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**Fistula Formation RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**
TEAE, n (%)	23 (3.7)	6 (1.0)
TEAE, no. of episodes (episodes/SY)	N/A	N/A
TEAE with maximum CTCAE Grade of [b], n (%)		
1	1 (0.2)	0
2	4 (0.6)	3 (0.5)
3	13 (2.1)	3 (0.5)
4	3 (0.5)	0
5	2 (0.3)	2 (0.3)
SAE	16 (2.6)	1 (0.2)
TEAE leading to treatment discontinuation, n (%)	6 (1.1)[c]	2 (0.4)[d]
TEAE leading to study drug modification[d], n (%)		
Reduction	3 (0.6)[c]	0

Interruption	8 (1.5)[c]	4 (0.8)[d]

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, GI = gastrointestinal, HCC = hepatocellular carcinoma, N/A = not applicable, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor-generated query, SY = subject-year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).
d: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

For GI Perforation and Fistula Formation-SGQ, subjects with at least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	11 (2.4)	9 (1.8)
TEAE, no. of episodes (episodes/SY)	19 (0.03)	9 (0.03)
TEAE with maximum CTCAE Grade of[b], n (%)		
1	0	1 (0.2)
2	3 (0.7)	3 (0.6)
3	8 (1.7)	4 (0.8)
4	0	0 (0.0)
5	0	1 (0.2)
SAE	8 (1.7)	3 (0.6)
TEAE leading to treatment discontinuation, n (%)	2 (0.4)[c]	0
TEAE leading to study drug modification[d], n (%)		
Reduction	1 (0.2)[c]	0
Interruption	7 (1.5)[c]	3 (0.6)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, GI = gastrointestinal, HCC = hepatocellular carcinoma, N/A = not applicable, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor-generated query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).
d: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

	Overview of GI Perforation and Fistula Formation Events (SGQ)

For GI perforation -SGQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**ALL RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	21 (4.0)	8 (1.6)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	0 (0.0)	0 (0.0)
2	6 (1.1)	1 (0.2)
3	6 (1.1)	5 (1.0)
4	5 (0.9)	2 (0.4)
5	4 (0.8)	0 (0.0)
SAE	17 (3.2)	7 (1.4)
TEAE leading to lenvatinib discontinuation, n (%)	15 (2.8)	1 (0.2)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	0 (0.0)	2 (0.4)
Lenvatinib drug interruption	2 (0.4)	7 (1.4)
For Fistula Formation-SGQ, Subjects With At Least 1:		
TEAE, n (%)	15 (2.8)	3 (0.6)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	1 (0.2)	2 (0.4)
2	3 (0.6)	0 (0.0)
3	11 (2.1)	1 (0.2)
4	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)
SAE	8 (1.5)	1 (0.2)
TEAE leading to lenvatinib discontinuation, n (%)	6 (1.1)	0 (0.0)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	0 (0.0)	0 (0.0)
Lenvatinib drug interruption	1 (0.2)	1 (0.2)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, GI = gastrointestinal, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor generated query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Risk factors and risk groups:	In the majority of cases, perforation occurred in subjects with evidence of intra-abdominal malignant disease, but in some cases, GI perforation was not associated with apparent intra-abdominal tumour. Gastrointestinal perforations were also noted to occur in subjects who were ≥65 years of age. Events of fistulae formation involving the GI tract have been reported, with the majority of these events occurring in areas of local tumour involvement.

	Multiple confounding factors were present in subjects with GI perforation and fistula formation events. Many of these subjects had a medical history of GI bleed, gallstones, rectal abscess, diverticulitis, vaginal mass, diverticulosis of the large intestine, and colon resection for colon cancer. Subjects with esophageal or tracheal fistula had prior neck surgery such as thyroidectomy and neck lymph node dissection. Many subjects also had prior medical history of surgery or radiotherapy. Some relevant comorbidities reported were abdominal or stomach pain, infections (pelvic abscess or peritonitis), and diarrhea. Patients with liver cirrhosis are at increased risk of developing spontaneous bacterial peritonitis, a severe and often fatal infection. The incidence of spontaneous bacterial peritonitis in these patients ranges from 10% to 30% and mortality from 10% to 46% in hospitalised patients (Dever and Sheikh, 2015). According to Chen and Cleck (2009), cancer risks include colorectal, ovarian, and gastric cancer. Non-cancer risks include diverticulitis, ulcer, infection, obstruction, prior surgery, ischemic bowel, and prior radiotherapy.
Preventability	In most cases, GI perforation and fistula formation occurred in subjects with risk factors such as prior surgery or radiotherapy. In the case of a GI perforation or fistula formation, dose interruptions, adjustments, or permanent discontinuation may be necessary.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures in place.
Public health impact:	Not identified

Identified Risk: Non-Gastrointestinal Fistula Formation (any fistula which does not involve the stomach or intestine) **and Pneumothorax**	
Potential mechanisms:	Potential mechanisms: The potential mechanism of non-GI fistula formation is assumed to be similar to that of GI perforation and fistula formation, which are well known AEs associated with treatment with TKIs (Chen and Cleck, 2009). A number of effects on local tissues by VEGF blockage, including hypoxia and impaired wound healing, could increase the risk of bowel perforation and fistula formation in the setting of tumour involvement or bowel inflammation. Lenvatinib inhibits VEGF- and FGF-driven angiogenesis, lymphangiogenesis, and has a direct antitumour effect on some types of tumours through its actions on VEGFR1-3, FGFR1-4, KIT, PDGFRα, and RET. There is a potential that lenvatinib-responsive lung metastases may undergo marked tumour shrinkage which, depending on their positions and health of the surrounding pulmonary tissue, could result in pneumothoraces or bronchopulmonary fistula. The same process may apply to lenvatinib-responsive metastases in other organs, resulting in fistulae or bowel perforations.
Evidence source(s) and strength of evidence:	Postmarketing reports of Non-Gastrointestinal Fistula Formation and pneumothorax in association with lenvatinib have been received.
Characterisation of the risk:	**Non-GI Fistula** • Frequency The following events were reported for the All DTC Lenvatinib Safety Set, the RCC Lenvatinib + Everolimus Safety Set, the HCC Lenvatinib Safety Set, and the

Non-DTC, Non-HCC Safety Set:

MedDRA Preferred Term[a]	n (%)			
	All DTC N=458	RCC Len+Eve N=623	Non-DTC, Non-HCC N=656	HCC N=496
Anal fistula*	5 (1.1)	4 (0.6)	0	1 (0.2)
Fistula	0	0	2 (0.3)	0
Oesophageal fistula	0	0	1 (0.2)	0
Oesophagobronchial fistula*	1 (0.2)	0	0	0
Pharyngeal fistula	0	0	1 (0.2)	0
Tracheal fistula	0	0	1 (0.2)	0
Tracheo-oesophageal fistula	0	0	1 (0.2)	0
Female genital tract fistula	0	1 (0.2)	0	0

DTC = differentiated thyroid carcinoma, HCC = hepatocellular carcinoma, RCC = renal cell carcinoma.
a: Adverse event terms for the All DTC Safety Set and RCC Lenvatinib + Everolimus Safety Set were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Adverse event terms for the HCC Lenvatinib Safety Set were coded using MedDRA Version 19.1.
*Also reported under 'GI perforation and fistula formation' risk.

The following events of non-GI fistula formation SGQ were reported for the Lenvatinib + Pembrolizumab Safety Sets:

MedDRA Preferred Term[a]	Safety Set, n (%)	
	All EC Lenvatinib + Pembrolizumab N=530	All RCC Lenvatinib + Pembrolizumab N=497
Female genital tract fistula*	7 (1.3)	-
Anal fistula*	-	2 (0.4)
Urogenital fistula*	2 (0.4)	-
Fistula*	1 (0.2)	-
Infected fistula*	1 (0.2)	-
Oroantral fistula*	-	1 (0.2)

EC = endometrial carcinoma, GI = gastrointestinal, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.
a: Adverse event terms were coded using MedDRA Version 23.0.
* Also reported in the GI fistula formation risk.

Non-DTC, Non-HCC Safety Set (N=656): Treatment-emergent AEs for non-GI fistula formation were reported in 0.9% of subjects (n=6).

All DTC Lenvatinib Safety Set (N=458): There was 1 event (0.2%) of non-GI fistula.

RCC Lenvatinib + Everolimus Safety Set (N=623): Female genital tract fistula was reported in 1 subject (0.2%) and anal fistula was reported in 4 subjects (0.6%).

HCC Lenvatinib Safety Set (N=496): Anal fistula was reported in 1 subject (0.2%). This event was also included under the risk of GI perforation and fistula formation.

The incidence of non-GI fistula across the pooled analysis of safety data from clinical trials with lenvatinib monotherapy (n=1166) was 0.6%.

All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs for non-GI fistula formation SGQ were reported in 0.6% of subjects (n=3).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): The incidence of non-GI fistula SGQ in this safety set was 1.9%.

Post-authorisation events of non-GI fistula formation have been in accordance with the safety profile of lenvatinib in clinical trials.

- Seriousness/outcomes

Non-DTC, Non-HCC Safety Set (N=656): Of the 6 events of non-GI fistula, 3 events (0.5%) were reported as SAEs. These were oesophageal fistula, tracheal fistula, and trachea-oesophageal fistula. Lenvatinib treatment was discontinued in 3 subjects and interrupted in 2 subjects.

All-DTC Lenvatinib Safety Set (n=458): 1 event (0.2%) was reported as an SAE.

RCC Lenvatinib + Everolimus Safety Set (N=623): There was 1 SAE (anal fistula).

HCC Lenvatinib Safety Set (N=496): There were no SAE reports of non-GI fistula formation.

All RCC Lenvatinib + Pembrolizumab (N=497): There was 1 SAE report of anal fistula.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Seven subjects (1.3%) reported SAEs of non-GI fistula SGQ. Lenvatinib treatment was discontinued due to non-GI fistula events in 4 subjects (0.8%).

- Severity and nature of risk

All-DTC Lenvatinib Safety Set (n=-458): The event of non-GI fistula was Grade 3.

RCC Lenvatinib + Everolimus Safety Set (N=623): The event of female genital tract fistula was Grade 2. There were 2 Grade 2 and 2 Grade 3 events of anal fistula. Treatment was discontinued in 1 subject (0.2%) due to an event of female genital tract fistula.

In the Non-DTC, Non-HCC Safety Set (n=656) there was 1 Grade 1 event, 3 Grade 2 events, and 4 Grade 3 events.

All RCC Lenvatinib + Pembrolizumab (N=497): Two events of non-GI fistula SGQ were Grade 1 and 1 event was Grade 3. Lenvatinib treatment was interrupted in 1 subject due to an event of anal fistula.

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): All events of non-GI fistula SGQ were either Grade 2 (0.4%, n=2) or Grade 3 (1.5%, n=8).

Non-GI Fistula (excluding pneumothorax)				
For Non-GI Fistula Formation-subjects with at least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**Non-DTC Lenvatinib Safety Set N=656 SY[a]=331.1**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	2 (0.4)	5 (0.8)	6 (0.9)	1 (0.2)
TEAE, no. of episodes (episodes/SY)	2 (<0.01)	N/A	7 (0.02)	1 (<0.1)
TEAE with maximum CTCAE Grade of [b], n (%)				
1	0	0	0	0
2	0	3 (0.5)	3	1 (0.2)
3	2 (0.4)	2 (0.3)	3	0
4	0	0	0	0
5	0	0	0	0
SAE	1 (0.2)	0	3 (0.5)	0
TEAE leading to treatment discontinuation, n (%)				

	0	1 (0.2)[c]	2 (0.3)	0
TEAE leading to study drug modification[d], n (%)				
Reduction	0	0[c]	0	0
Interruption	0	2 (0.4)[c]	1 (0.2)	0

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, GI = gastrointestinal, HCC = hepatocellular carcinoma, N/A = not applicable, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor-generated query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).
d: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Overview of Non-GI Fistula Formation Events (excluding pneumothorax)		
For Non-GI Fistula Formation-SGQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**All RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	10 (1.9)	3 (0.6)
TEAE with maximum CTCAE Grade of[b], n (%)		
1	0 (0.0)	2 (0.4)
2	2 (0.4)	0 (0.0)
3	8 (1.5)	1 (0.2)
4	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)
SAE	7 (1.3)	1 (0.2)
TEAE leading to lenvatinib discontinuation, n (%)	4 (0.8)	0 (0.0)
TEAE leading to study drug modification[c], n (%)		
Lenvatinib dose reduction	0 (0.0)	0 (0.0)
Lenvatinib drug interruption	0 (0.0)	1 (0.2)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, GI = gastrointestinal, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor generated query, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total Treatment Subject-Years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Pneumothorax/Spontaneous Pneumothorax

- Frequency

The following events were reported for the All DTC Lenvatinib Safety Set, the

RCC Lenvatinib + Everolimus Safety Set, the HCC Lenvatinib Safety Set, and the Non-DTC, Non-HCC Safety Set:

Overview of Pneumothorax/Spontaneous Pneumothorax				
For Pneumothorax and Pneumothorax Spontaneous, Subjects with at least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**	**Non DTC Lenvatinib Safety Set N=656 SY = 331.1**
TEAE, n (%)	6 (1.3)	8 (1.3)	2 (0.4)	3 (0.5)
TEAE, no. of episodes (episodes/SY)	7 (0.01)	N/A	2 (<0.01)	3 (0.01)
TEAE with maximum CTCAE Grade of [b], n (%)				
1	2 (0.4)	1 (0.2)	0	1 (0.2)
2	1 (0.2)	2 (0.3)	1 (0.2)	1 (0.2)
3	2(0.4)	4 (0.6)	1 (0.2)	1 (0.2)
4	1 (0.2)	0	0	0
5	0	1 (0.2)	0	0
SAE	4 (0.9)	6 (1.0)	1 (0.2)	1 (0.2)
TEAE leading to treatment discontinuation, n (%)	0	1 (0.2)[c]	0	0
TEAE leading to study drug modification[d], n (%)				
Reduction	0	0[c]	0	0
Interruption	2 (0.4)	3 (0.6)[c]	0	1 (0.2)

The preferred terms for pneumothorax and spontaneous pneumothorax were searched. For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, N/A = not applicable, RCC = renal cell carcinoma, SMQ = standard MedDRA query, SAE = serious adverse event, SY = subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).
d: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Non-DTC, Non-HCC Safety Set (N=656): Treatment-emergent AEs for pneumothorax AEs were reported in 0.5% of subjects (n=3).

All DTC Lenvatinib Safety Set (N=458): There were 6 events of pneumothorax (1.3%).

RCC Lenvatinib + Everolimus Safety Set (N=623): Pneumothorax was reported in 6 subjects (1.0%), and pneumothorax spontaneous was reported in 2 subjects (0.3%).

	HCC Lenvatinib Safety Set (N=496): Pneumothorax was reported in 2 subjects (0.4%). The incidence of pneumothorax or pneumothorax spontaneous across the pooled analysis of safety data from clinical trials with lenvatinib monotherapy (n=1823) was 0.9%. All RCC Lenvatinib + Pembrolizumab Combination (N=497): There were 2 subjects with pneumothorax (both Grade 2) and 1 subject with pneumothorax spontaneous (Grade 2). The dose of lenvatinib was interrupted and subsequently reduced in 1 subject with pneumothorax. There was 1 subject with an SAE of pneumothorax and 1 subject with an SAE of pneumothorax spontaneous. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Two subjects (0.4%) had events of pneumothorax. Post-authorisation events of pneumothorax have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes Non-DTC, Non-HCC Safety Set (N=656): Of the 3 pneumothorax events, 1 was reported as a SAE and lenvatinib treatment was interrupted in 1 subject. All-DTC Lenvatinib Safety Set (n=458): Four of the 6 pneumothorax events were considered serious and lenvatinib treatment was interrupted in 2 subjects. RCC Lenvatinib + Everolimus Safety Set (N=623): There was 1 death due to a TEAE for pneumothorax spontaneous. Four pneumothorax and 2 pneumothorax spontaneous events were considered serious. Pneumothorax and pneumothorax spontaneous led to dose interruption in 2 subjects (0.4%) and 1 subject (0.2%), respectively. Treatment was discontinued in 1 subject (0.2%) due to pneumothorax spontaneous. HCC Lenvatinib Safety Set (N=496): There were 2 reports of pneumothorax, of which 1 was considered serious. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There was an SAE event of pneumothorax reported in 1 subject that led to lenvatinib drug interruption. • Severity and nature of risk All-DTC Lenvatinib Safety Set (n=-458): There were 2 events of Grade 3 pneumothorax and 1 event of Grade 4 pneumothorax. In the Non-DTC, Non-HCC Safety Set (n=656): There was one Grade 1, one Grade 2 and one Grade 3 event of pneumothorax. HCC Lenvatinib Safety Set (N=496): There were 2 pneumothorax events of which 1 was Grade 2 and 1 was Grade 3. In the RCC Lenvatinib + Everolimus Safety Set (n=623): There was 1 report of Grade 1, 2 reports of Grade 2, and 4 reports of Grade 3 pneumothorax events. There was 1 report of Grade 3 and 1 report of Grade 5 pneumothorax spontaneous. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There were 2 events of pneumothorax; 1 was Grade 2 and 1 was Grade 3 (also an SAE).
<u>Risk factors and risk groups:</u>	Prior surgery or radiotherapy may be risk factors for the development of non-GI fistulae and pneumothorax. Patients with pre-existing fistulae treated with lenvatinib are at increased risk of worsening, and some reactions have resulted in fatal haemorrhage. Data from ongoing studies in solid tumours indicates that the risk of pneumothorax may be higher in certain types of tumours such as soft tissue sarcoma, possibly due to their predilection for lung metastasis. It is possible that cavitation of lung tumours associated with high therapeutic response to lenvatinib may also contribute to the risk of pneumothorax. Some reports of gastrointestinal

	perforation, fistula and pneumothorax occurred in association with tumour regression or necrosis.
Preventability	Lenvatinib should not be started in patients with fistula to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula.
Impact on the risk-benefit balance of the product:	Routine risk minimisation measures in place.
Public health impact:	Not identified

Important Potential Risk: Venous Thromboembolic Events (VTEs)	
Potential mechanisms:	Although an association between VEGF/VEGFR-targeted therapies and VTEs has not been established, a mechanism has been hypothesised as follows: Angiogenesis-induced VTEs may be directly related to inhibitory effect on VEGF signaling pathway: angiogenesis inhibitors can disrupt the regenerative capacity of endothelial cells (ECs) and cause vascular wall defects, exposing prothrombotic phospholipids on the luminal plasma membrane and the underlying matrix, thus leading to thrombosis. In addition, reduction in NO and prostaglandin I2 (PG I2) by a VEGF inhibitor can also predispose to thrombosis (Qi, et al., 2013b).
Evidence source(s) and strength of evidence:	Randomised clinical trials. In randomised clinical trials events of pulmonary embolism were reported in more patients treated with lenvatinib than placebo and there is a recognised potential class effect.
Characterisation of the risk:	• Frequency Events reported were as follows in the All DTC Lenvatinib Safety Set (N=458), RCC Lenvatinib + Everolimus Safety Set (N=623), the HCC Lenvatinib Safety Set (N=496), the All RCC Lenvatinib + Pembrolizumab Safety Set (N=497), and the All EC Lenvatinib + Pembrolizumab Safety Set (N=530):

MedDRA Preferred Term[a]	**n (%)**		
	All DTC N=458	**RCC Len+Eve N=623**	**HCC N=496**
Portal vein thrombosis	0	2 (0.3)	9 (1.8)
Pulmonary embolism	13 (2.8)	13 (2.1)	4 (0.8)
Deep vein thrombosis	5 (1.1)	6 (1.0)	1 (0.2)
Pulmonary infarction		1 (0.2)	2 (0.4)
Thrombophlebitis superficial	2 (0.4)	0	0
Embolism venous		1 (0.2)	1 (0.2)
Jugular vein thrombosis	1 (0.2)	1 (0.2)	0
Metastatic pulmonary embolism	1 (0.2)	0	0
Pelvic venous thrombosis	1 (0.2)	1 (0.2)	0
Retinal vein occlusion	1 (0.2)	1 (0.2)	1 (0.2)
Retinal vein thrombosis	1 (0.2)	0	0
Thrombophlebitis	1 (0.2)	2 (0.3)	1 (0.2)
Vena cava thrombosis	1 (0.2)	2 (0.3)	1 (0.2)
Venous thrombosis	1 (0.2)	2 (0.3)	0

DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, Len + Eve = Lenvatinib + Everolimus, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.

a: Adverse event terms for the All DTC Safety Set and RCC Lenvatinib + Everolimus Safety Set were coded using MedDRA Version 23.0. Adverse event terms for the HCC Lenvatinib Safety Set were coded using MedDRA Version 19.1.

MedDRA Preferred Term[a]	Safety Set, n (%)	
	All EC Lenvatinib + Pembrolizumab N=530	All RCC Lenvatinib + Pembrolizumab N=497
Pulmonary embolism	19 (3.6)	10 (2.0)
Deep vein thrombosis	13 (2.5)	3 (0.6)
Embolism	4 (0.8)	-
Embolism venous	2 (0.4)	2 (0.4)
Jugular vein thrombosis	2 (0.4)	-
Portal vein thrombosis	2 (0.4)	1 (0.2)
Thrombosis	2 (0.4)	-
Vena cava thrombosis	2 (0.4)	3 (0.6)
Venous thrombosis	2 (0.4)	-
Haemorrhoids thrombosed	1 (0.2)	-
Pelvic venous thrombosis	1 (0.2)	-
Renal vein thrombosis	1 (0.2)	-
Retinal vein occlusion	1 (0.2)	-
Thrombophlebitis	-	1 (0.2)
Thrombophlebitis superficial	1 (0.2)	1 (0.2)

EC = endometrial carcinoma, MedDRA = Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma.

a: Adverse event terms were coded using MedDRA Version 23.0.

All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs related to VTEs (SGQ) were reported in 5.2% of subjects (n=24). The most frequent TEAEs included pulmonary embolism (n=13) and deep vein thrombosis (n=5).

RCC Lenvatinib + Everolimus Safety Set (N=623): Treatment-emergent AEs related to VTEs (SGQ) were reported in 4.5% of subjects (n=28). The most frequent TEAE was pulmonary embolism reported in 2.1% (n=13).

HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs related to VTEs (SGQ) were reported in 3.8% of subjects (n=18). The most frequent TEAE was portal vein thrombosis reported in 1.8% (n=9). Post-authorisation VTEs have been in accordance with the safety profile of lenvatinib in clinical trials.

All RCC Lenvatinib + Pembrolizumab (N=497): TEAEs related to VTEs were reported in 4.0% of subjects (n=20). The most frequent TEAEs included pulmonary embolism (n=10), deep vein thrombosis (n=3) and vena cava thrombosis (n=3).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): TEAEs related to VTEs (SGQ) were reported in 8.9% of subjects (n=47). The most frequent TEAEs were pulmonary embolism and deep vein thrombosis reported in 3.6% (n=19) and 2.5% (n=13) of subjects, respectively.

Post-authorisation VTEs have been in accordance with the safety profile of lenvatinib in clinical trials.

- Seriousness/outcomes

All DTC Lenvatinib Safety Set (N=458): There were 2 deaths due to AEs for VTEs. Serious AEs for VTEs were reported in 3.1% of subjects (n=14). The SAEs reported in more than 1 subject included pulmonary embolism (n=10) and deep vein thrombosis (n=2).

RCC Lenvatinib + Everolimus Safety Set (N=623): Serious AEs for VTEs were reported in 1.6% of subjects (n=10). The SAEs reported in more than 1 subject included pulmonary embolism (n=13), deep vein thrombosis (n=6), and portal vein thrombosis, thrombophlebitis, venous thrombosis, and vena thrombosis limb (n=2 for each).

HCC Lenvatinib Safety Set (N=496): There were 4 deaths due to AEs for VTEs. Serious AEs for VTEs were reported in 2.0% of subjects (n=10). The SAEs reported in more than 1 subject included portal vein thrombosis (n=4) and pulmonary embolism (n=4).

All RCC Lenvatinib + Pembrolizumab (N=497): There was 1 death due to a TEAE for VTEs pulmonary embolism). Serious AEs of VTEs were reported in 9 subjects (1.8%) and included pulmonary embolism (n=6) and deep vein thrombosis (n=3).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There was 1 death due to TEAEs for VTEs SGQ (pulmonary embolism). SAEs for VTEs SGQ were reported in 2.1% of subjects (n=11).

- Severity and nature of risk

All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs of Grade 3 or higher for VTEs occurred in 3.9% of subjects. The Grade 4 TEAEs were pulmonary embolism (n=4). Two subjects (0.4%) had events that led to dose reduction and in 5 subjects (1.1%) lenvatinib treatment had to be discontinued.

RCC Lenvatinib + Everolimus Safety Set (N=623): Eighteen events were ≥Grade 3; 16 events were Grade 3 and 2 events were Grade 4. One subject (0.2%) had an event that led to dose reduction, and 7 subjects (1.3%) had events that led to dose interruption. Treatment was discontinued in 2 subjects (0.4%).

HCC Lenvatinib Safety Set (N=496): There were 10 events ≥Grade 3; 5 events were Grade 3, 1 event was Grade 4 and 4 events were Grade 5. Two subjects each had events that led to dose reduction or interruption, and in 4 subjects lenvatinib treatment had to be discontinued.

All RCC Lenvatinib + Pembrolizumab (N=497): Treatment-emergent AEs of Grade 3 or higher for VTEs SGQ occurred in 2.0% of subjects (n=10). One subject (0.2%) and 5 subjects (1.0%) had events that led to dose reduction and dose interruption, respectively. Treatment was discontinued in 1 subject (0.2%).

All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Nineteen subjects had events of VTEs SGQ of Grade 3 or higher; 17 subjects (3.2%) with Grade 3 VTE events, 1 (0.2%) with a Grade 4 event and 1(0.2%) with a Grade 5 VTE SGQ. Lenvatinib dose was reduced in 9 subjects and was interrupted in 5 subjects; lenvatinib treatment was discontinued in 4 subjects.

Overview of VTEs (SGQ)			
For Venous Thromboembolic Events-SGQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	24 (5.2)	28 (4.5)	18 (3.6)
TEAE, no. of episodes (episodes/SY)	30 (0.05)	N/A	20 (0.06)
TEAE with maximum CTCAE Grade of [b], n (%)			

1	2 (0.4)	2 (0.3)	0
2	4 (0.9)	8 (1.3)	8 (1.6)
3	12 (2.6)	16 (2.6)	5 (1.0)
4	4 (0.9)	2 (0.3)	1 (0.2)
5	2 (0.4)	0	4 (0.8)
SAE	14 (3.1)	10 (1.6)	10 (2.0)
TEAE leading to treatment discontinuation, n (%)	5 (1.1)	2 (0.4)[c]	4 (0.8)
TEAE leading to study drug modification[d], n (%)			
Reduction	2 (0.4)	1 (0.2)[c]	2 (0.4)
Interruption	8 (1.7)	7 (1.3)[c]	2 (0.4)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, N/A = not applicable, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor-generated query, SY = subject year, TEAE = treatment-emergent adverse event, VTE = venous thromboembolic event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.
c: Percentages are based on subjects from Studies 307, 112, and 218 where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).
d: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Overview of VTEs (SGQ)		
For VTEs-SGQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**All RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	47 (8.9)	20 (4.0)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	5 (0.9)	4 (0.8)
2	23 (4.3)	6 (1.2)
3	17 (3.2)	8 (1.6)
4	1 (0.2)	1 (0.2)
5	1 (0.2)	1 (0.2)
SAE	11 (2.1)	9 (1.8)
TEAE leading to lenvatinib discontinuation, n (%)	4 (0.8)	1 (0.2)
TEAE leading to study drug modification [c], n (%)		
Lenvatinib dose reduction	9 (1.7)	1 (0.2)
Lenvatinib drug interruption	5 (0.9)	5 (1.0)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, RCC = renal cell carcinoma, SAE = serious adverse event, SGQ = sponsor generated query, SY = subject year, TEAE = treatment-emergent adverse event, VTE = venous thromboembolic event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).
b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

	c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
Risk factors and risk groups:	Risk factors associated with VTEs include underlying malignant disease, age ≥65 years, and immobility. In the lenvatinib clinical database, the incidence (approximately 5%) of VTEs per SGQ did not differ much among the groups, including placebo, indicating that there is a significant background rate of these events in this population. All subjects had extensive malignant disease at study entry and this might constitute the major predisposing factor. This observation is consistent with published data showing that the risk of VTEs associated with TKIs is likely to be due to the underlying malignancy (Qi, et al., 2013b). A number of subjects also had predisposing factors including prior medical history of hypertension, diabetes, hyperlipidemia, and obesity, and most of the women were in the postmenopausal age group. Lastly, at the time of the event, a number of subjects were hospitalised for various SAEs (infection, renal disorder, surgery); thus, immobilisation could have contributed to venous stasis, leading to deep vein thrombosis and pulmonary embolism. Portal vein thrombosis is common in patients with HCC (up to a 40% incidence at the time of diagnosis) and is associated with a poor prognosis (Quirk, et al., 2015).
Preventability	Published data show that the risk of VTEs associated with TKIs is likely to be due to the underlying malignancy (Qi, et al., 2013b) rather than VEGF/VEGFR-targeted therapies.
Impact on the risk-benefit balance of the product:	Routine pharmacovigilance in place; if the risk is further characterised it is unlikely to have an impact on the risk-benefit of the product.
Public health impact:	These events could have a significant impact on public health; however, an association with lenvatinib has not been established.

Important Potential Risk: Abnormal pregnancy outcome, excretion of lenvatinib in breast milk	
Potential mechanisms:	The mechanism of potential abnormal pregnancy is unclear, although it may be related to the antiangiogenic properties of lenvatinib. Embryo-foetal toxicities including skeletal malformations at multiple sites, reduced ossification, generalised oedema and microhepatia have been documented in animal studies with other TKIs, suggestive of abnormal pregnancy as a class effect among TKIs (Abruzzese, et al., 2014).
Evidence source(s) and strength of evidence:	Nonclinical data. There are insufficient clinical data to exclude a risk.
Characterisation of the risk:	• Frequency

	All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs of abnormal pregnancy outcome and excretion of lenvatinib in breast milk were reported in 0.4% of subjects (n=2; chloasma and porokeratosis [1 subject each]). However these reports are not relevant as all of these subjects are male. RCC Lenvatinib + Everolimus Safety Set (N=623): A TEAE of abnormal pregnancy outcome and excretion of lenvatinib in breast milk SMQ was reported in 0.2% of subjects (n=1; subgaleal haematoma). HCC Lenvatinib Safety Set (N=496): There were no reported TEAEs of abnormal pregnancy outcome or excretion of lenvatinib in breast milk. All RCC Lenvatinib + Pembrolizumab (N=497): A TEAE of abnormal pregnancy outcome and excretion of lenvatinib in breast milk SGQ was reported in 0.2% of subjects (n=1; epidermolysis). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): TEAEs of abnormal pregnancy outcome and excretion of lenvatinib in breast milk SGQ were reported in 1.3% of subjects (n=7). The most frequent event was failure to thrive in 0.8% of subjects (n=4). Although the protocols for lenvatinib clinical studies require that female subjects of childbearing potential use an acceptable method of contraception, 1 case of pregnancy has been recorded during the clinical development of lenvatinib: a healthy, PPD black woman who had a positive pregnancy test 5 days after administration of the third of 3 single 10 mg doses administered in a PK study over the course of 3 weeks. It is currently unknown whether lenvatinib is excreted in human breast milk. Lenvatinib and its metabolites are excreted in rat milk. • Seriousness/outcomes All DTC Lenvatinib Safety Set (N=458): There were no SAEs of abnormal pregnancy outcome and excretion of lenvatinib in breast milk. The event of pregnancy was deemed to be serious, and the subject had an outcome of a confirmed spontaneous abortion 14 days after receiving the third and final dose of lenvatinib. The subject was subsequently lost to follow up and no further information was available. There were no SAEs of abnormal pregnancy outcome and excretion of lenvatinib in breast milk in the All RCC Lenvatinib + Pembrolizumab Safety Set. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There were 2 SAEs (0.4%; failure to thrive) of abnormal pregnancy outcome and excretion of lenvatinib in breast milk SGQ. • Severity and nature of risk All DTC Lenvatinib Safety Set (N=458): There were 2 TEAEs of abnormal pregnancy outcome and excretion of lenvatinib in breast milk (chloasma and porokeratosis); these were both Grade 1. The event of pregnancy recorded during the clinical development of lenvatinib was deemed severe, and possibly related to study drug. RCC Lenvatinib + Everolimus Safety Set (N=623): There was 1 TEAE of abnormal pregnancy outcome and excretion of lenvatinib in breast milk (subgaleal haematoma), the grade was missing. All RCC Lenvatinib + Pembrolizumab (N=497): There was 1 TEAE of abnormal pregnancy outcome and excretion of lenvatinib in breast milk SGQ (epidermolysis), which was Grade 1 in severity. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There were 3 subjects with Grade 3 TEAEs of abnormal pregnancy outcome and excretion of

	lenvatinib in breast milk SGQ; these TEAEs were failure to thrive (n=2) and muscular dystrophy (n=1).
Risk factors and risk groups:	Women of childbearing potential and lactating females.
Preventability	Lenvatinib should not be administered to pregnant women, unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus. Women of childbearing age should avoid becoming pregnant and use effective contraception during treatment with lenvatinib and for at least one month after finishing treatment. It is not known whether lenvatinib is excreted in human breast milk. Lenvatinib and its metabolites are excreted in rat milk. A risk to newborns or infants cannot be excluded and, therefore, lenvatinib should not be used during breastfeeding.
Impact on the risk-benefit balance of the product:	Routine pharmacovigilance monitoring; further characterisation is unlikely to have a significant impact on the risk-benefit balance of the product.
Public health impact:	None identified

Important Potential Risk: Male and female fertility	
Potential mechanisms:	The changes observed in male and female reproductive organs are considered class effects due to the pharmacologic activity of lenvatinib. In males, the VEGF receptor has an important role in maintaining the function of testicular microvasculature and in regulating the initial stages of the process of spermatogonial proliferation and spermatogenesis (Ergün, et al., 1997; Nalbandian, et al., 2003).
Evidence source(s) and strength of evidence:	Nonclinical data. There are insufficient clinical data to exclude a risk.
Characterisation of the risk:	• Frequency All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs of male and female fertility were reported in 1.1% of subjects (n=5). TEAEs included hypogonadism (n=2), amenorrhea (n=1), menstruation irregular (n=1), and varicocele (n=1). RCC Lenvatinib + Everolimus Safety Set (N=623): There were no reported TEAEs of male and female fertility. HCC Lenvatinib Safety Set (N=496): Treatment-emergent AEs of male and female fertility were reported in 1 subject (0.2%). The TEAE was menstruation irregular. All RCC Lenvatinib + Pembrolizumab (N=497): A TEAE of male and female fertility was reported in 0.2% of subjects (n=1; irregular menstruation in a PPD female subject at study entry). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There were no reported TEAEs of female fertility SGQ. Post-authorisation events of male and female fertility have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes There were no reported SAEs of male and female fertility in either the All DTC Lenvatinib Safety Set, the RCC Lenvatinib + Everolimus Safety Set, or the HCC Lenvatinib Safety Set.

	There were no reported SAEs of male and female fertility SGQ in the All RCC Lenvatinib + Pembrolizumab Safety Set. • Severity and nature of risk All DTC Lenvatinib Safety Set (N=458): Treatment-emergent AEs of male and female fertility were mainly Grade 1 or Grade 2 (2 subjects [0.4%] for each Grade). Grade 3 male and female fertility was reported in 1 subject (0.2%). RCC Lenvatinib + Everolimus Safety Set (N=623): There were no reported TEAEs of male and female fertility. HCC Lenvatinib Safety Set (N=496): The reported TEAE of male and female fertility was Grade 3. All RCC Lenvatinib + Pembrolizumab (N=497): The reported TEAE of male and female fertility SGQ was Grade 1. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): There were no reported TEAEs of female fertility SGQ. No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, in repeated-dose studies in animals testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) were observed at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum recommended human dose. These findings were reversible at the end of a 4-week recovery period.
Risk factors and risk groups:	Men and women of reproductive age
Preventability	The nonclinical evidence of reversibility and the absence of degenerative effects, suggests that any impairment of fertility in males or females would be short-term; hence, sperm or egg cryopreservation for patients is not considered necessary for lenvatinib patients.
Impact on the risk-benefit balance of the product:	Routine pharmacovigilance monitoring in place. Further characterisation is considered unlikely to have a significant impact on the risk-benefit balance of the product.
Public health impact:	None identified

Important Potential Risk: Bone and teeth abnormalities in the paediatric population	
Potential mechanisms:	VEGF is an essential coordinator of chondrocyte death, chondroclast function, extracellular matrix remodeling, angiogenesis, and bone formation in the growth plate (Gerber, et al., 1999b). VEGF is also actively responsible for hypertrophic cartilage neovascularization through a paracrine release by chondrocytes (Carlevaro, et al., 2000). The expression of VEGFR-2 has been shown to be positive in dental pulp odontoblasts in primary teeth in humans and more uniformly in young permanent teeth. VEGF may therefore play a role in permanent tooth development and maturation (Mattuella, et al., 2007).
Evidence source(s) and strength of evidence:	Nonclinical data. There are currently insufficient clinical data to exclude or confirm a risk.
Characterisation of the risk:	Not applicable. There are insufficient data to characterise the risk.

Risk factors and risk groups:	Paediatric patients with an active growth plate and young enough to not yet have developed their permanent teeth
Preventability	No information is available
Impact on the risk-benefit balance of the product:	No information is available
Public health impact:	None identified

Important Potential Risk: Impaired wound healing	
Potential mechanisms:	Wound healing is a complex process involving angiogenesis and closely regulated interactions between endothelial cells, platelets, and the coagulation cascade. Inhibition of the VEGF pathway has a diverse effect on local tissues that could disrupt the normal healing process. Antiangiogenic agents are known to delay cutaneous wound healing in a dose-dependent manner in animal models (Chen and Cleck, 2009).
Evidence source(s) and strength of evidence:	Known effect of some other medicines in the class; insufficient clinical data to exclude a risk.
Characterisation of the risk:	• Frequency All DTC Lenvatinib Safety Set (N=458): Impaired wound healing was reported in 1.3% of subjects (n=6). RCC Lenvatinib + Everolimus Safety Set (N=623): Impaired wound healing was reported in 3 subjects (0.5%). HCC Lenvatinib Safety Set (N=496): Impaired wound healing was reported in 1 subject (0.2%). All RCC Lenvatinib + Pembrolizumab (N=497): A TEAE of impaired wound healing SGQ was reported in 0.2% of subjects (n=1; impaired healing). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): An event of impaired wound healing SGQ was reported in 1 subject (0.2%). Post-authorisation events of impaired wound healing have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes One event of Grade 3 impaired wound healing involving a chest wall mass was serious and resulted in hospitalization of the subject and discontinuation of the treatment, after which the event resolved. One Grade 3 event of nonserious impaired wound healing occurred in a subject in the HCC Lenvatinib Safety Set (wound healing delayed at left tibia). The event was initially reported at Grade 1 and did not resolve, resulting in study drug discontinuation and the subject being withdrawn from the study. No SAEs of impaired wound healing SMQ and no Grade 5 events were reported in the All RCC Lenvatinib + Everolimus Safety Set. No SAEs of impaired wound healing SGQ and no Grade 5 events were reported in the All RCC Lenvatinib + Pembrolizumab Safety Set. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): An event of Grade 2 impaired healing was reported in 1 subject (0.2%), which was resolved without any treatment modification. • Severity and nature of risk

	The majority of events of impaired wound healing were Grade 1 or 2; 1 Grade 3 event was reported in the All DTC Lenvatinib Safety Set and the HCC Lenvatinib Safety Set. The TEAE of impaired wound healing was Grade 1 in the All RCC Lenvatinib + Everolimus Safety Set. The TEAE of impaired healing was Grade 2 in severity in the All RCC Lenvatinib + Pembrolizumab Safety Set.
Risk factors and risk groups:	Surgery or radiotherapy within 4 weeks of treatment with a VEGF/VEGFR targeted therapy.
Preventability	Patients with major surgery within the 3 to 4 weeks prior to study entry were excluded from the lenvatinib clinical trials as a precaution and in Study 307 those who had not recovered adequately from ensuing toxicity and/or complications were also excluded; therefore, clinical evidence regarding this risk is limited. Of the few cases observed, none was life-threatening and all resolved. The risk factors (prior surgery or radiotherapy) are already noted in Section 4.4 of the SmPC as being implicated in GI perforation and fistula formation; hence, this risk is essentially covered in the product information.
Impact on the risk-benefit balance of the product:	Routine pharmacovigilance monitoring in place; impaired wound healing could have a substantial effect on an individual patient's recovery but is considered unlikely to have significant impact on the risk-benefit profile of the product.
Public health impact:	Patients with impaired wound healing may use additional health service resources.

Important Potential Risk: Interstitial Lung Disease (ILD)-like Conditions	
Potential mechanisms:	The mechanism of EGFR-TKI-induced ILD is currently unclear. In a murine model of bleomycin-induced pulmonary fibrosis, gefitinib therapy may augment any underlying pulmonary fibrosis via a decrease in EGFR phosphorylation with a coincident decrease in regenerative epithelial proliferation. Additionally, inhibition of EGFR signaling by EGFR TKIs may impair the repair of pulmonary injury (Shi, et al., 2014).
Evidence source(s) and strength of evidence:	"Interstitial lung disease-like events" have been reported for several other medicinal products from the same pharmacological class.
Characterisation of the risk:	• Frequency In a review of ILD-like conditions for lenvatinib, no events of ILD were reported across the pooled analysis of safety data from clinical trials with lenvatinib (including 458 subjects with RAI-refractory DTC and 656 subjects with other tumour types). In the All DTC Safety Set, ILD-like conditions such as pneumonitis and lung infiltration were reported in 6 subjects (1.3%). In the Non-DTC, Non-HCC monotherapy Safety Set, ILD-like conditions were reported in 4 subjects (0.6%). In the RCC Lenvatinib + Everolimus Safety Set, ILD-like conditions were reported in 43 subjects (6.9%). These events included pneumonitis (n=30), interstitial lung disease (n=10), and bronchiolitis, lung infiltration, and lung opacity (n=1 for each). In the HCC Lenvatinib Safety Set, ILD-like conditions were reported in 3 subjects (0.6%).

	In the All RCC Lenvatinib + Pembrolizumab Safety Set (N=497), ILD-like conditions were reported in 24 subjects (4.8%). These events included pneumonitis in 4.0% of subjects (n=20), lung infiltration in 0.4% of subjects (n=2), and eosinophilia myalgia syndrome and interstitial lung disease each in 0.2% of subjects (n=1). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): TEAEs of ILD-like conditions SMQ were reported in 9 subjects (1.7%). The most frequent ILD-like event was pneumonitis reported in 1.3% of subjects (n=7). Post-authorisation events of ILD-like conditions have been in accordance with the safety profile of lenvatinib in clinical trials. • Seriousness/outcomes ILD-like conditions were mainly Grade 1 or 2, with 1 Grade 3 event of pneumonitis reported from the Non-DTC, Non-HCC monotherapy Safety Set. Four events of pneumonitis were reported: 3 from the All DTC Lenvatinib Safety Set (2 Grade 2 events, and 1 Grade 1 event); and 1 Grade 3 event from the Non-DTC, Non-HCC Monotherapy Safety Set. Three events of lung infiltration were reported, 2 Grade 2 events from the All DTC set and 1 Grade 1 event from the Non-DTC, Non-HCC Monotherapy Safety Set. In the RCC Lenvatinib + Everolimus Safety Set, ILD-like conditions were Grade 1 or 2 (22 Grade 1 and 18 Grade 2). There were 3 events of Grade 3 severity. In the HCC Lenvatinib Safety Set, there was 1 event each of Grade 1, Grade 2, and Grade 3 severity. Events of idiopathic pulmonary fibrosis and necrotizing bronchiolitis were reported in the same subject, and additionally 1 event each of pneumonitis and radiation pneumonitis was reported in individual subjects. All EC Lenvatinib + Pembrolizumab Safety Set (N=530): TEAEs of ILD-like SMQ conditions were Grade 2 or 3 (4 subjects [0.8%] for each Grade). Seven events of pneumonitis were reported (1 Grade 1, 3 Grade 2, and 3 Grade 3) and 2 events of immune-mediated pneumonitis (1 Grade 2 and 1 Grade 3) were reported. • Severity and nature of risk In the All DTC Safety Set there was 1 subject who had an SAE of pneumonitis, which did not lead to treatment discontinuation, and this event resolved with no sequelae of death. No dose reductions of lenvatinib were necessary and only 1 subject required treatment interruption. All RCC Lenvatinib + Everolimus Safety Set (N=623): Four subjects had SAEs of ILD-like conditions SMQ. Two subjects (0.4%) had a dose reduction and 9 subjects (1.7%) had a dose interruption due to ILD-like conditions. Treatment was discontinued in 3 subjects (0.6%). In the HCC Lenvatinib Safety Set, there was 1 subject who had an SAE of pneumonitis, which resulted in hospitalization and interruption of study drug. Following improvement of the pneumonitis, study drug was resumed at the original dose. All RCC Lenvatinib + Pembrolizumab Safety Set (N=497): One subject (0.2%) died due to an ILD-like condition SMQ (pneumonitis). SAEs were reported in 2.4% of subjects (n=12). One subject (0.2%) had a dose reduction of lenvatinib and 6 subjects (1.2%) had a dose interruption of lenvatinib due to ILD-like conditions. Lenvatinib treatment was discontinued in 3 subjects (0.6%). All EC Lenvatinib + Pembrolizumab Safety Set (N=530): Four subjects had SAEs of ILD-like conditions SMQ (pneumonitis). Lenvatinib was interrupted in 4 subjects (0.8%) and discontinued in 1 subject (0.2%).

Overview of severe ILD-like conditions per SMQ Analysis			
For ILD-like conditions-SMQ, Subjects With At Least 1:	**All DTC Lenvatinib Safety Set N=458 SY[a]=608.1**	**RCC Lenvatinib + Everolimus Safety Set N=623 SY[a]=654.6**	**HCC Lenvatinib Safety Set N=496 SY[a]=340.0**
TEAE, n (%)	6 (1.3)	43 (6.9)	3 (0.6)
TEAE, no. of episodes (episodes/SY)	7 (0.01)	N/A	4 (0.01)
TEAE with maximum CTCAE Grade of [b], n (%)			
1	1 (0.2)	22 (3.5)	1 (0.2)
2	4 (0.9)	18 (2.9)	1 (0.2)
3	1 (0.2)	3 (0.5)	1 (0.2)
4	0	0	0
5	0	0	0
SAE	2 (0.2)	4 (0.6)	1 (0.2)
TEAE leading to treatment discontinuation, n (%)	0	3 (0.6)[c]	0
TEAE leading to study drug modification[d], n (%)			
Reduction	0	2 (0.4)[c]	1 (0.2)
Interruption	1 (0.2)	9 (1.7)[c]	1 (0.2)

For each row category, a subject with 2 or more adverse events in that category is counted only once.
AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, DTC = differentiated thyroid cancer, HCC = hepatocellular carcinoma, ILD = interstitial lung disease, MedDRA = Medical Dictionary for Regulatory Activities, N/A = not applicable, RCC = renal cell carcinoma, SMQ = standard MedDRA query, SAE = serious adverse event, SY -= subject year, TEAE = treatment-emergent adverse event.

a: Total treatment subject-years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions).

b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade.

c: Percentages are based on subjects from Studies 307, 112, and 218 (Arm A [Lenvatinib 18 mg + Everolimus]) where treatment discontinuations or modifications of each individual drug (lenvatinib, everolimus) due to AEs are available (N=530).

d: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Overview of severe ILD-like conditions per SMQ Analysis		
For ILD-like conditions-SMQ, Subjects With At Least 1:	**All EC Lenvatinib + Pembrolizumab Safety Set N=530 SY[a]=399.8**	**All RCC Lenvatinib + Pembrolizumab Safety Set N=497 SY[a]=641.8**
TEAE, n (%)	9 (1.7)	24 (4.8)
TEAE with maximum CTCAE Grade of [b], n (%)		
1	1 (0.2)	4 (0.8)
2	4 (0.8)	10 (2.0)
3	4 (0.8)	8 (1.6)
4	0 (0.0)	1 (0.2)
5	0 (0.0)	1 (0.2)
SAE	4 (0.8)	12 (2.4)

	TEAE leading to lenvatinib discontinuation, n (%) | 1 (0.2) | 3 (0.6) TEAE leading to study drug modification [c], n (%) Lenvatinib dose reduction | 0 (0.0) | 1 (0.2) Lenvatinib drug interruption | 4 (0.8) | 6 (1.2) For each row category, a subject with 2 or more adverse events in that category is counted only once. CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, ILD = interstitial lung disease, Medical Dictionary for Regulatory Activities, RCC = renal cell carcinoma, SAE = serious adverse event, SMQ = standard MedDRA query, SY = subject year, TEAE = treatment-emergent adverse event. a: Total Treatment Subject-Years = sum of treatment time (in years) for all subjects in the respective treatment group (including dose interruptions). b: If a subject had more than 1 TEAE, the subject is only counted once at the maximum grade. c: A subject may be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.
Risk factors and risk groups:	Patients with underlying respiratory disorders may be at higher risk of developing ILD-like events with lenvatinib treatment. Combination with Pembrolizumab: Pembrolizumab is a humanised monoclonal antibody which may trigger immune-related reactions. Pneumonitis (including ILD and organizing pneumonia) has been reported in subjects receiving pembrolizumab and is an ADR of pembrolizumab (Keytruda SmPC). Combination with everolimus Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) has been frequently reported in patients receiving everolimus and is an ADR of everolimus (see Afinitor SmPC).
Preventability	The development of ILD-like events such as pneumonitis should be monitored and managed in patients. Pneumonitis is a potentially life-threatening condition and may require urgent intervention.
Impact on the risk-benefit balance of the product:	Routine pharmacovigilance monitoring in place; If severe, ILD-like events can have a substantial negative effect on patient quality of life due to symptoms such as dyspnea, tachypnoea, fatigue, and dizziness but considered unlikely to have significant impact of the risk-benefit profile of the product.
Public health impact:	None identified

Important Potential Risk: Overdose (concomitant everolimus) (RCC)	
Potential mechanisms:	Not applicable.
Evidence source(s) and strength of evidence:	Primarily based on potential for dosing errors as dose of everolimus when used concomitantly with lenvatinib is lower than when everolimus is used alone; there was one report of concomitant everolimus overdose involving a single administration in randomised clinical trials.
Characterisation of the risk:	• Frequency In the RCC Lenvatinib + Everolimus Safety Set, everolimus overdose was recorded in 4 subjects (0.6%). Two subjects in Study 307 had a planned dose of 0 mg and took 5 mg for 1 day. At a planned dose of 5 mg, 1 subject in Study 205 took 10 mg for 1 day and 1 subject in Study 307 took 10 mg for

	4 days. • Seriousness/outcomes No AEs were reported as a result of overdose. • Severity and nature of risk Unknown, no AEs were reported.
Risk factors and risk groups:	Molecularly targeted drugs given in combination are usually administered at a dosage lower than that of their individual monotherapies, so one might expect physicians and pharmacists prescribing or dispensing such drugs to be alert to this risk. If a prescribing error did occur which was not detected at the point of dispensing, then it is conceivable that a patient might receive a combination dose of 18 mg lenvatinib + 10 mg everolimus unchecked for several weeks.
Preventability	Patients commencing this combination therapy (who would be at most at risk of such a medication error) are closely monitored on a weekly (BP) then fortnightly (BP and liver function) basis for the first 2 months of treatment, hence it seems unlikely that a medication error would go unchecked for longer than 2 weeks.
Impact on the risk-benefit balance of the product:	Routine pharmacovigilance monitoring in place. None identified
Public health impact:	None identified

SVII.3.2. Presentation of the missing information

Missing information: None

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 24 Summary of Safety Concerns	
Important identified risks	• Proteinuria and nephrotic syndrome • Renal failure or impairment • Cardiac failure • Posterior reversible encephalopathy syndrome (PRES) • Hepatotoxicity • Haemorrhagic events • Arterial thromboembolic events (ATEs) • QTc prolongation • Hypothyroidism • Gastrointestinal perforation and fistula formation • Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax
Important potential risks	• Venous thromboembolic events (VTEs) • Abnormal pregnancy outcome, excretion of lenvatinib in breast milk • Male and female fertility • Bone and teeth abnormalities in the paediatric population

Table 24 Summary of Safety Concerns	
	• Impaired wound healing • Interstitial lung disease (ILD)-like conditions • Overdose (concomitant everolimus) (RCC)
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

For all safety concerns routine pharmacovigilance is conducted. There are no modifications or additional routine pharmacovigilance activities for lenvatinib.

III.2 Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities. The requested studies have been completed. Only routine pharmacovigilance activities are necessary.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 25 Ongoing and Planned Additional Pharmacovigilance Activities

None

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 26 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Identified Risk:	
Proteinuria and Nephrotic Syndrome	Routine risk communication: • SmPC section 4.8 • package leaflet (PL) section 4 Routine risk minimisation activities to address risk: • Recommendations for dose modifications in the event of proteinuria are included in SmPC section 4.2 and recommendations for monitoring urine protein and discontinuing treatment in the event of nephrotic syndrome in section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Renal Failure or Impairment	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations for dose modifications in the event of renal impairment are included in SmPC section 4.2 and recommendation to actively manage GI toxicity as the major risk factor for renal impairment in section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Cardiac Failure	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations for dose modifications in the event of cardiac dysfunction are included in SmPC section 4.2 and recommendation to monitor patients for clinical symptoms or signs of cardiac decompensation in section 4.4. Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.

Posterior Reversible Encephalopathy Syndrome (PRES)	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations to monitor and control BP as a risk factor in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Hepatotoxicity	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations for liver function monitoring are included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Haemorrhagic events	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations to consider the potential degree of tumour invasion/infiltration of major blood vessels included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Arterial Thromboembolic Events (ATEs)	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendation that lenvatinib should be discontinued in the case of an arterial thrombotic event included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
QT interval prolongation	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations to monitor and correct any electrolyte abnormalities and to consider ECG monitoring included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.

Hypothyroidism	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations to monitor thyroid function before and during treatment and to treat any hypothyroidism to maintain euthyroid state in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Gastrointestinal perforation and fistula formation	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendations for dose modifications/ withdrawal in the event of perforation/ fistula are included in SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Non-gastrointestinal fistula formation and pneumothorax	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Recommendation that lenvatinib should not be started in patients with fistulae to avoid worsening and should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement included in section 4.4 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine.
Potential risks	
Venous Thromboembolic Events	Routine risk communication: • SmPC section 4.8 • PL section 4
Abnormal pregnancy outcome, excretion of lenvatinib in breast milk	Routine risk communication: • SmPC section 4.6 • PL section 2
Male and female fertility	Routine risk communication: • SmPC section 4.6
Bone and teeth abnormalities in the paediatric population	Routine risk communication: • SmPC section 5.3

Impaired Wound Healing	Routine risk communication: • 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. Other routine risk minimisation measures beyond the Product Information: Prescription only medicine.
Interstitial Lung Disease (ILD)like conditions	Routine risk communication: Not applicable.
Overdose (concomitant everolimus) (RCC)	Routine risk communication: • SmPC section 4.2 • PL section 2
Missing information	
None	Not applicable

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 27 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Identified Risks		
Proteinuria and Nephrotic Syndrome	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC sections 4.2 and 4.4 where advice on monitoring urine protein and managing proteinuria or nephrotic syndrome is provided. • PL section 4	Additional pharmacovigilance activities: None
Renal failure or impairment	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on managing risk factors and managing renal failure or impairment is provided • PL section 4	Additional pharmacovigilance activities: None
Cardiac failure	Routine risk minimisation measures: • SmPC section 4.8	Additional pharmacovigilance activities:

Table 27 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC Sections 4.2 and 4.4 where advice on monitoring patients and managing cardiac failure is provided. • PL section 4	None
Posterior reversible encephalopathy syndrome (PRES)	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL section 4	Additional pharmacovigilance activities: None
Hepatotoxicity	Routine risk minimisation measures: • SmPC section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring liver function and managing hepatotoxicity is provided. • PL section 4	Additional pharmacovigilance activities: None
Haemorrhagic events	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL section 4	Additional pharmacovigilance activities: None
Arterial thromboembolic events (ATEs)	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice to discontinue in case of ATE is given • PL section 4	Additional pharmacovigilance activities: None
QTc prolongation	Routine risk minimisation measures: • SmPC section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring electrolytes and managing QT interval prolongation is provided • PL section 4	Additional pharmacovigilance activities: None
Hypothyroidism	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice on monitoring thyroid function is given • PL section 4	Additional pharmacovigilance activities: None
Gastrointestinal perforation and fistula formation	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • Sections 4.2 where recommendations for dose modifications/ withdrawal are provided • PL section 4	Additional pharmacovigilance activities: None
Non-gastrointestinal	Routine risk minimisation measures: • SmPC section 4.8	Additional pharmacovigilance activities:

Table 27 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
fistula formation and Pneumothorax	• SmPC section 4.4 where advice that lenvatinib should not be started in patients with fistulae and when to permanently discontinue lenvatinib is given • PL section 4	None
Potential Risks		
Venous thromboembolic events (VTEs)	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4	Additional pharmacovigilance activities: None
Abnormal pregnancy outcome, excretion in breast milk	Routine risk minimisation measures: • SmPC section 4.6 • PL section 2	Additional pharmacovigilance activities: None.
Male and female fertility	Routine risk minimisation measures: • SmPC section 4.6	Additional pharmacovigilance activities: None.
Bone and teeth abnormalities in the paediatric population	Routine risk minimisation measures: • SmPC section 5.3	Additional pharmacovigilance activities: None.
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. Prescription only medicine.	Additional pharmacovigilance activities: None
Interstitial lung disease (ILD)¬like conditions	Not applicable.	Additional pharmacovigilance activities: None
Overdose (concomitant everolimus)	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2	Additional pharmacovigilance activities: None.
Missing information		
None	Not applicable	Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Lenvima / Kisplyx (lenvatinib)

This is a summary of the risk management plan (RMP) for Lenvima/Kisplyx. The RMP details important risks of Lenvima/Kisplyx, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) associated with Lenvima/Kisplyx.

The summary of product characteristics (SmPC) for Lenvima/Kisplyx and its package leaflet (PL) give essential information to healthcare professionals and patients on how Lenvima/Kisplyx should be used.

This summary of the RMP for Lenvima/Kisplyx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the RMP for Lenvima/Kisplyx.

I. The medicine and what it is used for

Lenvima/Kisplyx is authorised as monotherapy for the treatment of adult patients with progressive, locally advanced DTC and for the treatment of adult patients with advanced or unresectable HCC who have received no prior systemic therapy. Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced RCC, Kisplyx is indicated in combination with pembrolizumab for the first-line treatment of adult patients with advanced RCC. Lenvima is indicated in combination with pembrolizumab in adult patients with advanced EC who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. It contains lenvatinib mesilate as the active substance and it is given orally once daily.

Further information about the evaluation of the benefits of Lenvima/Kisplyx can be found in the EPAR, including a plain-language summary, available on the EMA website under the medicine's webpage (web link to be provided by EMA).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lenvima/Kisplyx, together with measures to minimise such risks and the proposed studies for learning more about the risks of Lenvima/Kisplyx are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (eg, with or without prescription) can help minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

If important information that may affect the safe use of Lenvima/Kisplyx is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lenvima/Kisplyx are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lenvima/Kisplyx. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Proteinuria and nephrotic syndrome • Renal failure or impairment • Cardiac failure • Posterior reversible encephalopathy syndrome (PRES) • Hepatotoxicity • Haemorrhagic events • Arterial thromboembolic events (ATEs) • QTc prolongation • Hypothyroidism • Gastrointestinal perforation and fistula formation • Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax
Important potential risks	• Venous thromboembolic events (VTEs) • Abnormal pregnancy outcome, excretion of lenvatinib in breast milk • Male and female fertility • Bone and teeth abnormalities in the paediatric population • Impaired wound healing • Interstitial lung disease (ILD)-like conditions • Overdose (concomitant everolimus) (RCC)
Missing information	• None

II.B Summary of important risks

Important Identified Risk: Proteinuria and Nephrotic Syndrome	
Evidence for linking the risk to the medicine	Evidence from randomised clinical studies. In randomised clinical trials proteinuria was reported in more patients treated with lenvatinib than placebo. Nephrotic syndrome was identified from post-marketing surveillance and the pathological mechanism is similar to that of proteinuria.
Risk factors and risk groups	DTC The presence of hypertension during lenvatinib treatment appeared to be correlated with the development of protein in the urine (proteinuria). In addition, proteinuria was more common in women, Asians, people aged 75 years or more, and people with diabetes and kidney problems. RCC Proteinuria was more common in men and in those people with hypertension.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring urine protein and managing proteinuria and nephrotic syndrome is provided. • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Renal Failure or Impairment	
Evidence for linking the risk to the medicine	Evidence from randomised clinical studies. In randomised clinical trials renal failure and impairment was reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Risk factors associated with renal impairment or failure in patients receiving lenvatinib included underlying chronic renal impairment, adrenal mass, sepsis, and dehydration and/or hypovolemia. The main risk factor for kidney failure or injury is dehydration (excessive loss of body water) resulting from diarrhoea or vomiting.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on managing risk factors and managing renal failure or impairment is provided • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Cardiac failure	
Evidence for linking the risk to the medicine (not missing information)	In randomised clinical trials decreased ejection fraction/cardiac failure was reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Most of the patients affected with heart failure during treatment with lenvatinib had other risk factors such as pre-existing heart disease, breathing difficulties, obesity, trouble with blood sugar control (diabetes mellitus), high BP, and prior anthracycline use (a type of chemotherapy drug).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring patients and managing cardiac failure is provided • PL Section 4 No additional risk minimisation measure.
Additional pharmacovigilance activities	None

Important Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES)	
Evidence for linking the risk to the medicine	A small number of events of PRES were reported in patients treated with lenvatinib and PRES is a known effect associated with other antiangiogenic agents.
Risk factors and risk groups	Blood pressure is elevated from baseline in most patients and systemic hypertension is a major risk factor. There are multiple well-defined conditions that can cause PRES in cancer patients, including hypertension and renal dysfunction, as can immunosuppressants, chemotherapeutic drugs, bone marrow/stem cell transplants, corticosteroids, and growth factors.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	In randomised clinical trials liver-related reactions were reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Multiple confounding factors were observed in subjects in the clinical trial program, such as the presence of liver metastases or progression of preexisting liver metastases, concurrent medications, and contributing comorbidities. However, there were a few cases without any confounding factors that occurred

Important Identified Risk: Hepatotoxicity	
	shortly after the start of treatment with lenvatinib and that resolved upon discontinuation of lenvatinib.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring liver function and managing hepatotoxicity is provided. • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Haemorrhage	
Evidence for linking the risk to the medicine	In randomised clinical trials haemorrhage was reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	The majority of intracranial haemorrhagic events in the lenvatinib clinical database were associated with the presence of tumour in the area of the bleed. These events were also often associated with the confounding factor of hypertension.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Arterial Thromboembolic Events	
Evidence for linking the risk to the medicine	In randomised clinical trials ATEs were reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups (not missing information)	Risk factors associated with thromboembolic events in addition to the underlying malignant disease include age ≥65 years, smoking, hypertension, diabetes mellitus, obesity, atrial fibrillation, hyperlipidaemia, and prior thromboembolic disease.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.4 where advice to discontinue in case of ATE is given • PL section 4 No additional risk minimisation measures

Important Identified Risk: Arterial Thromboembolic Events	
Additional pharmacovigilance activities	None

Important Identified Risk: QTc Prolongation	
Evidence for linking the risk to the medicine	In randomised clinical trials QT/QTc prolongation was reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Many of the patients who had QTc prolongation also had risk factors such as hypocalcaemia (low calcium), hypothyroidism (underactive thyroid), arterial hypertension, and obesity, and many patients had changes in their body salt balance at the time of the event.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring electrolytes and managing QT interval prolongation is provided • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Hypothyroidism	
Evidence for linking the risk to the medicine	In randomised clinical trials events of blood thyroid stimulating hormone increased were reported in more patients treated with lenvatinib than placebo and there were reports of hypothyroidism in patients treated with lenvatinib.
Risk factors and risk groups	Subjects with DTC who have undergone thyroidectomy and are receiving thyroid replacement therapy could develop low TSH due to thyroxine substitution. It is possible that treatment with lenvatinib may exacerbate thyroid dysfunction due to a direct effect on TSH levels.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.4 where advice on monitoring thyroid function is given • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Gastrointestinal (GI) Perforation and Fistula Formation	
Evidence for linking the risk to the medicine	In randomised clinical trials events of GI perforation or fistula were reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	The majority of these events occurred in areas of local tumour involvement. Many of the subjects had a medical history of GI bleed, gallstones, rectal abscess, diverticulitis, vaginal mass, diverticulosis of the large intestine, and colon resection for colon cancer. Subjects with oesophageal or tracheal fistula had prior neck surgery such as thyroidectomy and neck lymph node dissection.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • Sections 4.2 where recommendations for dose modifications/ withdrawal are provided • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Identified Risk: Non-Gastrointestinal (GI) Fistula Formation and Pneumothorax	
Evidence for linking the risk to the medicine	Post-marketing reports of non-gastrointestinal fistula formation and pneumothorax in association with lenvatinib have been received.
Risk factors and risk groups	Prior surgery or radiotherapy may be risk factors for the development of non-GI fistulae. Patients with pre-existing fistulae treated with lenvatinib are at increased risk of worsening. Data from ongoing studies in solid tumours indicates that the risk of pneumothorax may be higher in certain types of tumours such as soft tissue sarcoma. The presence of lung metastases and tumours with high therapeutic responses to lenvatinib may increase the risk of pneumothorax.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.4 where advice that lenvatinib should not be started in patients with fistulae and when to permanently discontinue lenvatinib is given. • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Potential Risk: Venous Thromboembolic Events (VTEs)	
Evidence for linking the risk to the medicine	In randomised clinical trials events of pulmonary embolism were reported in more patients treated with lenvatinib than placebo and there is a recognised potential class effect

Important Potential Risk: Venous Thromboembolic Events (VTEs)	
Risk factors and risk groups	Risk factors associated with VTEs include underlying malignant disease, age ≥65 years, and immobility.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	None

Important Potential Risk: Abnormal Pregnancy Outcome, Excretion of Lenvatinib in Breast Milk	
Evidence for linking the risk to the medicine	Nonclinical data. There are insufficient clinical data to exclude a risk.
Risk factors and risk groups (not missing information)	Women of childbearing potential and lactating females.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 No additional risk minimisation measures

Important Potential Risk: Effect on Male and Female Fertility	
Evidence for linking the risk to the medicine	Nonclinical data. There are insufficient clinical data to exclude a risk.
Risk factors and risk groups	Men and women of reproductive age
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 No additional risk minimisation measures

Important Potential Risk: Bone and Teeth Abnormalities in the Paediatric Population	
Evidence for linking the risk to the medicine	Nonclinical data. There are currently insufficient clinical data to exclude or confirm a risk.
Risk factors and risk groups (not missing information)	Paediatric patients with an active growth plate and young enough to not yet have developed their permanent teeth.

Important Potential Risk: Bone and Teeth Abnormalities in the Paediatric Population	
Risk minimisations measures	Routine risk minimisation measures: • SmPC Section 5.3 No additional risk minimisation measures

Important Potential Risk: Impaired Wound Healing	
Evidence for linking the risk to the medicine	Known effect of some other medicines in the class; insufficient clinical data to exclude a risk.
Risk factors and risk groups	Surgery or radiotherapy within 4 weeks of treatment with a VEGF/VEGFR targeted therapy are risk factors for impaired wound healing.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	None

Important Potential Risk: Interstitial Lung Disease (ILD) like Conditions	
Evidence for linking the risk to the medicine	"Interstitial lung disease-like events" have been reported for several other medicinal products from the same pharmacological class.
Risk factors and risk groups	Patients with underlying respiratory disorders may be at higher risk of developing ILD-like events with lenvatinib treatment
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	None

Potential Risk: Overdose (concomitant everolimus) (RCC)	
Evidence for linking the risk to the medicine	There is a potential for dosing errors as the dose of everolimus when used concomitantly with lenvatinib is lower than when everolimus is used alone in monotherapy. In the RCC Lenvatinib + Everolimus Safety Set, everolimus overdose was recorded in 4 subjects (0.6%). Two subjects in Study 307 had a planned dose of 0 mg and took 5 mg for 1 day. At a planned dose of 5 mg, 1 subject in Study 205 took 10 mg for 1 day and 1 subject in Study 307 took 10 mg for 4 days.
Risk factors and risk groups	Molecularly targeted drugs given in combination are usually administered at a dosage lower than that of their individual monotherapies so physicians and pharmacists prescribing or dispensing such drugs should be alert to this risk.
Risk minimisations measures	Routine risk minimisation measures: • SmPC Section 4.2

Potential Risk: Overdose (concomitant everolimus) (RCC)	
	• PL Section 2 No additional risk minimisation measures

Missing Information: None	
Risk minimisations measures	Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lenvima/Kisplyx.

II.C.2 Other studies in post-authorisation development plan

Study Short Name	Purpose of the Study
DTC	
None	
RCC	
None	

PART VII: Annexes Pages 140 to 144 removed - Out of Scope - Annexes 1-3

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Annex 4 – Specific adverse drug reaction follow-up forms

Not Applicable.

Annex 5 – Protocols for proposed and ongoing studies in RMP part IV

Out of Scope

[redacted]

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not Applicable.

Annex 7 – Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
7.0	H0004224 11 Dec 2015	Safety concerns • Identified Risks: Hypothyroidism has been added as an important identified risk since hypothyroidism has been frequently observed in subjects with RCC treated with lenvatinib, and is thought to be the result of a direct effect of lenvatinib on thyroid function. • Potential Risks: The potential for lenvatinib for induction/inhibition of CYP-3A4 mediated drug metabolism has been moved from the section describing important potential risks to a section describing potential for drug interaction, since there is insufficient clinical evidence to establish this as an important potential risk. The potential for interaction between lenvatinib and warfarin has been removed from planned study exclusion criteria. Lenvatinib does not significantly inhibit or induce CYP3A4, CYP1A2, or CYP2C9 (the cytochrome complexes that are involved in the metabolism of the R- and S- enantiomers of warfarin). Consequently, lenvatinib exhibits little potential to alter the effect (increase or decrease INR) of warfarin by decreasing or

Version	Approval date Procedure	Change
		increasing its rate of elimination, and there would be minimal drug-drug interaction risk when lenvatinib is co-administered with warfarin.
7.1	H0004224 15 Jun 2016	Safety concerns • Potential Risks: The potential for lenvatinib for induction/inhibition of CYP-3A4 mediated drug metabolism has been recategorised as an important potential risk.
7.2	H0004224 14 Jul 2016	Safety concerns • Missing Information: Long-term use of lenvatinib (>12 months) has been added as missing information.
9.0	EMEA/H/C/PSUSA/00010380/201608 13 Oct 2016	Inconsistencies in the wording of the indication for RCC have been corrected. Safety concerns • Identified risks: Gastrointestinal perforation and fistula formation has been upgraded from a potential risk to an identified risk. Non-Gastrointestinal fistula formation has been added as an identified risk. Lenvatinib may increase the risk of GI perforation and development of fistulae (GI and non-GI). Worsening has been reported in some cases of patients with non-GI fistula treated with lenvatinib.
9.1	EMEA/H/C/003727 / II /0008 14 Jun 2017	Submission of Study 208 (to determine the long-term safety profile of lenvatinib in Japanese patients with advanced thyroid cancer).
10.1	EMEA/H/C/003727/II/0008 12 Sep 2017	Safety concerns – No major changes Pharmacovigilance Plan • Removal of Study 208 as an additional pharmacovigilance measure. No changes to SmPC wording are recommended at present; however, further analyses will be conducted following integration of the data into the ISS.
10.2	EMEA/H/C/003727/II/0008 26 Oct 2017	Safety concerns – No major changes Pharmacovigilance Plan • Addition of commitment to provide an ISS including data from DTC subjects in Studies E7080-G000-201,

Version	Approval date Procedure	Change
		E7080-J-081-208, and E7080-G000-303. Commitment originated from response to RfSI-2 on Type II variation submitting results of PASS study E7080-J081-208.
10.6	EMEA/H/C/003727/II/11G 28 Jun 2018	Safety concerns • Missing information: The following was removed from the list of missing information: - Use of lenvatinib in the paediatric population (since lenvatinib is indicated for use in the adult population). - Use of lenvatinib in patients aged ≥75 years (the reduced tolerability of this age group is addressed in sections 4.2 and 4.4 of the SmPC, and the differences in safety profile compared with younger patients is addressed in section 4.8 of the SmPC. Additionally, the majority of adverse reactions occurring at higher frequency in this age group are included as important identified risks). Pharmacovigilance Plan • Removal of Study 207 as an additional pharmacovigilance measure • Added Category 3 Observational study E7080-M000-508 as a pharmacovigilance measure to characterise hepatic related toxicity and overall safety profile in real-life conditions in the EU in HCC patients.
11.0	EMEA/H/C/003727/WS1396 12 Sep 2018	Updates were made throughout the RMP in accordance with the guidance in EU RMP format Rev.2. This RMP version also consolidates changes from RMP version 10.6, reflecting the new indication of hepatocellular carcinoma. Updates to patient exposure were made. Safety concerns • Identified risks: The following safety concerns, previously classified as important potential risks, were removed from the list of safety concerns - Pancreatitis The PRAC assessment report for the PSUR covering the period 13 Aug 2016 to 12 Feb 2017 (Procedure no.: EMEA/H/C/PSUSA/00010380/201702) included that in the next RMP update “Pancreatitis can be

Version	Approval date Procedure	Change
		removed as an important potential risk." (This followed the submission of a Type II variation by the MAH and the addition of pancreatitis as an undesirable effect to the SmPC for Lenvima and Kisplyx (Procedure No. EMEA/H/C/WS1123). - Potential of lenvatinib for induction/inhibition of CYP-3A4 Mediated Drug Metabolism. This was due to changes in the level of scientific evidence following the completion of study E7080-A001-109, a Phase 1 study to determine the effect of lenvatinib on the PK of midazolam, a CYP3A4 substrate. The study concluded that co-administration of lenvatinib had no clinically relevant effect on the PK of midazolam, either following a single dose of lenvatinib or when lenvatinib concentrations were at steady-state.
11.3	EMEA/H/C/004224/II/0030 16 Jan 2020	E7080-G000-307: Protocol date was changed to reflect the date of the current amendment (10 Sep 2019). Milestone dates were updated to reflect the interim analysis report and final report submission dates. • Pharmacovigilance Plan E7080-G000-307: Protocol date was changed to reflect the date of the current amendment. Milestone dates were updated to reflect the interim analysis report and final report submission dates. Updated protocol: 10 Sep 2019 Interim analysis report submission: 31 Mar 2020 Final report submission: 31 May 2021
11.4	EMEA/H/C/003727/R/0031 26 Mar 2020	<u>Safety concerns</u> The following important identified risks were removed as a safety concern in the RMP: • Hypertension • Hypokalaemia • Hypocalcaemia • The following area of missing information was removed as a safety concern in the RMP: Use in

Version	Approval date Procedure	Change
		patients from ethnic origins other than Caucasian and Asian Modification of identified risks coming out of assessment of Type II variation to add nephrotic syndrome and pneumothorax to EU SmPC (CHMP opinion 25 Oct 2018): • Addition of pneumothorax as identified risk to non GI fistula (New title: Non-Gastrointestinal Fistula Formation and Pneumothorax). • Addition of nephrotic syndrome as identified risk to proteinuria (New title: Proteinuria and Nephrotic Syndrome). <u>Pharmacovigilance Plan</u> Changes in dates of post-authorisation measure (PAM) studies: • E7080-M001-221: Final study report date was updated to 30 Mar 2020. • E7080-G000-218: Protocol submission date was updated to reflect the date of latest protocol amendment The Category 3 studies E7080-G000-205 and E7080-A001-010 were completed and hence removed from the list of ongoing studies in the pharmacovigilance plan. • E7080-G000-211: Study design was updated to reflect the objectives per current protocol version. Per protocol amendment 03 dated 13 Feb 2017, the study design was updated to change the lower starting doses of lenvatinib from 14 mg and 20 mg to a single lower dose level of 18 mg. Study milestones were updated as follows: Study end (corresponding to last patient last visit) updated from February 2020 to September 2020 Study report date (corresponding to the date of submission of study report with the Type II variation) was updated from 31 Aug 2021 to 30 Apr 2021. • E7080-G000-201 and E7080-G000-303: - Date for final safety update reports updated from 31 Jan 2020 to 31 Aug 2020 as agreed.
12.0	10 Dec 2020	Completion of PAM studies

Version	Approval date Procedure	Change
	EMEA/H/C/WS 1861/G	• E7080-G000-201, E7080-G000-303, Integrated safety summary for DTC study subjects - Moved to completed studies with final report dates • E7080-M001-221 - Study milestone date for final CSR revised per SIAMED listings. • E7080-G000-307 Study milestone date for interim analysis report is removed based on the outcome from the independent data monitoring committee (IDMC)
12.1	EMEA/H/C/004 224/II/0041 18 Mar 2021	Safety concerns – No major changes Pharmacovigilance Plan Completion of PAM study • E7080-M001-221 - Moved to completed studies with final report dates
12.2	EMEA/H/C/004 224/II/0042 11 Feb 2021	Safety concerns – No major changes Pharmacovigilance Plan Completion of PAM study • E7080-G000-218 - Moved to completed studies with final report dates Summary of the risk management plan The summary of risk management plan was updated to reflect changes in Part II and Part III.
12.3	08 Jul 2021 EMEA/H/C/004 224/II/0048	Completion of PAM study • E7080-G000-211
14.1	26 Nov 2021 EMEA/H/C/004 224/II/0045 and EMEA/H/C/003 727/II/0042	New clinical study data were added regarding the new indications for renal cell carcinoma and endometrial carcinoma. No new identified and potential risks were noted.
15.0	14 April 2023	No new identified and potential risks were noted.

Version	Approval date Procedure	Change
	EMEA/H/C/004224/II/0052	New clinical study data were added for lenvatinib plus everolimus. The following areas of missing information were previously listed as safety concerns and are now removed, because summary of product characteristics, Sections 4.2 and 5.2, address these risks, and no additional pharmacovigilance is planned to further characterize risks (as recommended by the assessor following WS/1607). • Use in severe hepatic impairment • Use in severe renal impairment
15.1	09 Nov 2023 EMEA/H/C/003727/II/0050	Part II Module SIV - Populations not studied in clinical trials • Table 20 was updated with the efficacy and safety conclusions for the 2 paediatric clinical studies conducted under the agreed European Union (EU) paediatric investigational plan (PIP) (EMEA-001119-PIP02-12-M08). Administrative changes for internal consistency added the following: • "and pneumothorax" to Table 22 for the important identified risk Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax (per EMEA/H/C/003727/R/0031). • "and nephrotic syndrome" to Table 22 for the important identified risk Proteinuria and nephrotic syndrome. • "breast" for important potential risk Abnormal pregnancy outcome, excretion of lenvatinib in breast milk (Important Potential Risk table and Table 23). Summary of the safety concerns • Updated characterisation of the risk for bone and teeth abnormalities in the paediatric population. Summary of Risk Minimisation Measures was updated to reflect the removal of Study 207 from the additional pharmacovigilance activities for the potential risk of bone and teeth abnormalities in the paedeatric population.

Version	Approval date Procedure	Change
15.2	30 Nov 2023 EMEA/H/C/003727/II/0053	Updated milestone dates of final report submission for Studies E7080-G000-307 and E7080-M000-508, and added date of interim report for Study E7080-M000-508.
15.3	21 Mar 2024 EMEA/H/C/WS/2631	Part II Module SIV - Populations not studied in clinical trials Table 20 was updated with the efficacy and safety conclusions for the 2 paediatric clinical studies conducted under the agreed European Union (EU) paediatric investigational plan (PIP) (EMEA-001119-PIP03-19-M03). Administrative change (Annex VIII): Updated the summary of changes to the RMP over time to include the latest approved version 15.0 EMEA/H/C/004/224/II/0052
16.0	21 Mar 2024 EMEA/H/C/WS/2631	Consolidated versions 15.1, 15.2, and 15.3 of the RMP into version 16.0 at the end of the procedure
17.0	31 Oct 2024 EMEA/H/C/003727/II/0056	Removed completed Study 508 as an additional pharmacovigilance measure for the risk of hepatotoxicity.

CHMP = Committee for Medicinal Products for Human Use