28 June 2018
EMA/582721/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lenvima

International non-proprietary name: lenvatinib

Procedure No. EMEA/H/C/003727/II/0011/G

Note

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

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

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List of abbreviations

AASLDA	American Association for Study of Liver Disease Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special safety interest
AF	Alpha-fetoprotein
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase (also known as SGPT)
AST	Aspartate aminotransferase (also known as SGOT)
BCLC	Barcelona Clinic Liver Cancer
BMI	Body mass index
BSC	Best supportive care
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQoL-5 Dimensions questionnaire
EU	European Union
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded FWB Functional well-being
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practices
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCS	Hepatobiliary Cancer Subscale
HCV	Hepatitis C virus
HFSR	Hand foot skin reaction
HGF	Hepatocyte growth factor
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonization
ITT	Intention to treat
IVRS	Interactive voice response system
KIT	Gene encodes the ligand of the tyrosine-kinase receptor
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen activated protein kinase
MID	minimally important difference
mRECIST	modified Response Evaluation Criteria in Solid Tumours

MRI	Magnetic Resonance Imaging
NA	Not assessed
NASH	Non-Alcoholic steatohepatitis
NCI	National Cancer Institute
NRAS	Neuroblastoma RAS viral oncogene homolog New York Heart Association
OD	once daily
ORR	Objective tumour response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
p.o.	per os (by mouth)
PR	Partial response
PRO	Patient reported outcome
PS	Performance status score
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
ROW	Rest of the World
SAE	Serious adverse event
SAS	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TACE	trans catheter arterial chemoembolization
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumour, node, metastasis
TOI	Trial Outcome Index
TTP	Time to progression
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Eisai Europe Ltd. submitted to the European Medicines Agency on 24 July 2017 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Extension of indication to include treatment of hepatocellular carcinoma (HCC) based on pivotal Study 304; consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are being updated and the package leaflet is updated accordingly. In addition, section 4.2 of the SmPC is being updated to add that the product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include the unique identifier. An updated RMP version 10 was provided a part of the application.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

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

The new indication, which is the subject of this application, falls within a separate orphan designation EU/3/15/1460 granted on 19 March 2015.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) will review the designation of Lenvima as an orphan medicinal product in the approved indication.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/345/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with the authorised orphan medicinal product Nexavar. However, as the orphan market exclusivity of Nexavar expired on 1 November 2017, it was no longer necessary for the CHMP to conclude on possible similarity with Nexavar. At the time of adoption of the CHMP opinion, there were no authorised orphan medicinal products for the concerned indication.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bart Van der Schueren Co-Rapporteur: Robert James Hemmings

Timetable	Actual dates
Submission date	24 July 2017
Start of procedure:	12 August 2017
CHMP Co-Rapporteur Assessment Report	5 October 2017
CHMP Rapporteur Assessment Report	10 October 2017
PRAC Rapporteur Assessment Report	13 October 2017
PRAC members comments	18 October 2017
Updated PRAC Rapporteur Assessment Report	23 October 2017
PRAC Outcome	26 October 2017
CHMP members comments	30 October 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	2 November 2017
Request for supplementary information (RSI)	9 November 2017
CHMP Rapporteur (Joint) Assessment Report	25 January 2018
PRAC Rapporteur Assessment Report	25 January 2018
PRAC members comments	31 January 2018
PRAC Outcome	8 February 2018
CHMP members comments	12 February 2018
Updated CHMP Rapporteur (Joint) Assessment Report	15 February 2018
Request for supplementary information (RSI)	22 February 2018
CHMP Rapporteur (Joint) Assessment Report	9 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteur (Joint) Assessment Report	25 May 2018
Request for supplementary information (RSI)	31 May 2018
CHMP Rapporteur (Joint) Assessment Report	18 June 2018
CHMP members comments	20 June 2018
Updated CHMP Rapporteur (Joint) Assessment Report	22 June 2018
CHMP opinion:	28 June 2018

2. Scientific discussion

2.1. Introduction

Disease or condition

Hepatocellular carcinoma (HCC) is an invasive carcinoma of the liver.

Epidemiology

HCC is a cancer that usually occurs in the setting of liver cirrhosis, because of chronic infections with hepatitis B virus or hepatitis C virus, alcohol consumption, non-alcoholic steatohepatitis, or diabetes (EASL&EORTC 2012).

It is the third-leading cause of cancer-related death, and the global incidence is rising, with approximately 700,000 cases diagnosed worldwide in 2012 alone (Lozano et al. 2010, Torre et al. 2015).

In the US, the incidence of HCC is approximately 9.18 per 100,000 persons, in Southern Europe 9.8/3.2, in Western Europe 7.2/2.1, and in Northern Europe 3.8/1.6 (male/female, respectively) per 100,000 persons (Jemal et al. 2011). The incidence of HCC is rising in the last decennia and it varies geographically largely due to variations in the incidences of hepatitis B and C infection, with the majority of the cases (> 80%) occurring in sub-Saharan Africa and eastern Asia. One country alone, China, accounts for 40% to 50% of worldwide cases. Chronic HBV infection is the predominant risk factor for HCC in Southeast Asia and Africa, whereas chronic infection with hepatitis C virus (HCV) is the risk factor for HCC in Western countries and Japan. Unlike the rest of Asia, HCV infection accounts for up to 70% of HCCs in Japan. Currently, there is a rising HCC trend in the West, where the incidence used to be low, such as in the United States and Canada; this rise is attributed in part to the HCV epidemic in the 1960s and the prevalence of obesity and diabetes mellitus, which are associated with the metabolic syndrome and with nonalcoholic fatty liver disease (NAFLD). In Southern Europe, HCV and alcohol consumption account for the factors contributing to rising HCC incidence. Recent genomic studies have highlighted differences in genetic mutations and signatures among different groups of patients who have HCC with various etiologies. HCC outcomes also differ between Asian and non-Asian patients because of variations in management practices between East and West (Choo et al, 2016).

Management

Individual treatment decisions largely depend on the stage of disease, but not on its aetiology. Surgical resection, transplantation, and ablation are potential curative options for early-stage disease, whereas chemoembolisation is recommended for patients with preserved liver function and disease confined to the liver generally without vascular invasion. In most HCC patients, the disease is diagnosed at advanced stages, when curative treatments, including resection, liver transplantation, and ablation, are no longer suitable. For patients who are not or who are no longer candidates for loco regional therapy, the oral multikinase inhibitor sorafenib is the only systemic treatment currently approved in the EU. The approval was based on the results of a large Phase-3 clinical trial (Study 100554 SHARP) conducted in 602 HCC patients (Llovet et al. 2008). The study demonstrated significantly increased survival under sorafenib (plus BSC) compared to placebo (plus BSC) (HR 0.69; p=0.0005), with a median survival rate for the sorafenib arm of 10.6 months, compared with 7.9 months for the placebo arm. Another trial (Study 11849) similarly designed as SHARP and conducted in Asian subjects, confirmed the favourable SHARP results (Cheng et al. 2009). Subgroup analyses from studies conducted with sorafenib have demonstrated that the survival benefit of sorafenib is independent of the underlying aetiology of liver disease and independent of prior treatments such as TACE (transarterial chemoembolization) which is usually administered in intermediate-stage HCC. Other compounds (e.g., the anti-PD1 antibody nivolumab) are currently tested in clinical trials as first line treatment options in comparison with sorafenib.

Currently, another oral multikinase inhibitor regorafenib (Stivarga) is indicated as monotherapy for the treatment of adult patients with HCC who have been previously treated with sorafenib.

About the product

Lenvatinib is an oral multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor receptors (VEGFRs) VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor receptors (FGFRs) FGFR1, 2, 3, and 4; the platelet-derived growth factor receptor α (PDGFRα); KIT; and RET.

It is currently authorised as monotherapy for the treatment of patients with radio-iodine refractory differentiated thyroid cancer (orphan designation) and under the name of Kisplyx in combination with everolimus for treatment of advanced renal cell carcinoma (RCC) following a prior anti-angiogenic therapy (non-orphan designation).

With this variation application, the marketing authorisation holder (MAH) would like to extend the indication to the treatment of adult patients with HCC supported by the results of a Phase 3 trial (REFLECT).

Lenvima was designated as an orphan medicinal product EU/3/15/1460 on 19 March 2015 in the following indication: “Treatment of hepatocellular carcinoma (HCC)”. Orphan Designation for the treatment of HCC was granted on the grounds of prevalence (less than 5 in 10,000 patients) and an assumption of significant benefit of lenvatinib over the other medicinal product approved in the EU for treatment of hepatocellular carcinoma at that time (sorafenib).

CHMP scientific advice on the HCC clinical development programme was received on 15 Nov 2012 (EMA/CHMP/SAWP/698149/2012). For the Phase 3 study, the choice of comparator (sorafenib) and primary endpoint (overall survival) were endorsed. The CHMP preferred a blinded study to enhance the objectivity of the assessment of the secondary endpoints and safety. However, if the study were to be conducted open-label, measures should be implemented to ensure symmetric study conduct in both treatment arms.

An addendum to the non-clinical part of the dossier is submitted with this application and the Environmental Risk Assessment has been updated based on the expected wider use of Lenvima due to the new indication.

As part of the current grouped variation, to aid administration to patients who have difficulty swallowing, it is proposed to introduce alternative instructions to allow the capsule shells to be dissolved first in either water or apple juice, to produce a suspension prior to administration. Consequently, changes are proposed to Section 4.2 of the SmPC and the relevant section of the PL.

An RMP (version 10.0 dated 4 July) has been provided which covers the new indication with this variation. The adult indication of this extension is covered by a respective paediatric class waiver. Furthermore, the MAH has included a critical report addressing the possible similarity with authorised orphan medicinal products (Nexavar (INN: sorafenib tosylate) in the HCC condition.

The MAH applied for the following indication:

LENVIMA is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC).

The CHMP adopted a positive opinion for the following indication:

LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy (see section 5.1).

The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. Dose adjustments are based only on toxicities observed and not on body weight changes during treatment. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

Dose adjustment and Discontinuation

Management of some adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Details for monitoring, dose adjustment and discontinuation are provided in Table 2.

Table 1: Dose modifications from recommended lenvatinib daily dose in HCC patients

Starting Dose		**≥60 kg BW 12 mg (three 4 mg capsules orally once daily)**	**<60 kg BW 8mg (two 4 mg capsules orally once daily)**
Persistent and Intolerable Grade 2 or Grade 3 Toxicities [a]			
Adverse Reaction	**Modification**	**Adjusted Dose[b] (≥60 kg BW)**	**Adjusted Dose[b] (<60 kg BW)**
First occurrence [c]	Interrupt until resolved to Grade 0-1 or baseline [d]	8 mg (two 4 mg capsules) orally once daily	4 mg (one 4 mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline [d]	4 mg (one 4 mg capsule) orally once daily	4 mg (one 4 mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline [d]	4 mg (one 4 mg capsule) orally every other day	Discontinue
Life-threatening toxicities (Grade 4): Discontinue[e]			

a. Initiate medical management for nausea, vomiting, or diarrhoea prior to interruption or dose reduction.
b. Reduce dose in succession based on the previous dose level (12 mg, 8 mg, 4 mg or 4 mg every other day).
c. Haematologic toxicity or proteinuria-no dose adjustment required for first occurrence.
d. For haematologic toxicity, , dosing can restart when resolved to Grade 2; proteinuria, resume when resolves to less than 2g/24 hours
e. Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.

2.2. Non-clinical aspects

2.2.1. Introduction

To evaluate the primary pharmacodynamic effects of lenvatinib against HCC, the following additional *in vitro* and *in vivo* studies were conducted (limited to those not previously submitted in the RCC or DTC marketing authorization applications).

Primary PD, *in vitro* studies:

• Crystal structure of FGFR1-lenvatinib complex

• Inhibition of FGFR signaling in HCC cells

• Direct antiproliferative effects against HCC cells

Primary PD, *in vivo* studies:

• Antitumour effects in human HCC xenograft models

• Immunostimulatory effect in an HCC isograft model

Unless otherwise noted, all doses or concentrations on a weight basis described for lenvatinib in the

nonclinical studies are expressed in terms of the mesilate salt.

Four additional pharmacokinetics (PK) studies have been completed, and one study has been reanalysed. With the exception of the study conducted to evaluate substrate recognition and inhibition of multidrug and toxin extrusion (MATE) by lenvatinib, these studies were conducted to further address questions raised during the review of the original marketing application.

These studies include:

• Calculation of pharmacokinetic parameters of radioactive peaks in monkey plasma

• Protein binding in human liver microsomes (HLMs)

• Reversibility of covalently bound lenvatinib-related components to human plasma protein

• Reanalysis of modeling and simulation using Simcyp®

• Substrate recognition and inhibition of MATE

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

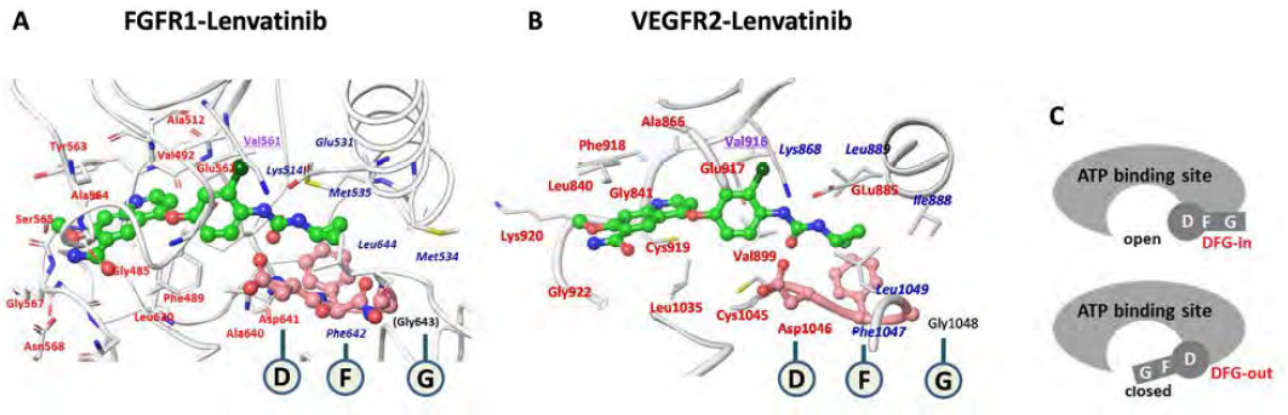
• Crystal structure of FGFR1-lenvatinib complex

In the original Marketing Authorization Application (MAA) for radio-iodine refractory DTC, crystal structure analysis of VEGFR2-lenvatinib complex revealed that lenvatinib binds to both the ATP-binding site and a neighboring allosteric region of VEGFR2 with the DFG motif adopting a “DFG-in” conformation, indicating a novel binding mode termed type V, which is distinct from that for most other multikinase inhibitors (type I or type II) on market (Okamoto, et al., 2015). A new study was conducted to confirm whether lenvatinib binds to another major target kinase, FGFR1 with the same binding mode.

The amino acid residues in the FGFR1-lenvatinib complex located in the vicinity of lenvatinib, with a maximum distance of 3.9 Å. They are identified as those belonging to the ATP-binding site. The result is comparable to that obtained from VEGFR2-lenvatinib complex, where the same analysis results in 13 residues for ATPbinding site, the Val916 residue for gate-keeper, and 5 residues for neighboring region.

As shown in0, in both the FGFR1-lenvatinib and VEGFR2-lenvatinib complexes, lenvatinib (colored green in the ball-and-stick model) binds to the ATP-binding site (amino acid residues are shown in red letters) at the common core from the urea group to the quinoline ring, and binds to the neighboring allosteric region (amino acid residues are shown in black letters) via the cyclopropane ring, which might have a strong hydrophobic interaction with the phenyl ring of Phe642 (FGFR1) or Phe1047 (VEGFR2).

These results indicated that the binding mode of lenvatinib to FGFR1 should be type V like the binding mode to VEGFR2, since the binding of lenvatinib to FGFR1 meets the 3 criteria that define a type V kinase inhibitor: 1) binds to the ATP-binding site, 2) binds to the neighboring allosteric region, and 3) fits to the kinase adopting the DFG-in conformation.



A: FGFR1-lenvatinib, B: VEGFR2-lenvatinib C: Schema for "DFG-in" and "DFG-out" Lenvatinib and the DFG-motif are shown as ball-and-stick models colored in green (●) and pink (●), respectively. Neighboring protein side chains are shown as ribbon models. Amino acid residues located less than 3.9 Å from lenvatinib are shown in red letters (ATP-binding site), violet letters (gate-keeper), or ***blue*** letters (the neighboring region). ATP = adenosine triphosphate, DFG = aspartic acid- phenylalanine-glycine, FGFR = fibroblast growth factor.

Figure 1: X-ray Analysis for Crystal Structure of FGFR1-Lenvatinib and VEGFR2-Lenvatinib Complexes

- **Inhibition of FGFR signalling in HCC cells**

The inhibitory effects of lenvatinib on the FGFR signal transduction in human HCC cell lines, Hep 3B2.1-7, HuH-7, and SNU-449 cells were studied by measuring the phosphorylation of FRS2, which is a pan-FGFR specific downstream signalling molecule. The effect of sorafenib, a multikinase inhibitor clinically used for the treatment of HCC, was also evaluated under the same study conditions (see 0).

Hep 3B2.1-7 and HuH-7 cells overexpress FGF19 and express its cognate receptor FGFR4. SNU-449 cells mainly express FGFR1.

Lenvatinib inhibited the phosphorylation of FRS2 in HuH-7 and Hep 3B2.1-7 human HCC cells at concentrations 0.03 to 3 µmol/L in a concentration-dependent manner and completely inhibited the phosphorylation of FRS2 at concentrations ≥1 µmol/L. In contrast, sorafenib showed incomplete inhibition of the phosphorylation of FRS2 at concentrations from 0.1 to 3 µmol/L. In SNU-449 cells lenvatinib inhibited the phosphorylation of FRS2 in a concentration-dependent manner at concentrations from 0.3 to 3 µmol/L and completely inhibited the phosphorylation of FRS2 at 3 µmol/L. In contrast, sorafenib showed incomplete inhibition of the phosphorylation of FRS2 at concentrations from 0.1 to 3 µmol/L.

Table 2: Tabulated summary of new *in vitro* primary pharmacodynamics studies

Type of Study	Methods	Species/ Strain	Dose or Concentration	Observations	Study/ Report No.
Crystal structure analysis	Recombinantly expressed human FGFR1 including kinase domain (Ser461-Asp774) was crystalized with lenvatinib. The resulting crystals of kinase-inhibitor complexes were subjected to x-ray structural analysis	Human/ FGFR1 (recombinant)	NA	Lenvatinib binds to the ATP-binding site and the neighboring allosteric region. The DFG motif adopts the DFG-in conformation in the FGFR1-lenvatinib complex.	W-20160357
Effect on FGFR signaling	Effect of the FGFR signal transduction in HCC cells was evaluated by a western blot analysis using antibodies against FRS2 and phosphorylated FRS2.	Human/ Hep 3B2.1-7 (HCC)	lenvatinib: 0.03, 0.1, 0.3, 1, 3 µmol/L sorafenib: 0.1, 0.3, 1, 3 µmol/L	Lenvatinib inhibited FGF19-driven phosphorylation of FRS2 at concentrations from 0.03 to 3 µmol/L in a concentration-dependent manner and completely inhibited the phosphorylation of FRS2 at ≥1 µmol/L. Sorafenib showed incomplete inhibition at concentrations from 0.1 to 3 µmol/L.	M16014
Effect on FGFR signaling	Effect of the FGFR signal transduction in HCC cells was evaluated by a western blot analysis using antibodies against FRS2 and phosphorylated FRS2.	Human/ HuH-7 (HCC)	lenvatinib: 0.03, 0.1, 0.3, 1, 3 µmol/L sorafenib: 0.1, 0.3, 1, 3 µmol/L	Lenvatinib inhibited the phosphorylation of FRS2 at concentrations from 0.03 to 3 µmol/L in a concentration-dependent manner and completely inhibited the phosphorylation of FRS2 at ≥1 µmol/L. Sorafenib showed incomplete inhibition of the phosphorylation of FRS2 at concentrations from 0.1 to 3 µmol/L.	M16019
Effect on FGFR signaling	Effect of the FGFR signal transduction in HCC cells was evaluated by a western blot analysis using antibodies against FRS2 and phosphorylated FRS2.	Human/ SNU-449 (HCC)	lenvatinib: 0.1, 0.3, 1, 3 µmol/L sorafenib: 0.1, 0.3, 1, 3 µmol/L	Lenvatinib inhibited the bFGF-driven phosphorylation of FRS2 at concentrations from 0.3 to 3 µmol/L in a concentration-dependent manner and completely inhibited the phosphorylation of FRS2 at 3 µmol/L. Sorafenib showed incomplete inhibition of the phosphorylation of FRS2 at concentrations from 0.1 to 3 µmol/L.	M16015
Effect on tumor cell proliferation	Inhibition of the cell proliferation was measured by a colorimetric assay using WST-8.	Human/ Hep 3B2.1-7 (HCC) HuH-7 (HCC) PLC/PRF/5 (HCC)	Lenvatinib and sorafenib: 39.1 – 10,000 nmol/L	Lenvatinib: IC_{50} = 230, 420, >10,000 nmol/L against Hep 3B2.1-7, HuH-7, PLC/PRF/5 cells, respectively. Sorafenib: IC_{50} = 2300, 2200,5300 nmol/L against Hep 3B2.1-7, HuH-7, PLC/PRF/5 cells, respectively.	M16007

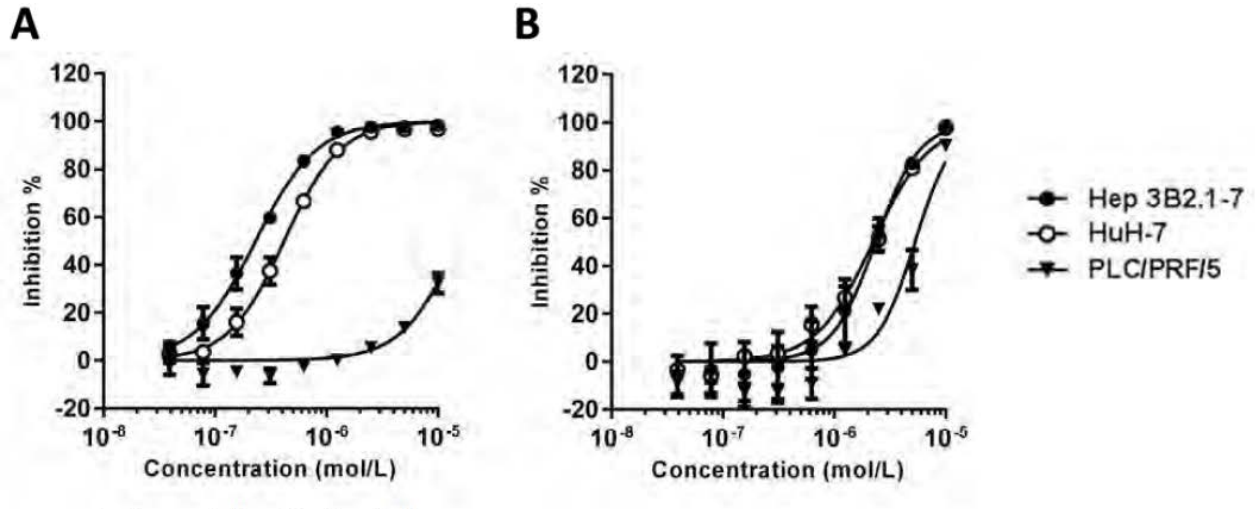
Doses or concentrations described for lenvatinib and sorafenib are expressed as those of the salt form.

ATP = adenosine triphosphate, DFG = aspartic acid-phenylalanine-glycine, FGF = fibroblast growth factor, FGFR = fibroblast growth factor receptor, HCC = hepatocellular carcinoma, IC50 = half-maximal inhibitory concentration, WST-8 = 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium.

- **Direct antiproliferative effects against HCC cell lines**

This study examined the antiproliferative activity of lenvatinib against 3 human HCC cell lines, Hep 3B2.1-7, HuH-7, and PLC/PRF/5 in vitro (see 0). The cell proliferation of Hep 3B2.1-7 and HuH-7 is dependent on enhanced FGFR signaling involving an autocrine loop of overexpressing FGF19 and FGFR4. Serial

dilutions of lenvatinib mesilate and sorafenib tosylate were added to the cells in culture wells, and the cells were cultured for 6 days to evaluate the antiproliferative effect of lenvatinib. As a blank control, the vehicle was added to wells without cells. The viable cell number was determined by colorimetric assay using WST-8 reagent. Percent inhibition was calculated. As shown in 0, lenvatinib showed stronger antiproliferative activity against Hep 3B2.1-7 and HuH-7 cells compared to PLC/PRF/5 cells. Sorafenib did not show remarkable selectivity against either of the cell systems. IC50 values are presented in 0



A: Lenvatinib, B: Sorafenib.
Each point represents the mean ±SD of 3 independent experiments performed in triplicate.

Figure 2: Antiproliferative activities of lenvatinib and sorafenib against HCC cell lines

In vivo studies

- **Antitumour effects in human HCC xenograft models**

The antitumour effect of lenvatinib was evaluated in 5 human HCC xenograft models in athymic mice, and compared with the antitumour activity of sorafenib in the same models.

Table 3: Tabulated summary of new *in vivo* primary pharmacodynamic xenograft studies

Type of Study	Methods	Species/ Strain	Number/ Gender	Route	Dose or Concentration	Observations	Study/ Report No.
Antitumor effect in human cancer xenograft model in mice	Xenografts were generated by SC inoculation of the cancer cells. Dosing was initiated after 12 days (Day 1). The TV and the body weight of mice were measured on Days 1, 3, 6, and 8.	Mouse/ CAnN.Cg-*Foxn1*^{nu}/CrlCrlj Human/ Hep 3B2.1-7 (HCC)	8 female / group	lenvatinib, sorafenib: PO, QD×7	lenvatinib: 3, 10, 30 mg/kg sorafenib: 10, 30 mg/kg	Lenvatinib (3, 10, 30 mg/kg) showed significant TGI with T/C values of 56%, 51%, and 31%, respectively at Day 8. Sorafenib (10, 30 mg/kg) showed significant TGI with T/C values of 73% and 47%, respectively at Day 8. No remarkable BWL was observed in all treated groups.	M16008
Antiangiogenic activity in human cancer xenograft model in mice	Xenografts generated in Study No. M16008 were used. One day after the last dose (Day 8), tumor was isolated and the MVD was evaluated by IHC staining for CD31.	Mouse/ CAnN.Cg-*Foxn1*^{nu}/CrlCrl Human/ Hep 3B2.1-7 (HCC)	8 female / group	lenvatinib, sorafenib: PO, QD×7	lenvatinib: 3, 10, 30 mg/kg sorafenib: 10, 30 mg/kg	Lenvatinib (3, 10, 30 mg/kg) significantly reduced MVD in the tumor with T/C values of 77%, 62%, and 51%, respectively at Day 8. Sorafenib at 30 mg/kg but not 10 mg/kg significantly reduced MVD with a T/C value of 72% at Day 8.	M16011
Antitumor effect in human cancer xenograft model in mice	Xenografts were generated by SC inoculation of the cancer cells. Dosing was initiated after 11 days (Day 1). The TV (3 times a week) and the body weight of mice (daily) were measured.	Mouse/ Crl:NU-*Foxn1*^{nu} Human/ LIXC-012 (HCC cell line generated from a patient-derived xenograft)	8 female / group	lenvatinib, sorafenib: PO, QD×14	lenvatinib: 3, 10, 30 mg/kg sorafenib: 10, 30 mg/kg	Lenvatinib (3, 10, 30 mg/kg) showed significant TGI with T/C values of 61%, 43%, and 25%, respectively at Day 11. Sorafenib at 30 mg/kg but not 10 mg/kg showed significant TGI with a T/C value of 55% at Day 11. BWL was observed in the vehicle controls accompanied by cachexia, resulting in RBW values of 0.85 to 0.87 at Day 11. This BWL was less in the lenvatinib (10, 30 mg/kg) groups with RBW values of 0.93 and 0.96, respectively. The BWL in sorafenib (10, 30 mg/kg) groups was similar to that in the vehicle control with RBW values of 0.87 and 0.85, respectively.	CPB-P16-5670
Antitumor effect in human cancer xenograft model in mice	Xenografts were generated by SC inoculation of the tumor fragment. Dosing was initiated after 19 days (Day 1). The TV and the body weight of mice were measured twice a week.	Mouse/ CAnN.Cg-*Foxn1*^{nu}/CrlChfk Human/ HuPrime®LI0050 (HCC, patient derived)	15 female / group	lenvatinib, sorafenib: PO, QD×28	lenvatinib: 10, 30 mg/kg sorafenib: 30 mg/kg	Lenvatinib (10, 30 mg/kg) showed significant TGI with T/C values of 46% and 33%, respectively without severe BWL at Day 29. Sorafenib was not tolerated; multiple dosing suspensions were necessary during the treatment and 5 of 15 mice died by Day 19. A maximum mean BWL of 13% (RBW = 0.87) was noted on Day 18.	E0606-U1602. LI0050
Antitumor effect in human cancer xenograft model in mice	Xenografts were generated by SC inoculation of the tumor fragment. Dosing was initiated after 46 days (Day 1). The TV and the body weight of mice were measured twice a week.	Mouse/ STOCK-*Foxn1*^{nu}/JNju Human/ HuPrime®LI0334 (HCC, patient derived)	15 female / group	lenvatinib, sorafenib: PO, QD×28	lenvatinib: 10, 30 mg/kg sorafenib: 30 mg/kg	Lenvatinib (10, 30 mg/kg) showed significant TGI with T/C values of 25% and 14%, respectively without severe BWL at Day 29. Sorafenib did not show significant TGI.	E0606-U1602. LI0334

Doses or concentrations described for lenvatinib and sorafenib are expressed as those of the salt form.
BWL = body weight loss, HCC = hepatocellular carcinoma, MVD = microvessel density, PO = oral, QD×X = once daily for X days, RBW = relative body weight, SC = subcutaneous, T/C = treatment/control, TGI = tumour growth inhibition, TV= tumour volume

In the **Hep 3B2.1-7 human HCC** xenograft model, lenvatinib (3, 10, and 30 mg/kg) showed dose-dependent and significant tumour growth inhibition (TGI) compared to the vehicle control with treatment/control (T/C) values of 56%, 51%, and 31%, respectively on Day 8. Sorafenib (10 and 30 mg/kg) also showed dose-dependent and significant TGI with T/C values of 73% and 47%, respectively. Body weight loss was similar in vehicle, lenvatinib- and sorafenib-treated groups with relative body weights (RBW) of 0.93, 0.87 and 0.89 respectively, at Day 8.

The antiangiogenic activity of lenvatinib and sorafenib was evaluated in the same Hep 3B2.1-7 xenograft model. Lenvatinib (3, 10, and 30 mg/kg) showed dose-dependent and significant decrease of microvessel density (MVD) compared to Vehicle 1 at Day 8 with T/C values of 77%, 62%, and 51%, respectively.

Sorafenib at 30 mg/kg showed significant decreases of MVD compared to Vehicle 2 with a T/C value of 72%; however, the effect on MVD at 10 mg/kg was not significant in this model. The good correlation of the TGI with the decrease of tumour MVD for lenvatinib suggests that the antiangiogenic activity contributes to the antitumour activity of lenvatinib.

In the **PDX-derived LIXC-012 HCC** xenograft model, lenvatinib (3, 10, and 30 mg/kg) showed dose-dependent and significant TGI with T/C values of 61%, 43%, and 25%, respectively at Day 11. Sorafenib at a dose of 30 mg/kg also showed significant TGI with T/C values of 55% at Day 11; but sorafenib at a dose of 10 mg/kg resulted in no TGI.

BWL was observed in the vehicle control groups due to cachexia, resulting in RBW values at Day 11 of 0.87 and 0.85, respectively. The BWL in the mid- and high-dose (10 and 30 mg/kg) lenvatinib groups was small with RBW values of 0.93 and 0.96 at Day 11, respectively, indicating that the TGI also alleviated cachexia-induced BWL. All mice survived in these groups.

In the **HCC PDX** model using **HuPrime® LI0050 tumour** derived from a HCC patient, lenvatinib (10 and 30 mg/kg) showed significant TGI against the LI0050 xenografts compared to vehicle control on Day 29 with T/C values of 46% and 33%, respectively. In the group treated with lenvatinib (30 mg/kg), dosing to 1/15 mice was suspended from Day 15 to Day 27 due to a transient BWL (the individual RBW = 0.79) at Day 15. Statistical analysis for TGI in the sorafenib-treated group was not performed since dosing was stopped several times during the course of the study and 5/15 mice died by Day 19.

No remarkable BWL was observed in lenvatinib treated groups (10 and 30 mg/kg) throughout the dosing period although 1/15 mice in the lenvatinib (30 mg/kg) group showed transient BWL (the individual RBW = 0.79) at Day 15 as described above. Sorafenib (30 mg/kg) was poorly tolerated in this HCC PDX model.

In another **HCC PDX** model using **HuPrime® LI0334 tumour** derived from an HCC patient, lenvatinib (10 and 30 mg/kg) showed significant TGI against the LI0334 xenografts compared to vehicle control on Day 29 with T/C values of 25% and 14%, respectively. Sorafenib (30 mg/kg) did not show significant TGI with a T/C value of 70%.

No remarkable BWL was observed in the treated mice.

- **Immunostimulatory effect in an HCC isograft model**

This study examined the antitumour effect of lenvatinib as well as the effect of lenvatinib on immune cell populations in the BNL 1ME A.7R.1 murine HCC isograft models (See 0).
As shown in 0, lenvatinib (3, 10 mg/kg) showed significant TGI on Day 8 in the BNL 1ME A.7R.1 murine HCC isograft model in immunocompetent mice with T/C values of -31% and –41%, respectively. The minus values indicate tumour regression compared with prior treatments (TV on Day 1). TGI for both doses of lenvatinib (3, 10 mg/kg) in the immunocompetent mice was significantly greater than those in the respective athymic mice. No remarkable BWL was noted in all treated groups.

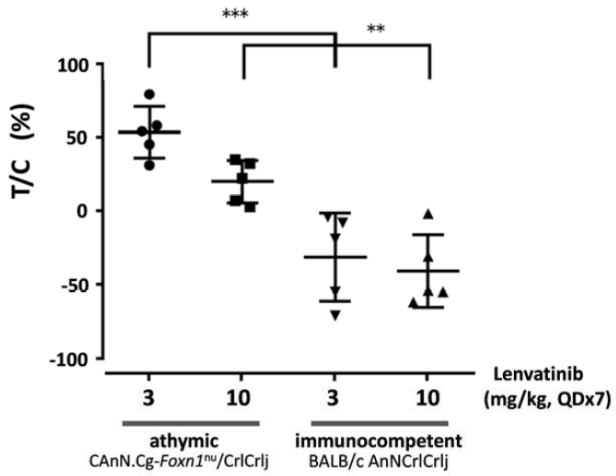


Figure 3: Antitumour Effects of Lenvatinib in the BNL 1ME A.7R.1 Murine HCC Isografts in Athymic Mice and Immunocompetent Mice

The effect of lenvatinib on the population of immune cells in tumours and draining lymph nodes was evaluated in the same model. Flow cytometric analysis of immune cells in the immunocompetent mice revealed that lenvatinib (10 mg/kg) decreased the population of TAM (defined CD45+CD11b+Ly6G–F4/80+Ly6C low). Lenvatinib (10 mg/kg) also increased activated-cytotoxic T cells in the draining lymph node. These results suggested that tumour immunity was enhanced in these tumour bearing mice treated with lenvatinib, since TAM acts as a suppressor, and activated-cytotoxic T cells as an effector for tumour immunity.

Therefore, the immune stimulatory effect of lenvatinib in the tumour microenvironment may contribute to the greater antitumour activity observed in the immunocompetent mice compared to that in athymic mice in this murine HCC isograft model.

Table 4: Tabulated summary of new in vivo primary pharmacodynamic isograft study

Type of Study	Methods	Species/ Strain	Number/ Gender	Route	Dose or Concentration	Observations	Study/ Report No.
Immunostimulatory Effect in murine cancer isograft model in mice	Isografts were generated by SC inoculation of the murine cancer cells to BALB/c immunocompetent mice or corresponding athymic mice. Dosing with lenvatinib was initiated after 50 days. The TV and body weight of mice were measured on Days 1, 3, 6, and 8 (Exp. 1). Tumors and draining lymph nodes were isolated from the immunocompetent mice 1 day after the end of dosing, and macrophages and cytotoxic T-cells were analyzed, respectively by flow cytometry (Exp. 2).	Mouse/ CAnN.Cg-*Foxn1*^{nu}/CrlCrlj (athymic) BALB/cAnNCrlCrlj, (wild type, immunocompetent) Mouse/ BNL 1ME A.7R.1 (HCC)	5 female / group (Exp.1) 10 female / group (Exp.2)	lenvatinib: PO, QD×7	lenvatinib: 3, 10 mg/kg (Exp.1) 10 mg/kg (Exp.2)	(Exp. 1) Lenvatinib (3, 10 mg/kg) showed significant TGI with tumor regression in the immunocompetent mice with T/C values of–31% and –41%, respectively, but not in the athymic mice. No remarkable BWL was observed. (Exp. 2) Lenvatinib significantly decreased TAM population ($CD45^+CD11b^+Ly6G^-F4/80^+Ly6C^{low}$ in the tumors and increased the activated $CD8^+$ T cell population ($IFN\text{-}\gamma^+ CD3^+CD8^+$) in the draining lymph node of immunocompetent mice.	W-20140959

Doses or concentrations described for lenvatinib and sorafenib are expressed as those of the salt form.
BWL = body weight loss, Exp. = experiment, PO = oral, QD×X = once daily for X days, SC = subcutaneous, TAM = tumour associated macrophage, T/C = treatment/control, TGI = tumour growth inhibition, TV= tumour volume

2.2.3. Pharmacokinetics

2.2.3.1. Metabolism

2.2.3.1.1. Analysis of In Vivo Metabolites

Calculation of pharmacokinetic parameters of radioactive peaks in monkey plasma

Lenvatinib was the main fraction of total radioactivity in plasma after administration of a single 3 mg/kg dose of either [14C]lenvatinib mesilate (radiolabeled on the quinoline ring) (maximum observed concentration [Cmax]: 89.9%, area under the concentration-time curve from zero time extrapolated to infinite time [AUC(0-inf)]: 69.7%) or [14C]CB-lenvatinib mesilate (radiolabeled on the chlorobenzene moiety) (Cmax: 78.4%, AUC(0-inf): 60.4%) to monkeys. After administration of [14C]lenvatinib mesilate, Cmax and AUC(0-inf) of all radioactive metabolite peaks did not individually exceed 1.9% of the total radioactivity.

After dosing of [14C]CB-lenvatinib mesilate, mCB9a was the major radioactive metabolite, with Cmax and AUC(0-inf) values of 12.1% and 17.0% of the total radioactivity, respectively. With the exception of mCB9a, Cmax and AUC(0-inf) of all radioactive metabolite peaks detected after dosing of [14C]CB-lenvatinib mesilate did not exceed 4.7% of total radioactivity.

2.2.4. Toxicology

No new toxicology data have been submitted in this application.

2.2.5. Ecotoxicity / environmental risk assessment

The maximum daily dose of lenvatinib in HCC patients is 12 mg/day to be administered during the entire disease period.

The log octanol-water partition coefficient (Kow) of lenvatinib is 3.30.

An Fpen default value of 0.01 (1%) is proposed in the guideline. The MAH however proposed to estimate a more accurate Fpen. Therefore, information based on epidemiological data is provided to support the prevalence of HCC for refinement of Fpen.

The public summary of opinion on ODD – Lenvatinib for the treatment of hepatocellular carcinoma (EMA/COMP/132959/2015, 06 May 2015) indicates that at the time of designation, HCC affected approximately **0.6 in 10,000 people** in the European Union (EU). From a re-examination of prevalence of HCC the prevalence is concluded to have increased slightly over the past years (less than one decimal). However, a worst-case prevalence of **1.5 per 10,000** making the extreme assumption that every reported case of primary liver cancer was in fact a case of HCC and that liver cancer is underreported by 45%.

Table 5: Calculation of the Phase I $PEC_{SURFACEWATER}$ of Lenvatinib (for HCC)

Input Parameter	Abbreviation	Value		Unit
		Based on ODD prevalence	Based on worst-case prevalence	
Maximum daily dose	$DOSE_{ai}$	12	12	mg/inh/day
Market penetration factor	F_{pen}	0.00006	0.00015	[refined value]
Amount of waste water per inhabitant per day	$WASTE_{inhab}$	200	200	L [default value]
Dilution from STP	DILUTION	10	10	[default value]
$PEC_{SURFACEWATER}$	**$PEC_{SURFACEWATER}$**	**0.00000036**	**0.00000090**	**mg/L**
		0.00036	**0.00090**	**µg/L**

ODD = orphan drug designation, PEC = Predicted Environmental Concentration, STP = sewage treatment plant..

The $PEC_{SURFACEWATER}$ is 0.00036 µg/L, or using the worst-case prevalence data 0.0009 µg/L. Both values are lower than the action limit of 0.01 µg/L. Hence, a phase II environmental fate and effects analysis is not applicable.

In addition, The PECSURFACEWATER for RR-DTC and RCC were calculated previously to be 0.00012 µg/L and 0.00396 µg/L, respectively. The combined PECSURFACEWATER for lenvatinib used in the treatment of RCC, RR-DTC and HCC patients was 0.0044 µg/L (based on ODD prevalence for HCC) and 0.0050 µg/L (based on worst-case prevalence for HCC). This combined value is lower than the action limit of 0.01 µg/L. Therefore, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.2.6. Discussion on non-clinical aspects

Several new in vitro and in vivo primary pharmacodynamics studies have been submitted to support the new proposed indication for Lenvima.

The new crystal structure analysis indicates that the binding mode of lenvatinib to FGFR1 is also type V, similar to the binding mode to VEGFR2.

The inhibition of FGFR by lenvatinib was further demonstrated in signal transduction assays where lenvatinib appeared to be a stronger inhibitor than sorafenib of phosphorylation of FRS2, a FGFR specific downstream signalling molecule, in several human HCC cell lines. The difference in potency in these assays was 10-fold.

Lenvatinib showed significant antiproliferative activity against HCC cell lines Hep 3B2.1-7 and HuH-7 but very weak antiproliferative activity against PLC/PRF/5 cells. Sorafenib did not show remarkable selectivity against either of the cell systems. When comparing lenvatinib and sorafenib, the difference in IC50 values for antiproliferative activity against the Hep 3B2.1-7 and HuH-7 cell lines was in the order of 10, which matches with the results of the FGFR signal transduction assays.

The weak in vitro antiproliferative activity which has been observed against PLC/PRF/5 cells but nevertheless the significant antitumour activity observed in the respective xenograft model suggest that the primary antitumour activity of lenvatinib is related to its antiangiogenic activity resulting from the

inhibition of VEGFR and FGFR, and not to a direct antiproliferative activity against a particular tumour cell line.

The results of 5 new murine HCC xenograft models demonstrated that lenvatinib showed significant tumour growth inhibition at doses from 3 or 10 to 30 mg/kg without severe BWL (more or less 10% body weight loss compared to the body weight at the initiation of dosing). The activity of lenvatinib was generally greater than the activity of sorafenib at the same dose level (factor 1.5 to 2 greater tumour volume reduction for lenvatinib compared to sorafenib, depending on the model used). Also the tolerability of lenvatinib in terms of BWL was overall slightly better compared to sorafenib in these models.

In a murine HCC isograft model, tumour inhibition by lenvatinib (doses of 3 and 10 mg/kg) was significantly greater in immunocompetent mice, compared to athymic mice. In addition, lenvatinib (10 mg/kg) decreased the population of tumour associated macrophages (TAM) and increased activated-cytotoxic T cells in the draining lymph node. These results suggest an immune stimulatory effect of lenvatinib, since TAM act as a suppressor, and T cells as an effector for tumour immunity.

A new analysis of previously submitted monkey plasma PK data was submitted but does not impact previous conclusions.

No new clinical toxicology data have been submitted in this application, which is considered acceptable.

The data submitted to support the DTC and RCC indications was in line with ICH S9. Although a first line indication is currently being proposed for HCC, the survival of these patients is short (~1 year) and there are no effective therapies available.

The applicant provided data regarding the prevalence of the disease population targeted by the HCC indication and this was used to refine Fpen. The PEC surfacewater value is below the action limit of 0.01 µg/L and it is not a PBT substance as log Kow does not exceed 4.5.

Therefore lenvatinib is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

The non-clinical data submitted as part of this application support the use of lenvatinib in HCC.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of lenvatinib.

Considering the above data, lenvatinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

The proposed indication for lenvatinib is ‘for the treatment of patients with hepatocellular carcinoma’. The pivotal study in support of this application is Study E7080-G000-304 (Study 304), a randomized,

controlled, open label multicentre, Phase 3 trial. Supportive evidence is provided by Phase 1/2 study E7080-J081-202 (Study 202), a proof of concept, dose-finding study.

Study ID	Number of Study Centers (Locations)	Study Start/ Clinical Cutoff Date	Study Design / Indication	Study Treatment(s): Dose, Route & Regimen	No. Subjects Planned/ Treated/ Ongoing[a]	Treated Subjects Sex (M/F); Median age, y (Range)	Efficacy Endpoints
Pivotal Phase 3 Study							
E7080-G000-304	183 sites: Asia (China, Japan, Republic of Korea, Singapore, Taiwan, Hong Kong, Thailand, Philippines, Malaysia), North America, the EU, Russia, Israel	01 Mar 2013 (1st subject signed ICF) 13 Nov 2016 (clinical cutoff for primary analysis)	Randomized (1:1), open-label, noninferiority of lenvatinib vs sorafenib in subjects with unresectable, BCLC stage B or C HCC and CP class A	Lenvatinib QD: 8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) oral capsules Sorafenib 400 mg BID oral tablets	Planned: Total N = 940 Treated/Ongoing: [b] Lenvatinib: 478/27 Sorafenib: 476/25	Lenvatinib: 405M/73F 63.0 y (20, 88) Sorafenib: 401M/75F 62.0 y (22, 88)	Primary: OS Secondary (sequential analysis): PFS, TTP, ORR Exploratory: DCR, CBR, HRQoL
Supportive Study							
E7080-J081-202	Phase 1: Japan (2 sites) Phase 2: Japan (12 sites), Korea (2 sites)	24 Jul 2009 (1st subject signed ICF) 15 Jun 2014 (clinical cutoff for primary analysis) 13 Aug 2015: (cutoff date for final analysis)	Phase 1/2, nonrandomized, multicenter, multidose, open-label study with a dose-escalation component (Phase 1) and an expansion component at the RP2 dose (Phase 2) in subjects with advanced HCC	Lenvatinib QD: Phase 1: 8, 12, or 16 mg Phase 2: 12 mg (RP2 dose) oral tablets	Phase 1: Group 1 (CP score 5-6): Planned: 12-18/ Actual: 9; Group 2 (CP score 7-8): Planned: 6-18/ Actual: 11 Ongoing: 0 (Groups 1+2) Phase 2: (CP score 5-6) 46/46/0	Phase 1: 17M/3F 63.5 y (47, 74) Phase 2: 33M/13F 66.5 y (37, 80)	Phase 1: Primary: NA[c] Secondary: BOR Phase 2: Primary: TTP Secondary: BOR, ORR, DCR, OS

BCLC = Barcelona Clinic Liver Cancer; BID = twice daily; BOR = best overall response; BW = body weight; CBR = clinical benefit rate; CP = Child-Pugh; DCR = disease control rate; HCC =hepatocellular carcinoma; HRQoL = health-related quality of life; ICF = informed consent form; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QD = once daily; RP2 = recommended Phase 2 (dose); TTP = time to progression.
a: The number ongoing is the number of subjects still receiving study drug as of the clinical cut-off date for the study.
b: Three subjects (2 lenvatinib, 1 sorafenib) in Study 304 did not receive treatment and were included in the Full Analysis Set but not the Safety Analysis Set.
c: The primary endpoint in Phase 1 of Study 202 was safety.

2.3.2. Pharmacokinetics

Introduction

Data from 21 studies were used to characterize the pharmacokinetics (PK) of lenvatinib. These included a Phase 1/2 dose finding study for subjects with HCC (Study E7080-J081-202) and an HCC Phase 3 safety and efficacy study (Study E7080-G000-304).

From a non-clinical and clinical perspective, 4 additional pharmacokinetics studies have been completed, and 1 study has been re-analysed. These studies include:

• Calculation of pharmacokinetic parameters of radioactive peaks in monkey plasma (see NC)

• Protein binding in human liver microsomes (HLMs)

• Reversibility of covalently bound lenvatinib-related components to human plasma protein

• Reanalysis of modeling and simulation using Simcyp®

• Substrate recognition and inhibition of MATE.

Bioanalytical methods

The additional data regarding bioanalytical methods are summarised in the table below.

Table 6: Additional bioanalytical method submitted as part of this application

Analyte	Human Matrix	Lab	Validation Reference	Assay Range (ng/mL)	Assay Volume (mL)	Clinical Study No.
Lenvatinib	Plasma	Wuxi-China	11BAS0295A2	0.250 - 250	0.1	E7080-G000-304 E7080-G000-209
Lenvatinib	Plasma	Wuxi-Philadelphia	P12BAS0005	0.250 - 250	0.1	E7080-703

Plasma lenvatinib was analysed using a validated LC-MS/MS method at Wuxi-China and Wuxi-Philadelphia in support of clinical studies E7080-G000-304 (11BAS0295A2), E7080-G000-209 (11BAS0295A2) and E7080-703 (P12BAS0005). Incurred sample reanalyses (ISR) were performed in 6 to 15 % of human plasma samples depending on the study.

All ISR samples met the regulatory guidance acceptance criteria; at least 2/3 of the ISR samples were no more than ±20% of the original measured values (FDA Guidance for Industry "Bioanalytical Methods Validation", May 2001, and EMA "Guideline on bioanalytical method validation", July 2011).

Bioequivalence

Study E7080-A001-009 has been submitted in the context of the Kisplyx marketing authorisation (EMEA/H/C/004224) evaluating the relative bioavailability and palatability of a lenvatinib suspension compared to the capsule formulation in adult healthy volunteers.

Subjects were asked to take either lenvatinib capsules with 240 mL of water or the lenvatinib suspension in water or apple juice.

Table 7: Analysis of Pharmacokinetic Parameters of Lenvatinib – Suspension vs Capsule (Pharmacokinetic Analysis Set)

Group Contrast (Test:Reference)	Parameter	Geometric Least Square Mean Ratio	(90% Confidence Interva
Suspension vs Capsule	C_{max} (ng/mL)	1.025	(0.8868, 1.1837)
	$AUC_{(0-t)}$ (h*ng/mL)	0.997	(0.9347, 1.0635)
	$AUC_{(0-inf)}$ (h*ng/mL)	0.999	(0.9379, 1.0641)

Log-transformed PK parameters were fitted using a linear model including formulation group, period and sequence as a fixed effects and subject as a random effect. Backtransformed ratios of geometric means and associated 2-sided 90% confidence intervals

Absorption

No new data regarding absorption, influence of food, influence of vehicle, bioequivalence was submitted.

Distribution

Two additional studies related to the protein binding have been submitted in this application.

Study DMPKT2013-020 - Protein binding of E7080 in human liver microsomes

In this study, protein binding of E7080 (lenvatinib) in human liver microsomes (HLM) solution was examined in an equilibrium dialysis method using RED Device (Thermo Scientific). Quantification of E7080 in PBS sample and HLM sample was performed by HPLC-UV, which was validated from 0.03 to 100 µg/mL of E7080 mesylate.

Protein binding of E7080 in HLM sample was calculated as follows:

$$\text{Protein binding (\%)} = \left(1 - \frac{\text{Concentration in PBS sample}}{\text{Concentration in HLM sample}}\right) \times 100$$

The results are summarised in the following table:

Added Concentration (μg/mL as mesylate)	n	Protein Binding (%)
		Human Liver Microsomes
0.3	3	29.24±0.91
1	3	26.93±1.26
3	3	25.49±0.21
10	3	24.53±0.52
30	9[a]	23.85±1.06

Each value represents the mean ±SEM.

a: Combination of 1st experiment (n=3) and 2nd experiment (n=6).

Study W-20140601 – formation of covalent binding of E7080 with human plasma protein and its reversibility

This study investigated the mechanism for the formation of covalent binding of E7080 with human plasma protein and its reversibility. E7080-related components which covalently bound to human plasma protein were substituted by endogenous nucleophiles such as glutathione (GSH) and cysteine, and their chemical structures were analysed.

This study suggested that E7080 and its metabolite, N-cysteine conjugate of quinolone moiety in E7080, could form covalent binding with human plasma protein via thioether and di-sulfide bonds, respectively. Nucleophiles such as GSH and cysteine successfully released E7080-related components which covalently bound to human plasma protein as the corresponding conjugates via substitution reaction, suggesting that the covalent binding would be reversible in humans in vivo since abundant amounts of GSH and cysteine exist.

Elimination

No additional data regarding elimination has been submitted with this application.

Inter- and intra-individual variability

In the population analysis of study 202, the %CV of apparent total clearance is 32.6 %.

Table 8: final population pharmacokinetic parameter estimates of lenvatinib – Study 202

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
Inter-individual variability (%CV)			
CL/F	32.6	6.99	–
V1/F	49.5	7.39	–

In the population analysis of study 304, inter-individual variability (IIV) in the model parameters was moderate ranging between 25.4% for CL/F and 93.6% for D1. IIV was well estimated with good precision for all the parameters (%RSE ≤ 14.0%). The residual variability in lenvatinib concentrations for TAD ≤ 2 h was high (%CV 49.0), moderate for cancer patient studies (%CV 36.3), and low for Phase 1 clinical pharmacology studies (%CV 17.0).

Dose proportionality and time dependencies

Dose proportionality

In the new study E7080-J081-202, exposure, as measured by C_{max}, $AUC_{(0-24h)}$, $AUC_{(0-t)}$, $C_{ss,max}$, and $AUC_{(0-\tau)}$, for lenvatinib appeared to increase with increasing doses.

Time-dependency

In the new study E7080-J081-202, plasma lenvatinib concentration accumulated after repeated dosing with a mean accumulation index (Rac) of $AUC_{(0\text{-}24h)}$ and C_{max} ranging from 1.23 to 2.11.

Special populations

Elderly

No new data have been submitted in elderly patients

Impaired renal function

No specific study investigating patients with impaired renal function was submitted.

Impaired hepatic function

No specific study investigating patients with impaired hepatic function was submitted.

●*Study E7080-J081-202*

The primary objective of the study was to determine the maximum tolerated dose (MTD) as defined by the dose limiting toxicity (DLT) of lenvatinib administered continuously once a day (QD) as 4 weeks cycle in subjects with advanced HCC and hepatic function of Child-Pugh (CP) scores of 5–6 or 7–8 (groups 1 and 2 respectively). One of the secondary objectives is to determine the PK profiles of lenvatinib.

In the Dose Escalation Component (Phase 1), PK parameters were determined after single (Cycle 1/Day1) and multiple doses (Cycle 1/Day 15), using non-compartmental analysis. The PK profile of lenvatinib was evaluated by concentration-time plots. PK results were summarized descriptively by dose level and hepatic function (Group 1 and Group 2). If possible, the relationships between pharmacokinetics, pharmacodynamics, and efficacy/safety were to be evaluated by plots.

In the Expansion Component (Phase 2), summary statistics of lenvatinib plasma concentration at each time point were calculated. If necessary, pooled data combining this component and the Dose Escalation Component (Phase 1) and other clinical studies (eg, E7080-J081-103) were to be analyzed using the population approach.

Table 9: Analysis Sets – Enrolled Subjects (Dose Escalation Component [Phase 1])

	Group 1 (Child-Pugh Score 5 or 6)			Group 2 (Child-Pugh Score 7 or 8)			
Analysis Set	12 mg QD (N=6) n (%)	16 mg QD (N=3) n (%)	Total (N=9) n (%)	8 mg QD (N=6) n (%)	12 mg QD (N=5) n (%)	Total (N=11) n (%)	Overall (N=20) n (%)
Enrolled Set	6	3	9	6	5	11	20
Efficacy Analysis Set	6 (100.0)	3 (100.0)	9 (100.0)	6 (100.0)	5 (100.0)	11 (100.0)	20 (100.0)
PK Analysis Set	6 (100.0)	3 (100.0)	9 (100.0)	6 (100.0)	5 (100.0)	11 (100.0)	20 (100.0)
PD Analysis Set	6 (100.0)	3 (100.0)	9 (100.0)	6 (100.0)	5 (100.0)	11 (100.0)	20 (100.0)
Safety Analysis Set	6 (100.0)	3 (100.0)	9 (100.0)	6 (100.0)	5 (100.0)	11 (100.0)	20 (100.0)

Percentages are based on the number of enrolled subjects in the relevant dose group.
PD = pharmacodynamic, PK = pharmacokinetic, QD = once a day.

Table 10: Summary of Pharmacokinetic Parameters of Lenvatinib in Group 1 (Child-Pugh Score 5, 6) – Cycle 1 Day 1 – Pharmacokinetic Analysis Set (study 202)

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	12 mg QD (n=6)	16 mg QD (n=3)
C_{max} (ng/mL)	212 ± 70.8	344 ± 166
t_{max} (h)	2.000 (0.97 – 5.95)	1.970 (0.97 – 4.00)
$AUC_{(0-24h)}$ (ng•h/mL)	2020 ± 170	3280 ± 961

$AUC_{(0-24h)}$ = area under the concentration-time curve from zero time to 24h, C_{max} = maximum observed concentration, t_{max} = time at which the highest drug concentration occurs.
Data is shown as mean ± SD except t_{max}; for t_{max}, median (minimum – maximum) is shown.

Table 11: Summary of Pharmacokinetic Parameters of Lenvatinib in Group 2 (Child-Pugh Score 7, 8)– Cycle 1 Day 1 – Pharmacokinetic Analysis Set

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	8 mg QD (n=6)	12 mg QD (n=5)
C_{max} (ng/mL)	146 ± 56.9	254 ± 169
t_{max} (h)	2.015 (0.50 – 3.93)	2.000 (1.00 – 3.98)
$AUC_{(0-24h)}$ (ng•h/mL)	1250 ± 399	2140 ± 1030

$AUC_{(0-24h)}$ = area under the concentration-time curve from zero time to 24h, C_{max} = maximum observed concentration, t_{max} = time at which the highest drug concentration occurs.
Data is shown as mean ± SD except t_{max}; for t_{max}, median (minimum – maximum) is shown.

Table 12: Summary of Pharmacokinetic Parameters of Lenvatinib in Group 1 (Child-Pugh Score 5,6) – Cycle 1 Day 15 – Pharmacokinetic Analysis Set

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	12 mg QD (n=5)	16 mg QD (n=2)
$C_{ss,max}$ (ng/mL)	346 ± 75.4	402
$C_{ss,min}$ (ng/mL)	43.1 ± 21.7	84.6
$C_{ss,av}$ (ng/mL)	130 ± 23.5	213
$t_{ss,max}$ (h)	1.950 (1.00 – 3.98)	3.915 (3.83 – 4.00)
$AUC_{(0-\tau)}$ (ng•h/mL)	3120 ± 566	5110
$R_{ac}(C_{max})$	1.67 ± 0.645	1.64
R_{ac}(AUC)	1.54 ± 0.290	1.73

$AUC_{(0-\tau)}$= area under the concentration-time curve over the dosing interval on multiple dosing, $C_{ss,av}$ = average steady-state concentration, $C_{ss,max}$ = maximum observed concentration at steady-state, $C_{ss,min}$ = minimum observed concentration at steady-state, R_{ac} = accumulation index, $t_{ss,max}$ = time at which the highest drug concentration occurs at steady-state.
$R_{ac}(C_{max}) = C_{ss,max}/C_{max}$; $R_{ac}(AUC) = AUC_{(0-\tau)}/AUC_{(0-24h)}$.
Data are shown as mean ± SD except $t_{ss,max}$; for $t_{ss,max}$, median (minimum – maximum) is shown.
Last sampling time point is 24 hours after administration.

Table 13: Summary of Pharmacokinetic Parameters of Lenvatinib in Group 2 (Child-Pugh Score 7,8) – Cycle 1 Day 15 – Pharmacokinetic Analysis Set

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	8 mg QD (n=6)	12 mg QD (n=2)
$C_{ss,max}$ (ng/mL)	167 ± 40.4	349
$C_{ss,min}$ (ng/mL)	29.9 ± 13.4	64.0
$C_{ss,av}$ (ng/mL)	73.8 ± 14.2	165
$t_{ss,max}$ (h)	2.025 (1.98 – 4.02)	1.995 (1.97 – 2.02)
$AUC_{(0-\tau)}$ (ng•h/mL)	1770 ± 340	3960
$R_{ac}(C_{max})$	1.23 ± 0.315	1.91
$R_{ac}(AUC)$	1.49 ± 0.385	2.11

$AUC_{(0-\tau)}$= area under the concentration-time curve over the dosing interval on multiple dosing, $C_{ss,av}$ = average steady-state concentration, $C_{ss,max}$ = maximum observed concentration at steady-state, $C_{ss,min}$ = minimum observed concentration at steady-state, R_{ac} = accumulation index, $t_{ss,max}$ = time at which the highest drug concentration occurs at steady-state.
$R_{ac}(C_{max}) = C_{ss,max}/C_{max}$; $R_{ac}(AUC) = AUC_{(0-\tau)}/AUC_{(0-24h)}$.
Data are shown as mean ± SD except $t_{ss,max}$; for $t_{ss,max}$, median (minimum – maximum) is shown.
Last sampling time point is 24 hours after administration.

No relationship between CP score and the PK of lenvatinib was observed in Study 202. This finding is similar to results from the hepatic impairment study for lenvatinib, E7080-A001-006.

Sparse PK sampling was performed for all subjects. A total of up to 6 samples per subject were to be obtained pre-dose on Days 1, 8, 15, 22 of Cycle 1 and on Day 1 of Cycle 2 and Cycle 3. These data are pooled for population PK analysis and are reported in a separate report (see population PK analysis below)

● *Study 304*

Based on the results of the initial Phase 1/2 lenvatinib trial, study 304 was designed and conducted to compare the safety and efficacy of lenvatinib versus sorafenib in subjects with Child-Pugh class A, unresectable/advanced HCC.main criteria for inclusion, adult subjects (≥18 years of age) with a histologically or cytologically confirmed diagnosis of unresectable HCC, or a clinically confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria, including cirrhosis of any etiology, or with chronic hepatitis B or C infection were eligible. In the other key inclusion criteria included, child-pugh score A was mentioned.

Pharmacokinetic samples were collected from all subjects who took lenvatinib. Exposure parameters such as maximum concentration and area under the concentration × time curve (AUC) were derived from posterior estimates of the PK parameters from the final population PK model.

In general, the incidence of TEAEs was similar for subjects with a baseline CP score of 5 or of 6 in lenvatinib treated subjects in HCC Study 304.The incidences of severe (Grade ≥3) TEAEs, SAEs, and TEAEs leading to study drug withdrawal were higher in subjects with baseline CP score of 6 than of 5. Subjects with baseline CP score of 6 compared with those with baseline CP score of 5 had a higher incidence of nonfatal SAEs. Subjects with a baseline CP score of 6 also had a higher incidence of TEAEs leading to study drug interruption or to study drug reduction or interruption.

Overall, the rate of major protocol deviations was low (2.5%; 24 of 954 subjects), and the incidence and nature of the protocol deviations were balanced across the treatment arms. Most of the major protocol deviations in both the lenvatinib and sorafenib arms were eligibility criteria not met, mostly due to laboratory levels outside the acceptable range or Child-Pugh score of 7 or 8 (Class B).

Gender

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

Race

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

In the new study 304, individual lenvatinib oral clearance and AUC at steady state for Western, Asian, Chinese and Japanese populations are summarized by starting dose group. The median value and range of AUC values are each comparable between the 8 mg group and 12 mg group. There were no differences of lenvatinib oral clearance and AUC at steady state among Western, Asian, Chinese and Japanese populations.

Weight

The effect of weight on the pharmacokinetics of lenvatinib was evaluated in the original population PK analysis (DTC). In this POP PK analysis, weight (37.8 – 178 kg) added as an allometric constant on CL/F and volume parameters showed a statistically significant effect, but only explained 1.2 % of the inter-individual variability on CL/F. PK simulations showed a major overlap in the steady-state exposure in the presence and absence of this covariate. Subjects with body weight <60 kg had 36% higher exposure compared with subjects >60 kg.

Study E7080-J081-202

The (POP) PK analysis for Study 202 (CPMS-E7080-005R-v1) showed that included statistically significant and clinically relevant effects of bodyweight on both clearance and volume increased with increasing body weight. Allometric functions were used to characterize these effects. As a consequence, fixed dosing as initially implemented in Study 202 led to high difference in exposures (AUC) across the range of bodyweight. Observed data and predictions from the final model showed that compared with subjects weighing ≥60 kg, subjects with a low body weight ([BW] <60 kg) had a higher lenvatinib area under the plasma concentration-time curve (AUC) and a high rate of dose reductions and discontinuations at the 12-mg starting dose.

In phase 2 part of study 202, the dose reduction occurred frequently and early in the course of treatment. Twenty-one patients (46.7 %) of PK/PD population experienced TEAEs leading to dose reduction or discontinuation during Cycle 1. The median body weight of these patients with early dose withdrawal or reduction was 54.3 kg, whereas the median body weight of patients without early dose modification was 67.6 kg. The final PK model for lenvatinib included body weight effect on oral clearance, whereby the relationship between the AUC and body weight shows an increase in AUC as the body weight decreases. The median AUC based on the starting dose of patients with early dose withdrawal or reduction was 2950 ng*h/mL, whereas the median AUC based on the starting dose of patients without early dose modification was 2050 ng*h/mL (see figure below).

The median steady state C_{min} of patients with early dose withdrawal or reduction was 46.8 ng/mL, whereas the median steady state C_{min} of patients without early dose modification was 30.6 ng/mL.

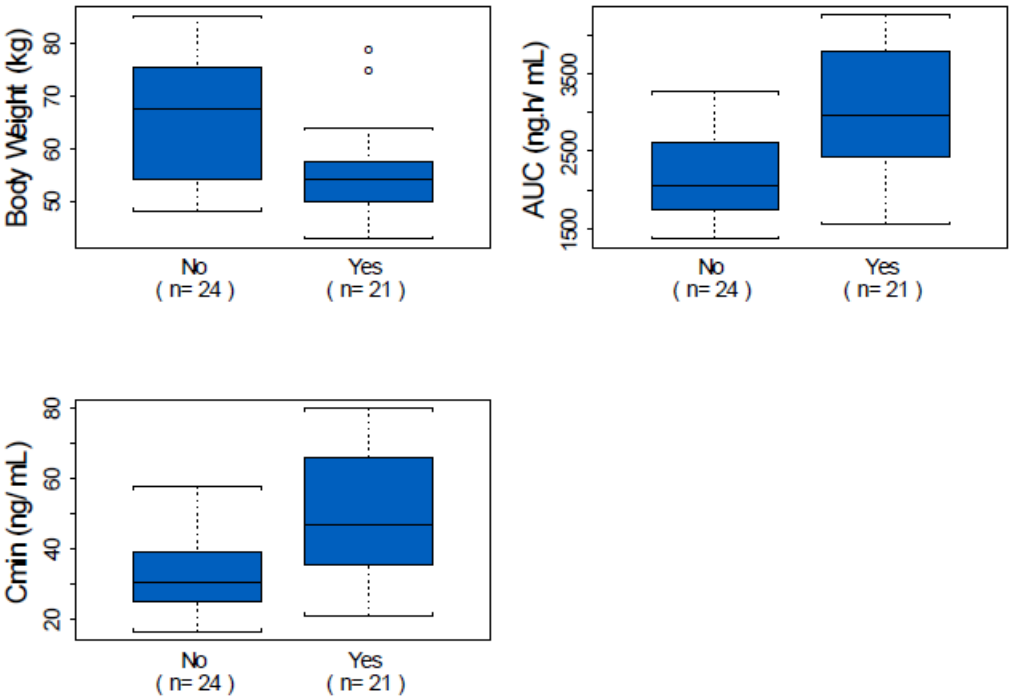


Figure 4: Boxplot of body weight, lenvatinib AUC and C_{min} for patients with vs without TEAEs that lead to dose reduction or study drug withdrawal during Cycle 1

Patients with low body weight experienced the early dose reduction or discontinuation, and this can be explained by the higher lenvatinib AUC for patients with low body weight.

The MAH explored the cut-off value of lenvatinib AUC to predict high risk group of the early dose reduction or discontinuation. To investigate the best cut-off value of lenvatinib exposure and body weight to predict high risk group of the occurrence of TEAEs leading to study drug withdrawal or dose reduction during Cycle 1, a receiver operating characteristics (ROC) curve was used. The classification table cross-classifies the binary response with prediction of whether the subject experiences TEAEs leading to study drug withdrawal/reduction during Cycle 1 or not for some cut-off value based on the final PK/PD logistic model.

ROC curve which was predicted from the developed logistic regression model indicates that the best cut-off value of lenvatinib AUC is 2430 ng*h/mL with 0.71 sensitivity and 0.71 specificity.

Based on the final PK model, simulated body weight (range: 40 – 120 kg) vs. lenvatinib AUC curve in 12 and 8 mg dose groups is shown in figure below. Based on the 2430 ng*h/mL of AUC as threshold to predict high risk group of the early dose reduction or discontinuation, the figure suggested that a simple body weight adjusted dosing regimen, namely 12 mg dose in subjects whose body weight are 60kg and over, and 8 mg dose in subjects whose body weight are less than 60kg, was recommended to avoid TEAEs leading the early dose reduction or discontinuation. Within the range between 40 kg and 120 kg of body weight, the predicted AUC of subjects whose body weight were less than 60kg, are calculated between 1540 and 2050 ng•h/mL, and the predicted AUC of subjects whose body weight are 60kg and over, are calculated between 1410 and 2310 ng•h/mL. The AUC range between two dose groups was similar, which supports the adequacy of the proposed dosing regimens based on a body weight cut-off at 60kg.Because of the reduced tolerability of the 12-mg dose observed in subjects with low body weight and the results of PK modelling, a 2-tier dosing strategy based on body weight was proposed for future clinical studies with lenvatinib in patients with advanced HCC: 12 mg for subjects weighing ≥60 kg and 8 mg for subjects weighing <60 kg.

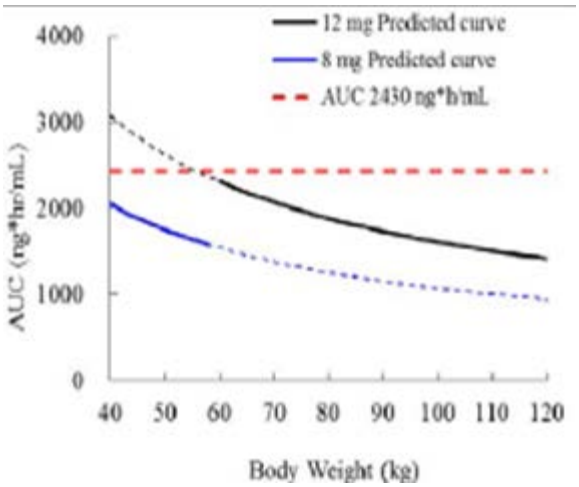


Figure 5*:* simulated body weight vs lenvatinib AUC curve for 12 and 8 mg dose groups

Study E7080-G000-304 and POP PK report CPMS-E7080-011R

While bodyweight effects on CL/F and V/F was fixed in model development when data from study 304 were used. The fitting performances from final PopPK model including data from Study 304 confirmed that lenvatinib PK was affected by body weight in subjects with HCC (Report CPMS-E7080-011R). Both CL/F and volume increase with increasing body weight. The lower CL/F in subjects with low body weight results in an increase in lenvatinib AUC. Based on individual lenvatinib AUC values for subjects with HCC in Study 304, however, the median value and range of individual AUC values at steady state were comparable between the 8-mg starting dose for subjects weighing <60 kg and the 12-mg dose for subjects weighing ⩾60 kg. The effect of changes in body weight was more pronounced in HCC than in previously studied tumour types (RR-DTC, RCC). In other tumour types, the effect of body weight on lenvatinib PK was small, not clinically relevant, and did not warrant any dose adjustment (CPMS-E7080 007R; CPMS-E7080-008R). These data confirm the use of the 2-tier dosing strategy based on bodyweight in HCC in study 304.

Table 14: Summary of Individual Predicted Pharmacokinetic Parameters for Lenvatinib in Study 304 by Starting Dose Group (All)

Starting Dose	Parameter (unit)	N	Mean (SD)	Median	Range (Min-Max)
8 mg	Oral clearance (L/h)	150	4.14 (0.98)	4.06	1.93 - 6.96
	AUC (ng•h/mL)	150	1969.6 (743.0)	1820.2	704.8 - 4980.7
	Baseline body weight (kg)	150	52.6 (4.9)	53.0	39.4 - 59.9
12 mg	Oral clearance (L/h)	318	5.64 (1.20)	5.64	2.66 - 8.97
	AUC (ng•h/mL)	318	2120.9 (685.6)	1996.0	925.5 - 5427.9
	Baseline body weight (kg)	318	75.9 (14.4)	72.0	59.6 - 142.2

Table 15: Summary of Individual Predicted Pharmacokinetic Parameters for Lenvatinib in Study 304 by Starting Dose Group (Western Population)

Starting Dose	Parameter (unit)	N	Mean (SD)	Median	Range (Min-Max)
8 mg	Oral clearance (L/h)	20	3.71 (0.92)	3.66	2.03 -6.21
	AUC (ng•h/mL)	20	2322.3 (855.4)	2179.9	889.4 – 4980.7
	Baseline body weight (kg)	20	52.1 (5.2)	51.5	40.0 – 59.0
12 mg	Oral clearance (L/h)	127	5.91 (1.20)	5.85	2.96 – 8.97
	AUC (ng•h/mL)	127	2010.2 (631.1)	1935.4	925.5 – 4337.2
	Baseline body weight (kg)	127	84.4 (17.3)	82.0	60.0 – 142.2

Western consists of North America and Europe including Russia and Israel.

Table 16: Summary of Individual Predicted Pharmacokinetic Parameters for Lenvatinib in Study 304 by Starting Dose Group (Asian Population)

Starting Dose	Parameter (unit)	N	Mean (SD)	Median	Range (Min-Max)
8 mg	Oral clearance (L/h)	130	4.20 (0.97)	4.18	1.93 - 6.96
	AUC (ng•h/mL)	130	1915.4 (712.5)	1737.6	704.8 - 4937.8
	Baseline body weight (kg)	130	52.7 (4.9)	53.3	39.4 - 59.9
12 mg	Oral clearance (L/h)	191	5.47 (1.17)	5.39	2.66 - 8.61
	AUC (ng•h/mL)	191	2194.5 (711.6)	2064.7	945.5 - 5427.9
	Baseline body weight (kg)	191	70.3 (8.1)	68.0	59.6 - 102.0

Asian consists of China, Japan, Korea, Hong Kong, Malaysia, Philippines, Singapore, Taiwan and Thailand.

Pharmacokinetic interaction studies

No new PK interaction studies were submitted in this application.

Pharmacokinetics using human biomaterials

With the exception of Study GE-1399-G, this section is unchanged from the DTC and RCC information.

Study GE-1399-G

This study was conducted to assess the potential of E7080 as a substrate or an inhibitor for MATE1 and MATE2-K using cells expressing respective transporters. Cells transfected with each control vector were used as the control cells.

The transports of [^{14}C]E7080 by each transporter at a concentration of 1 µmol/L in the presence and absence of each typical inhibitor were assessed. The inhibitory effects of E7080 on each transporter were determined at concentrations of 0.1, 0.3, 1, 3, 10, and 30 µmol/L using radiolabelled typical substrates. Assay system, and typical substrates and inhibitors used in this study are summarized below:

Transporter	Assay system	Typical substrate (concentration used)	Typical inhibitor (concentration used)
MATE1	HEK293 cells	Metformin (10 µmol/L)	Cimetidine (10 µmol/L)
MATE2-K			Cimetidine (100 µmol/L)

In all preparations of transporter-expressing cells and their control cells used in this study, the transport activities of typical substrates and inhibitory effects by typical inhibitors were retained normally, indicated that the test systems used in this study were adequate to evaluate the potentials of E7080 as a substrate and an inhibitor of MATE1 and MATE2-K.

Substrate recognition

Study GE-1399-G showed that lenvatinib was not a substrate of either multidrug and toxin extrusion (MATE) 1 or MATE2-K. No MATE1- and MATE2-K-mediated transports of [^{14}C]E7080 were detected, indicating that E7080 was not a substrate of either MATE1 or MATE2-K.

- *MATE 1*

In the absence of cimetidine, the uptakes of [^{14}C]E7080 in the MATE1-expressinc cells after incubation for 1, 2, and 5 minutes were 38.1, 44.1, and 53.8 µL/mg protein, respectively; those in the control cells were 41.1, 48.8, and 53.2 µL/mg protein, respectively. In the presence of cimetidine (10 µmol/L), the uptakes of [^{14}C]E7080 in the MATE1-expressing cells after incubation for 1, 2, and 5 minutes were 36.2, 43.4, and 46.2 µL/mg protein, respectively; those in the control cells were 39.7, 49.0, and 52.0 µL/mg protein, respectively.

The uptakes of [^{14}C]E7080 in the MATE1-expressing cells after incubation for 1, 2, and 5 minutes were comparable to those in the control cells. In addition, cimetidine, a typical MATE1 inhibitor, did not inhibit the uptake of [^{14}C]E7080 in the MATE1-expressing cells. These results indicated that E7080 was not a substrate of MATE1.

- *MATE 2*

In the absence of cimetidine, the uptakes of [^{14}C]E7080 in the MATE2-K-expressing cells after incubation for 1, 2, and 5 minutes were 38.8, 41.4, and 50.5 µL/mg protein, respectively; those in the control cells were 41.1, 43.1, and 55.9 µL/mg protein, respectively. In the presence of cimetidine (100 µmol/L), the uptakes of [^{14}C]E7080 in the MATE2-K-expressing cells after incubation for 1, 2, and 5 minutes were 40.4, 43.2, and 52.2 µL/mg protein, respectively; those in the control cells were 40.6, 42.4, and 55.8 µL/mg protein, respectively.

The uptakes of [^{14}C]E7080 in the MATE2-K-expressing cells after incubation for 1, 2, and 5 minutes were comparable to those in the control cells. In addition, cimetidine, a typical MATE2-K inhibitor, did not inhibit the uptake of [^{14}C]E7080 in the MATE2-K-expressing cells. These results indicated that E7080 was not a substrate of MATE2-K.

Table 17: [^{14}C]E7080 and [^{14}C]Metformin Uptake into MATE2-K-expressing HEK293 Cells and Control Cells

Compound	Typical inhibitor	Concentration of typical inhibitor (µmol/L)	Incubation time (min)	Uptake volume (µL/mg protein)		% of control (%)
				Control	MATE2-K	
[^{14}C]E7080	Cimetidine	0	1	41.1 ± 2.0	38.8 ± 3.1	–
(1 µmol/L)			2	43.1 ± 1.9	41.4 ± 3.7	–
			5	55.9 ± 8.4	50.5 ± 5.0	–
	Cimetidine	100	1	40.6 ± 0.4	40.4 ± 1.7	–
			2	42.4 ± 3.8	43.2 ± 4.4	–
			5	55.8 ± 8.2	52.2 ± 4.9	–
[^{14}C]Metformin	Cimetidine	0	5	0.952 ± 0.126	13.2 ± 0.8	100.0
(10 µmol/L)		100	5	0.442 ± 0.048	3.88 ± 0.22	28.1

Each value represents the mean ± SD of three samples.

–: % of control was not evaluated because E7080 was judged not to be a substrate for MATE2-K.

Inhibitory effect

Inhibitory effects of E7080 on MATE1 and MATE2-K were also assessed using the each transporter-expressing cells and their control cells. The uptake volumes of [14C]metformin in MATE1- or MATE2-K-expressing cells in the absence of inhibitors were higher than those in the control cells. In the presence of the typical inhibitors, cimetidine (10 µmol/L and 100 µmol/L for MATE1 and MATE2-K), the uptake volumes of [14C]metformin into MATE1- or MATE2-K-expressing cells decreased to 13.1% and 28.1% of control, respectively.

E7080 inhibited MATE1 with the IC50 value of 6.31 µmol/L. For MATE2-K, E7080 showed slight inhibition (87.3% or more of control, IC50 > 30 µmol/L).

Table 18: Inhibitory Effect of E7080 on MATE1 mediated Uptake of [14C]Metformin into HEK293 Cells

Compound	Additive	Concentration of additive (µmol/L)	Uptake volume (µL/mg protein)		% of control (%)
			Control	MATE1	
[^{14}C]Metformin	E7080	0	1.19 ± 0.06	37.3 ± 1.8	100.0
(10 µmol/L)		0.1	0.804 ± 0.069	32.5 ± 1.6	87.8
		0.3	1.21 ± 0.08	36.8 ± 1.7	98.6
		1	0.745 ± 0.155	29.9 ± 2.0	80.7
		3	0.980 ± 0.010	26.8 ± 1.0	71.5
		10	0.550 ± 0.011	12.4 ± 0.5	32.8
		30	0.603 ± 0.031	10.1 ± 0.2	26.3
	Cimetidine	10	0.466 ± 0.044	4.95 ± 0.03	12.4

Each uptake volume represents the mean ± SD of three samples.

Incubation time was 5 minutes

Table 19: Inhibitory Effect of E7080 on MATE2-K mediated Uptake of [14C]Metformin into HEK293 Cells

Compound	Additive	Concentration of additive (µmol/L)	Uptake volume (µL/mg protein)		% of control (%)
			Control	MATE2-K	
[^{14}C]Metformin (10 µmol/L)	E7080	0	1.20 ± 0.09	17.3 ± 0.3	100.0
		0.1	0.968 ± 0.089	18.6 ± 0.9	109.5
		0.3	1.22 ± 0.15	17.1 ± 0.8	98.6
		1	0.890 ± 0.062	20.0 ± 1.1	118.7
		3	0.960 ± 0.063	18.6 ± 1.2	109.6
		10	0.658 ± 0.023	17.7 ± 1.4	105.9
		30	0.549 ± 0.037	14.6 ± 2.2	87.3
	Cimetidine	100	0.488 ± 0.054	5.04 ± 0.26	28.3

Each uptake volume represents the mean ± SD of three samples.
Incubation time was 5 minutes

Target population

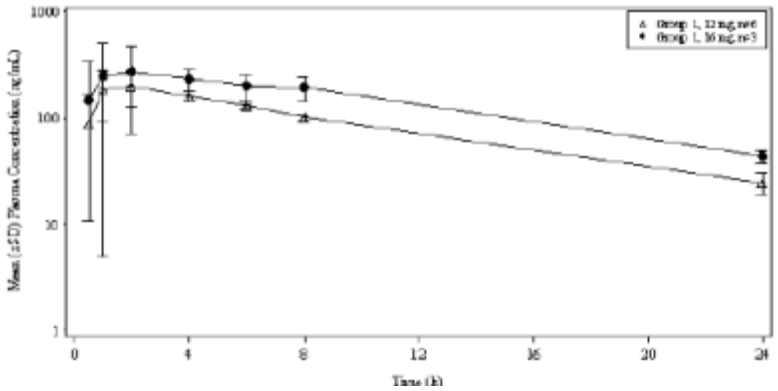
Study E7080-J081-202 - Phase 1/2 Study of E7080 in Patients with Advanced Hepatocellular Carcinoma (HCC)

Primary objective: To determine the MTD as defined by the dose limiting toxicity (DLT) of lenvatinib administered continuously once a day (QD) as 4 week cycles in subjects with advanced HCC and hepatic function of CP scores of 5–6 or 7–8. Secondary objectives included evaluating the safety and tolerability of lenvatinib, determining the PK profile of lenvatinib as well as determining the recommended dose for future studies, evaluating the antitumour efficacy and exploring the pharmacodynamic (PD) markers of lenvatinib.

Serial blood samples were collected at predose and 0.5, 1, 2, 4, 6, 8, and 24 hours after the first dose on Day 1 of Cycle 1, at predose and 0.5, 1, 2, 4, 6, 8, and 24 hours after repeated dose on Day 15 of Cycle 1, and at predose on Days 8 and Days 22 of Cycle 1.

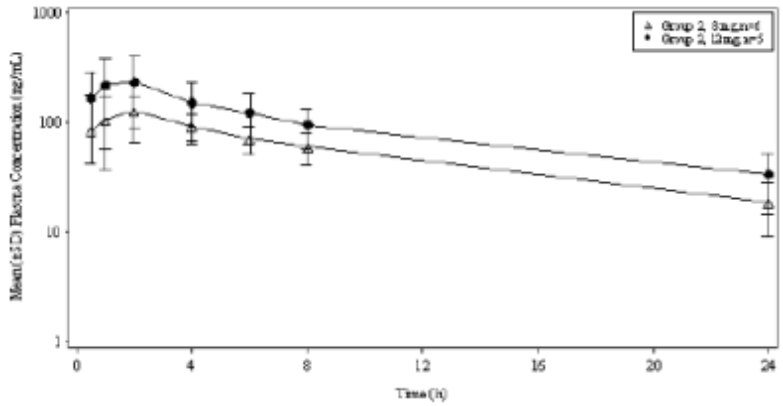
Lenvatinib was administered on an empty stomach or at least 1 hour after eating. Otherwise, lenvatinib was administered under fasting conditions on Day 1 and Day 15 of Cycle 1 to avoid a possible food effect on PK analysis.

Mean ± standard deviation (SD) plasma concentration-time curves of lenvatinib after first dose (Cycle 1 Day 1) in Group 1 (Child-Pugh score 5, 6) and Group 2 (Child-Pugh score 7, 8) are presented on a semi-log scale in the figures below. Analogous mean ± SD plasma concentration-time curves of lenvatinib after multiple doses (Cycle 1 Day 15) in group 1 and Group 2 are presented on a semi-log scale in the figures below as well.



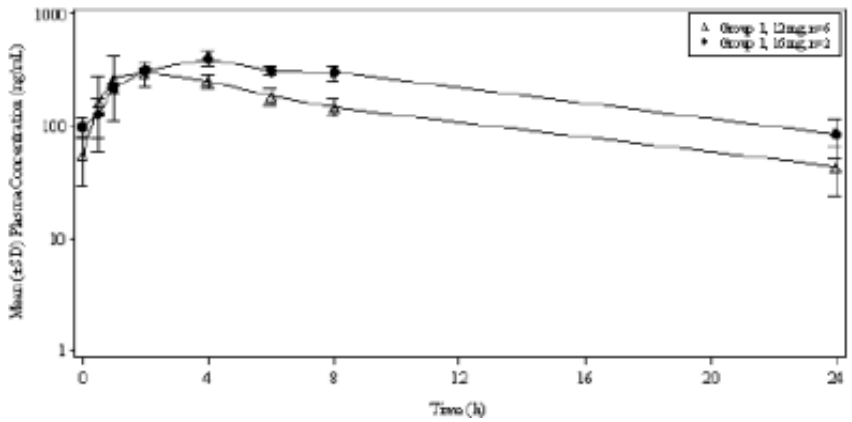
PK analysis set: (N=9). Data for 12 mg (n=6), and for 16 mg (n=5) is shown.

Figure 6: Mean ± standard deviation (SD) plasma concentration-time curves of lenvatinib after first dose (Cycle 1 Day 1) in Group 1 (Child-Pugh score 5,6)



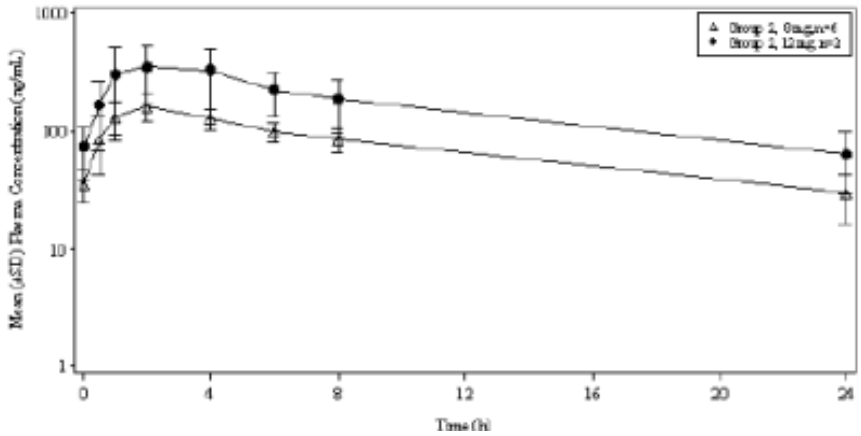
PK analysis set: (N=9). Data for 12 mg (n=6), and for 16 mg (n=5) is shown.

Figure 7: Mean ± standard deviation (SD) plasma concentration-time curves of lenvatinib after first dose (Cycle 1 Day 1) in Group 2 (Child-Pugh score 7,8)



PK analysis set: (N=8). Data for 12 mg (n=6), and for 16mg (n=2) is shown.

Figure 8: Mean ± standard deviation (SD) plasma concentration-time curves of lenvatinib after first dose (Cycle 1 Day 15) in Group 1 (Child-Pugh score 5,6)



PK analysis set: (N=8). Data for 12 mg (n=6), and for 16mg (n=2) is shown.

Figure 9: Mean ± standard deviation (SD) plasma concentration-time curves of lenvatinib after first dose (Cycle 1 Day 15) in Group 2 (Child-Pugh score 7,8)

Table 20: Summary of PK parameters of lenvatinib in Group 1 (Child-Pugh score 5,6) – Cycle 1 Day 1 – PK analysis set

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	12 mg QD (n=6)	16 mg QD (n=3)
C_{max} (ng/mL)	212 ± 70.8	344 ± 166
t_{max} (h)	2.000 (0.97 – 5.95)	1.970 (0.97 – 4.00)
$AUC_{(0-24h)}$ (ng•h/mL)	2020 ± 170	3280 ± 961

Data are shown as mean ± standard deviation except t_{max}; for t_{max}, median (minimum – maximum) is shown.

$AUC_{(0-24h)}$ = area under the concentration-time curve from zero time to 24h, C_{max} = maximum observed concentration, t_{max} = time at which the highest drug concentration occurs, QD = once daily.

Table 21: Summary of PK parameters of lenvatinib in Group 2 (Child-Pugh score 7,8) – Cycle 1 Day 1 – PK analysis set

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	8 mg QD (n=6)	12 mg QD (n=5)
C_{max} (ng/mL)	146 ± 56.9	254 ± 169
t_{max} (h)	2.015 (0.50 – 3.93)	2.000 (1.00 – 3.98)
$AUC_{(0-24h)}$ (ng•h/mL)	1250 ± 399	2140 ± 1030

Data are shown as mean ± standard deviation except t_{max}; for t_{max}, median (minimum – maximum) is shown.

$AUC_{(0-24h)}$ = area under the concentration-time curve from zero time to 24h, C_{max} = maximum observed concentration, t_{max} = time at which the highest drug concentration occurs, QD = once daily.

Table 22: Summary of PK parameters of lenvatinib in Group 1 (Child-Pugh score 5,6) – Cycle 1 Day 15 – PK analysis set

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	12 mg QD (n=5)	16 mg QD (n=2)
$C_{ss,max}$ (ng/mL)	346 ± 75.4	402
$C_{ss,min}$ (ng/mL)	43.1 ± 21.7	84.6
$C_{ss,av}$ (ng/mL)	130 ± 23.5	213
$t_{ss,max}$ (h)	1.950 (1.00 – 3.98)	3.915 (3.83 – 4.00)
$AUC_{(0-t)}$ (ng•h/mL)	3120 ± 566	5110
$R_{ac}(C_{max})$	1.67 ± 0.645	1.64
$R_{ac}(AUC)$	1.54 ± 0.290	1.73

Data are shown as mean ± standard deviation except $t_{ss,max}$; for $t_{ss,max}$, median (minimum – maximum) is shown.
Last sampling time point is 24 hours after administration.
$AUC_{(0-t)}$= area under the concentration-time curve over the dosing interval on multiple dosing, $C_{ss,av}$ = average steady-state concentration, $C_{ss,max}$ = maximum observed concentration at steady-state, $C_{ss,min}$ = minimum observed concentration at steady-state, R_{ac} = accumulation index, $t_{ss,max}$ = time at which the highest drug concentration occurs at steady-state.
$R_{ac}(C_{max}) = C_{ss,max}/C_{max}$; $R_{ac}(AUC) = AUC_{(0-t)}/AUC_{(0-24h)}$, QD = once daily.

Table 23: Summary of PK parameters of lenvatinib in Group 2 (Child-Pugh score 7,8) – Cycle 1 Day 15 – PK analysis set

Pharmacokinetic Parameter	Lenvatinib Dose Group	
	8 mg QD (n=6)	12 mg QD (n=2)
$C_{ss,max}$ (ng/mL)	167 ± 40.4	349
$C_{ss,min}$ (ng/mL)	29.9 ± 13.4	64.0
$C_{ss,av}$ (ng/mL)	73.8 ± 14.2	165
$t_{ss,max}$ (h)	2.025 (1.98 – 4.02)	1.995 (1.97 – 2.02)
$AUC_{(0-t)}$ (ng•h/mL)	1770 ± 340	3960
$R_{ac}(C_{max})$	1.23 ± 0.315	1.91
$R_{ac}(AUC)$	1.49 ± 0.385	2.11

Data are shown as mean ± standard deviation except $t_{ss,max}$; for $t_{ss,max}$, median (minimum – maximum) is shown.
Last sampling time point is 24 hours after administration.
$AUC_{(0-t)}$= area under the concentration-time curve over the dosing interval on multiple dosing, $C_{ss,av}$ = average steady-state concentration, $C_{ss,max}$ = maximum observed concentration at steady-state, $C_{ss,min}$ = minimum observed concentration at steady-state, R_{ac} = accumulation index, $t_{ss,max}$ = time at which the highest drug concentration occurs at steady-state.$R_{ac}(C_{max}) = C_{ss,max}/C_{max}$; $R_{ac}(AUC) = AUC_{(0-t)}/AUC_{(0-24h)}$, QD = once daily.

Summary of the relevant PK information from study 202:

- Maximum plasma concentration of lenvatinib was typically observed 2 hours after single and multiple doses.
- In general, exposure, as measured by Cmax, AUC(0-24h), AUC(0-t), Css,max, and AUC(0-τ), for lenvatinib appeared to increase with increasing doses.
- Plasma lenvatinib concentration accumulated after repeated dosing with a mean accumulation index (Rac) of AUC(0-24h) and Cmax ranging from 1.23 to 2.11.The pharmacokinetics of lenvatinib did not appear to change when evaluated by Child-Pugh score in subjects with HCC.

Study E7080-G000-304

In study 304, pharmacokinetic samples were collected from all subjects who took lenvatinib. Exposure parameters such as maximum concentration and area under the concentration × time curve (AUC) were derived from posterior estimates of the PK parameters from the final population PK model.

● Subjects with HCC had a 13.2% lower lenvatinib oral clearance than subjects with other cancer types, including DTC.

● Lenvatinib PK parameters were affected by body weight with both clearance and volume parameters increasing with increasing body weight. This was associated with an increase in lenvatinib exposure in

subjects with low body weight.

● Lenvatinib exposure was comparable between the 8-mg starting dose group with body weight <60 kg and the 12-mg dose group with body weight ⩾60 kg. This supports the 8-mg and 12-mg starting doses used in the lower and higher weight groups in Study 304.

● There were no differences in lenvatinib oral clearance or in AUC at steady-state values among Western, Asian, Chinese, and Japanese HCC populations in Study 304.

POP PK modelling

Two popPK analysis analyses supporting the HCC submission was performed and two different reports submitted: POP PK and PK/PD CPMS-E7080-005R-V1 (including data from study 202) and POP PK report CPMS-E7080-011R-V1 (including data from study 202 and from study 304).

Report CPMS-E7080-005R-V1

The primary objectives of the population PK analysis were:

- To describe the PK profile of lenvatinib in subjects with hepatocellular carcinoma and compare the PK with other cancer sub-types

- To identify covariates that explain between subject variability in lenvatinib PK.

The population PK analysis for lenvatinib was based on pooled data collected from 8 Phase 1 studies in healthy subjects (001-008), 4 Phase 1 MTD studies in subjects with solid tumours (101,102, 103 and 105), and study 202 in subjects with HCC.

Model-based analyses consisted of a population PK model for lenvatinib. The models was developed in NONMEM 7.2. Model building and covariate assessments were conducted using standard methods.

The final population PK model was used to derive individual PK parameters and lenvatinib exposures (AUC based on the starting dose and steady state Cmin), which were then incorporated into the PK/PD datasets to be used in the subsequent PK/PD analyses.

The PK population for lenvatinib from study 202 consisted of 65 HCC subjects, while the PK population from 4 Phase 1 MTD studies (101,102, 103 and 105) consisted of 155 subjects with solid tumours. HCC subjects in study 202 had lower body weights and lower liver function values (eg. higher ALP) than subjects with other tumour types.

The PK of lenvatinib was best described by a 3-compartment model with elimination from the central compartment.

The parameter estimates of the final PK model for lenvatinib are presented below:

Table 24: final population pharmacokinetic parameter estimates of lenvatinib

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
$CL/F\ [L/h] = \Theta_{CL} * (WGT/75)^{\Theta_{WGT1}} * \Theta_{INDU}^{INDU} * \Theta_{INHIB}^{INHIB} * \Theta_{TM}^{TM} * \Theta_{ALP}^{ALP}$			
Basal CL/F in L/h [Θ_{CL}]	6.43	2.19	6.15 – 6.71
Effect of inducer on CL/F [Θ_{INDU}]	1.30	0.534	1.29 – 1.31
Effect of inhibitor on CL/F [Θ_{INHIB}]	0.922	0.922	0.905 – 0.939
Effect of population (Healthy vs. Patients) on CL/F [Θ_{TM}]	1.19	3.26	1.11 – 1.27
Effect of ALP on CL/F [Θ_{ALP}]	0.852	1.24	0.831 – 0.873
Effect of body weight on CL/F, Q1/F and Q2/F [Θ_{WGT1}]	0.708	6.58	0.617 – 0.799
$Q1/F\ [L/h] = \Theta_{Q1} * (WGT/75)^{\Theta_{WGT1}}$			
Basal Q1/F in L/h [Θ_{Q1}]	3.96	3.03	3.72 – 4.20
$Q2/F\ [L/h] = \Theta_{Q2} * (WGT/75)^{\Theta_{WGT1}}$			
Basal Q2/F in L/h [Θ_{Q2}]	0.726	2.91	0.685 – 0.767
$V1/F\ [L] = \Theta_{V1} * (WGT/75)^{\Theta_{WGT2}}$			
Basal V1/F in L [Θ_{V1}]	47.0	4.40	42.9 – 51.1
Effect of body weight on V1/F, V2/F and V3/F [Θ_{WGT2}]	1.08	5.42	0.965 – 1.19
$V2/F\ [L] = \Theta_{V2} * (WGT/75)^{\Theta_{WGT2}}$			
Basal V2/F in L [Θ_{V2}]	31.2	6.76	27.1 – 35.3
$V3/F\ [L] = \Theta_{V3} * (WGT/75)^{\Theta_{WGT2}}$			
Basal V3/F in L [Θ_{V3}]	34.5	4.14	31.7 – 37.3
$Ka\ [1/h] = \Theta_{KA}$			
Basal Ka in 1/h [Θ_{Ka}]	1.04	6.80	0.901 – 1.18
$D1\ [h] = \Theta_{D1}$			
Basal D1 in h [Θ_{D1}]	1.06	5.77	0.940– 1.18
$F1 = \Theta_{F1}$			
Relative bioavailability of capsule vs tablet formulation [Θ_{F1}]	0.867	1.00	0.850 – 0.884
Inter-individual variability (%CV)			
CL/F	32.6	6.99	–
V1/F	49.5	7.39	–
Correlation between CL/F and V/F	R=0.599	10.1	–
V2/F	62.4	15.2	–

Report CPMS-E7080-011R-V1

The objectives of the population pharmacokinetics (PK) analysis of lenvatinib monotherapy on pooled data from multiple studies, including studies 304 and 202 were:

- To characterize the PK of lenvatinib in subjects with hepatocellular carcinoma (HCC) and compare to that in healthy subjects and subjects with other types of cancer

- Identify covariates that explain between-subject variability in lenvatinib PK.Population PK analysis of lenvatinib was based on PK data pooled from the 13 studies. Brief descriptions of the studies included are presented in the table below:

Table 25: brief description of studies with Pk sampling included in population PK analysis

Study	Dose Range and Regimen	N	Formulation	Subjects	Pharmacokinetic sampling
E7080-G000-304	12 mg (if baseline body weight ≥ 60 kg) or 8 mg (if baseline body weight < 60 kg) QD	468	Capsule	HCC	Day 1 of Cycle 1 and 2: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 1 Day 15: Pre-dose and 2-12 h post dose C_{trough}: Cycle 3-Cycle 6/Day1
E7080-J081-202	Phase 1: 8 - 16 mg QD continuous Phase 2: 12 mg QD continuous	20 46	Tablet	HCC	Days 1 and 15 of Cycle 1 :0.5, 1, 2, 4, 6, 8 and 24 h post dose C_{trough}: Days 1, 8, 15 and 22 of Cycle 1 C_{trough}: Days 1, 8, 15 and 22 of Cycle 1 Days 1 of Cycle 2 and 3
E7080-G000-303	24 mg QD continuous	260	Capsule	DTC	Day 1 and 15 of Cycle 1: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 2 Day 1: Pre-dose and 2-12 h post dose C_{trough}: Cycle 3-Cycle 6/Day1
E7080-E044-101	0.2 – 32 mg QD continuous	66	Tablet	Solid Tumors	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose C_{trough}: Days 1, 8, and 15 of Cycle 1
E7080-A001-102	Schedule 1: 0.1 – 3.2 mg BID x 7d/14d Schedule 2: 3.2 – 12 mg BID continuous 10 mg BID continuous	62	Tablet	Solid Tumors Melanoma	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose C_{trough}: Days 8, 15 and 22 of Cycle 1
E7080-J081-103	0.5 – 20 mg BID x 14d/21d	18	Tablet	Solid Tumors	1, 2, 3, 5, 6, 8, 12, 24, 48, 96, and 168 h post dose on Day1 of Cycle 0 and Day 14 of Cycle1 C_{trough}: Days 5, 8 and 11 of Cycle 1, Day 8 of Cycle 2
E7080-J081-105	20 and 24 mg QD continuous	9	Capsule	Solid Tumors	Day 1 and 15 of Cycle 1: 1, 2, 4, 8, and 24 h post dose C_{trough}: Days 8, 15 of Cycle 1, Day 15 of Cycle 2
E7080-A001-001	10 mg	20	Tablet/ capsule	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-002	32 mg	51	Capsule	Healthy volunteers	Pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h post-dose
E7080-A001-003	10 mg	16	Capsule	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-005	24 mg	26	Capsule	Healthy volunteers and renal impairment	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-006	5 and 10 mg	26	Capsule	Healthy volunteers and hepatic impairment	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h post-dose
E7080-A001-008	10 mg	60	Capsule	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, and 120 h post-dose

DTC: differentiated thyroid cancer
Subjects who received a starting dose of 3.2 mg and higher were included in PK dataset

Differences in the PK of lenvatinib in subjects with HCC and subjects with other tumour type were tested.

The final population PK model for lenvatinib was a 3-compartment model with simultaneous first and zero order absorption and linear elimination from the central compartment parameterized for CL/F, V1/F, Q2/F, V2/F, Q3/F, V3/F, Ka, D1 and F1. Inter-individual variability (IIV) was estimated on all parameters except Q2/F and Q3/F. A combined additive and proportional error for time after dose (TAD) ≤2 h and separate proportional errors for Phase 1 clinical pharmacology studies and cancer patient studies was used for estimation of residual variability. The final PK model for lenvatinib included body weight effect as an allometric constant on both clearance and volume parameters, whereby both parameters increased with increasing body weight. Lenvatinib CL/F decreased by 10.2% with albumin levels below 30 g/L and decreased by 8.6% with ALP above upper limit of normal (ULN). The HCC population was found to have a

13.2% lower lenvatinib CL/F compared to patients with other cancer types, and a 24.5% lower lenvatinib CL/F compared to healthy subjects. Population PK parameter estimates are presented in the table below.

Table 26: population pharmacokinetic parameter estimates of lenvatinib – final model

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
$CL/F\ [L/h] = \Theta_{CL} * (WGT/70)^{0.75} * \Theta_{INDU}^{INDU} * \Theta_{INHIB}^{INHIB} * \Theta_{ALB}^{ALB} * \Theta_{ALP}^{ALP} * \Theta_{HV}^{HV} * \Theta_{HCC}^{HCC}$			
Basal CL/F in L/h [Θ_{CL}]	6.25	1.81	6.03 – 6.47
Effect of inducer on CL/F [Θ_{INDU}]	1.30 FIX		
Effect of inhibitor on CL/F [Θ_{INHIB}]	0.922 FIX		
Effect of ALB(<30) on CL/F [Θ_{ALB}]	0.898	1.85	0.865 – 0.931
Effect of ALP (>ULN) on CL/F [Θ_{ALP}]	0.914	0.0941	0.912 – 0.916
Effect of Healthy population on CL/F [Θ_{HV}]	1.15	3.07	1.08 – 1.22
Effect of HCC population on CL/F [Θ_{HCC}]	0.868	2.15	0.831 – 0.905
$V1/F\ [L] = \Theta_{V1} * WGT/70$			
Basal V1/F in L [Θ_{V1}]	48.7	0.232	48.5 – 48.9
$V2/F\ [L] = \Theta_{V2} * WGT/70$			
Basal V2/F in L [Θ_{V2}]	25.4	4.33	23.2 – 27.6
$V3/F\ [L] = \Theta_{V3} * WGT/70$			
Basal V3/F in L [Θ_{V3}]	37.1 FIX		
$Q1/F\ [L/h] = \Theta_{Q1} * (WGT/70)^{0.75}$			
Basal Q1/F in L/h [Θ_{Q1}]	3.25	3.51	3.03 – 3.47
$Q2/F\ [L/h] = \Theta_{Q2} * (WGT/70)^{0.75}$			
Basal Q2/F in L/h [Θ_{Q2}]	0.798	3.28	0.747 – 0.849
$Ka\ [1/h] = \Theta_{Ka}$			
Basal Ka in 1/h [Θ_{Ka}]	1.02 FIX		
$D1\ [h] = \Theta_{D1}$			
Basal D1 in h [Θ_{D1}]	1.22 FIX		
$F1 = \Theta_{F1}$			
Relative bioavailability of capsule vs tablet formulation [Θ_{F1}]	0.9 FIX		
Inter-individual variability (%CV)			
CL/F	25.4	5.53	–
V1/F	28.3	10.2	–
V2/F	43.0	14.0	–
V3/F	32.4	11.3	–
Ka	51.7	13.4	–
D1	93.6	6.34	–
F1	26.2	7.19	–
Residual variability			
Proportional (%CV) (Clin pharm studies)	17.0	0.817	–
Proportional (%CV) (Patients studies)	36.3	1.40	–
Proportional (%CV) (TAD ≤ 2 h)	49.0	3.57	–
Additional (ng/mL) (TAD ≤ 2 h)	6.65	16.8	–

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100;
The %CV for both inter-subject and proportional residual variability is an approximation taken as the square root of the variance * 100; CL/F = apparent clearance, V1/F = apparent volume of central compartment; V2/F and V3/F = apparent volume of peripheral compartment; Q1 = inter-compartment clearance between V1 and V2; Q2 = inter-compartment clearance between V2 and V3; Ka = absorption rate constant; D1 = duration of zero order absorption; F1 = relative bioavailability of capsule to tablet formulation; TAD = Time after dose; CI = confidence interval; WGT = weight (kg); INDU = CYP3A4 inducers; INHIB = CYP3A4 inhibitors; ALB =albumin, 0 (≥ ALB 30 g/L) or 1 (< ALB 30 g/L); ALP = Alkaline phosphatase measurement (IU/L) 0 (ALP ≤ upper limit of normal) or 1 (ALP > upper limit of normal value); HV = 0 (cancer patients) or 1 (healthy subjects) ; HCC = 0 (non-HCC patients) or 1 (HCC patients)

Individual lenvatinib oral clearance (CL/F) and AUC at steady state for subjects with HCC in study 304 are summarized by starting dose group in the table below. The median value and range of AUC are comparable between 8 mg group and 12 mg group.

The final PK model for lenvatinib included body-weight effect as an allometric constant on both clearance and volume parameters, whereby both parameters increased with increasing body weight. The decrease in CL/F in subjects with low body weight results in an increase in lenvatinib AUC. Based on the individual lenvatinib AUC at steady state for subjects with HCC in study 304, the median value and range of AUC are comparable between the group of starting dose of 8 mg for body weight < 60 kg and 12 mg for body weight ≥ 60 kg in study 304, which supports the starting dose of 8 mg for body weight < 60 kg.

The final PK model for lenvatinib also included covariates related to liver function; CL/F decreased by 8.6% with ALP > the upper limit of normal, and by 10.2% with albumin levels below 30 g/L. HCC subjects had a 13.2% lower lenvatinib CL/F than subjects with other cancer types, including DTC.

2.3.3. Pharmacodynamics

Mechanism of action

No new data regarding mechanism of action has been submitted with this application.

Primary and secondary pharmacology

Biomarker analysis

Exploratory biomarker analyses were performed on blood and tumour tissue samples in the Biomarker Analysis Set from Study 304.

Archival tumour tissue and blood samples were collected pretreatment and at specified time points. The BM analysis set (BAS; n = 119) included pts who provided both archival tissue and serum samples. Serum samples from 114 pts were analyzed at baseline and over time with ELISA or chemiluminescence for VEGF, ANG2, FGF21, FGF23, and PIVKA-II. Gene-expression profiling was performed on tissue samples with nCounter® (NanoString). Results from BM analyses were correlated with OS.

Gene-expression analysis was performed in 58 pts (34 lenvatinib, 24 sorafenib).

Serum BM and gene expression levels appear to correlate with outcomes in the BAS. The correlation analyses for serum biomarkers and gene expression were limited by the small number of samples, as well as the observed imbalances between the Full Analysis Set (FAS) and the biomarker analysis subset. Therefore, no valid conclusion is possible to correlate the results of the biomarker analyses with the clinical outcomes of the overall study population as well as between treatment arms at this point.

2.3.4. PK/PD modelling

Report CPMS-E7080-005R-V1

In addition to the population PK analysis performed (described above) , a PK/PD analysis for safety for Study 202 was included in this report. The objectives of this analysis were:

- To describe the relationship between lenvatinib exposure and longitudinal platelet profile in patients with hepatocellular carcinoma
- To explore the relationship between lenvatinib exposure and the occurrence of treatment emergent adverse events (TEAE) leading to study drug withdrawal or dose reduction for Phase 2 part of Study 202.
- To explore the relationship between lenvatinib exposure and occurrence of the following TEAE for Phase 2 part of Study 202: Hypertension (During Cycle 1), proteinuria, palmar-plantar

erythrodysaesthesia syndrome (PPES), Fatigue, decreased appetite, diarrhoea, nausea and hepatic encephalopathy

The objectives of the population PK/PD analysis for efficacy for Phase 2 part of Study 202 were:

- To explore the relationship between lenvatinib exposure and efficacy endpoints (objective response rate (ORR), disease control rate (DCR), time to progression (TTP), overall survival (OS), progression free survival (PFS) and maximum tumour shrinkage in subjects with hepatocellular carcinoma

The objectives of the PK/PD analyses for biomarkers of Study 202 were:

Phase 1 part

- To explore the relationship between lenvatinib exposure and the change from baseline in the following serum biomarkers: VEGF, SDF-1α, SCF, IL-6, IL-8, IL-10, total CEP, total CEC, c-kit (-) CEP, c-kit (+) CEP, c-kit (-) CEC and c-kit (+) CEP

Phase 2 part

- To explore the relationship between lenvatinib exposure and the change from baseline in the following serum biomarkers: soluble VEGFR1, soluble VEGFR2, soluble VEGFR3, VEGFA, PGF, angiopoietin-2, soluble Tie-2, eotaxin, SDF-1α, G-CSF, IP-10, IL-8, RANTES and soluble CD40L.

The final population PK model was used to derive individual PK parameters and lenvatinib exposures (AUC based on the starting dose and steady state Cmin), which were then incorporated into the PK/PD datasets to be used in the subsequent PK/PD analyses.

Graphical analyses were performed to assess the relationship between AE and lenvatinib exposure for the occurrence of CTCAE grade ≥2 hypertension (During Cycle 1), proteinuria, palmar-plantar erythrodysaesthesia syndrome (PPES), fatigue, decreased appetite, diarrhoea, CTCAE grade ≥1 nausea and hepatic encephalopathy.

The population used for the PK/PD analysis of the platelet count consisted of a total of 65 subjects from study 202 only. The platelet count data were best described by an eight-compartment PK/PD lifespan model including four PK compartments and four PD compartments parameterized for a zero-order production rate constant (Kin), first-order transition rate constant (KT), and slope coefficient of lenvatinib plasma concentration (SLOP) where model predicted lenvatinib concentrations reduced the platelet proliferation rate or induced cell loss. The elimination rate constant (Kdeg) was defined using baseline platelet count (BASE) as Kdeg = Kin/BASE. Exponential IIV was estimated for BASE, KT and SLOP. The results from the covariate analysis indicated that the relationship between lenvatinib plasma concentration and platelet count change in study 202 was independent of gender, age, body weight, hepatic function markers, performance status, factor of carcinogenesis, portal vein involvement, previous systemic chemotherapy and surgery history.

: Parameter estimates of the PK/PD model for platelet count

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
Kin (*10^9/L/h)	1.51	19.5	0.934 – 2.09
SLOP of lenvatinib concentration effect (per 1 µg /mL) (mL/µg)	3.50	6.03	3.09 – 3.91
KT (h^{-1})	0.0335	6.03	0.0295 – 0.0375
Inter-individual variability (%CV)			
Kin	0 Fix	–	–
BASE	19.9	22.9	–
SLOP	33.5	24.9	–
KT	84.4	23.4	–
Residual variability			
Proportional (%CV)	19.0	9.42	–

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100;

The %CV for both inter-subject and proportional residual variability is an approximation taken as the square root of the variance * 100; Kin = zero-order production rate constant of platelet, BASE = baseline platelet count; SLOP = linear effect of lenvatinib on production rate of platelet precursor; KT = first-order transition rate constant

In the phase 2 part of study 202, 21 patients (46.7 %) of PK/PD population experienced any treatment emergent adverse events (TEAE) leading to dose reduction or discontinuation during Cycle 1. The median AUC based on the starting dose of patients with early dose withdrawal or reduction was 2950 ng*h/mL, whereas the median AUC based on the starting dose of patients without early dose modification was 2050 ng*h/mL. The occurrence of TEAE leading to study drug withdrawal or dose reduction during Cycle 1 as a function of lenvatinib exposure was modeled with the logit function. The exposure parameters, AUC based on the starting dose and steady state Cmin, were tested for linear relationship. Adding lenvatinib AUC based on the starting dose as a linear function resulted in higher drop in OFV than that of Cmin. Adding lenvatinib AUC as log-linear and Emax functions resulted in the worse OFV, thus adding lenvatinib exposure as linear AUC was selected as the base model.

The effects of the following covariates were tested in the univariate analysis, separately both on intercept of experiencing TEAE leading to study drug withdrawal or dose reduction as well as for the effect each covariate on slope of lenvatinib effect: demographics (sex, body weight and age), liver function markers, ECOG performance status, Child-Pugh score, factor of carcinogenesis (HBV or HCV vs. Others), portal vein involvement, previous systemic chemotherapy, prior antihypertensives, and with/without surgery at the baseline.

The model parameters estimated for the final model are represented below.

Table 27: Final model parameter estimates for the logistic model for occurrence of TEAE leading to study drug withdrawal or dose reduction during cycle 1

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% CI
*f(x) = INT + SLP*AUC*			
INT: Intercept	-4.71	29.3	-7.41 – -2.01
SLP: Slope of lenvatinib AUC effect (per 1000 ng·h/mL)	1.82	28.8	0.793 – 2.85
Odds ratio (per 1000 ng·h /mL of AUC)	6.17	-	-

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CI: confidence interval

The model predicted probability of TEAE leading to study drug withdrawal or dose reduction during Cycle 1 for HCC patients is shown in the figure below. The observed probability of TEAE leading to study drug withdrawal or dose reduction during Cycle 1 for lenvatinib AUC group are also plotted using median AUC

of each quantile AUC group (Q1: 1700, Q2: 2120, Q3: 2690, Q4: 3550 ng·h/mL). The probability increased with higher AUC.

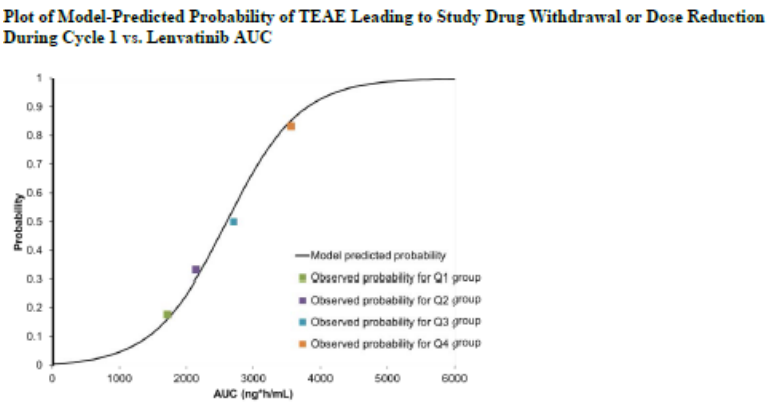


Figure 10: Graphical relationship of lenvatinib exposure with time to TEAE leading to study drug withdrawal or dose reduction (study 202 Phase 2 part)

Graphical analysis suggested that lenvatinib exposures are higher in subjects experiencing CTCAE grade ≥2 palmar-plantar erythrodysaesthesia syndrome, fatigue, decreased appetite, diarrhoea and CTCAE grade ≥1 hepatic encephalopathy than those in subjects not experiencing these AEs.

Clear relationship was seen between the occurrence of TEAEs leading to dose reduction or discontinuation during Cycle 1 and body weight, whereby patients with low body weight experienced early dose reduction or discontinuation, and this can be explained by the higher lenvatinib AUC of patients with low body weight.

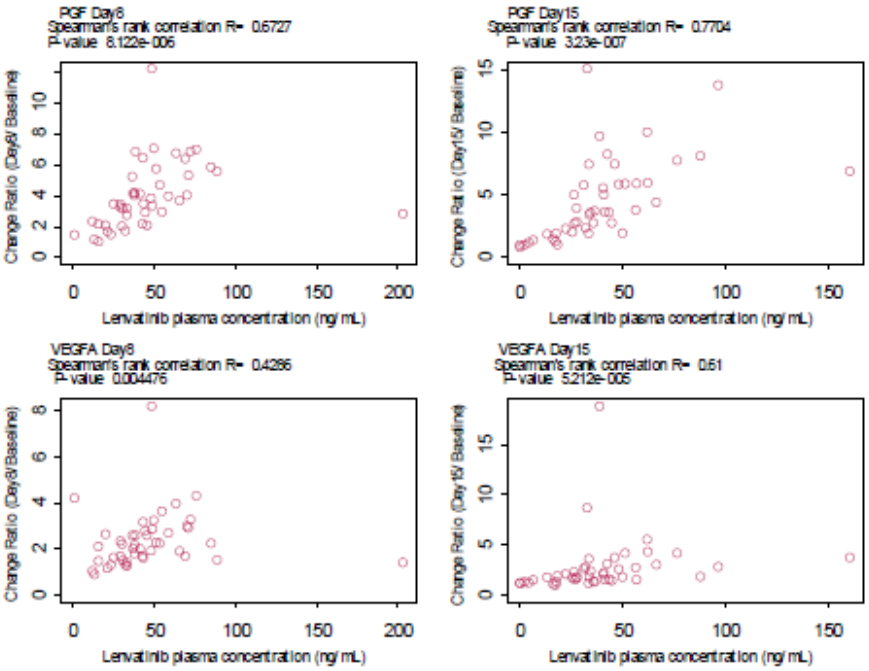
Therefore, the exploratory assessment for the adjustment of the starting dose of lenvatinib by body weight was performed in further clinical study for HCC.

ROC curve which was predicted from the developed logistic regression model indicated that the best cut-off value of lenvatinib AUC is 2430 ng*h/mL with 0.71 sensitivity and 0.71 specificity.

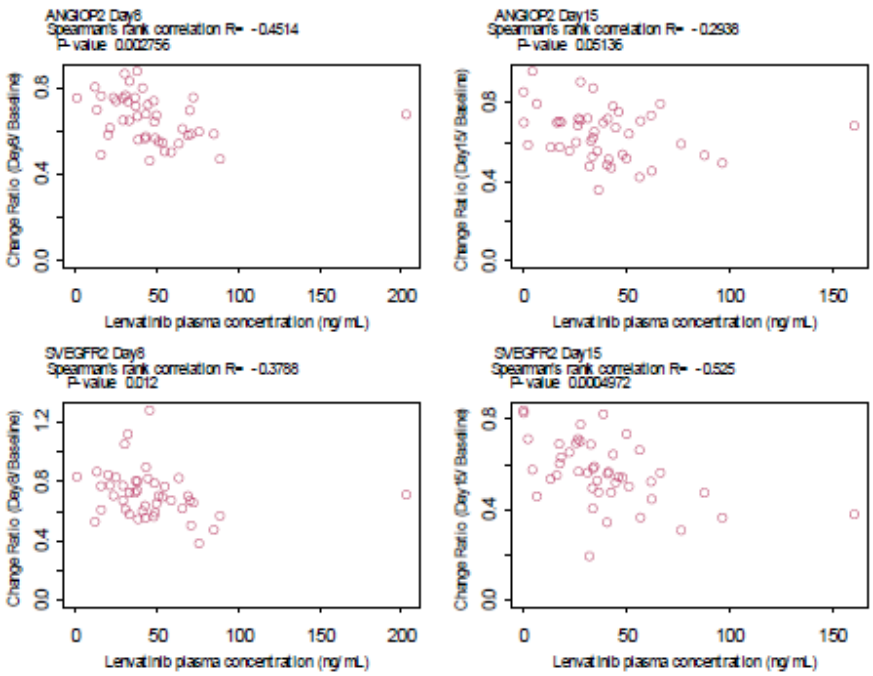
Within the range between 40 kg and 120 kg of body weight, the predicted AUC of subjects whose body weight were less than 60kg, are calculated between 1540 and 2050 ng•h/mL, and the predicted AUC of subjects whose body weight are 60kg and over, are calculated between

No clear relationship between the efficacy endpoints (TTP, PFS, OS, BOR, ORR, DCR and maximum tumour shrinkage) with lenvatinib AUC based on starting dose could be detected. Thus use of a lower starting dose (8 mg) in patients with body weights less than 60 mg is not expected to impact efficacy.

Clear trend of ratio change in each of the following serum biomarkers with lenvatinib concentration was observed: PGF and VEGFA increased with lenvatinib concentration and angiopoietin-2 and soluble VEGFR2 decreased with lenvatinib concentration, as shown in the figures below.



: Plot of ratio change (post dose / baseline) of PGF and VEGFA verus lenvatinib concentration (cycle 1 day 8 and day 15)



: Plot of ratio change (post dose / baseline) of angiopoietin-2 and soluble VEGFR-2 verus lenvatinib concentration (cycle 1 day 8 and day 15)

No clear exposure relationships were found for soluble VEGFR1, soluble VEGFR3, soluble Tie-2, eotaxin, SDF-1α, G-CSF, IP-10, IL-8, RANTES and soluble CD40L.

CPMS-E7080-011R-V1

The same approach as described above was implemented for exposure-response analysis with only data from study 304 been used.

Exposure-Response Analysis for Overall Survival and Other Efficacy Variables

• After accounting for effects of baseline albumin, bilirubin, tumour size, Alpha-fetoprotein (AFP), Child-Pugh score, macroscopic portal vein invasion, extrahepatic spread or both, no exposure-response relationship for OS was observed in the multivariate Cox regression analysis within the exposure range of study 304.

• No exposure-response relationship for PFS and ORR was observed within the exposure range of study 304.

• In the absence of a relationship between % change in tumour size and lenvatinib exposure as well as the absence of data following placebo in Eisai-sponsored studies to accurately estimate tumour growth rate constant in HCC, or a published value, a PK/PD model for tumour size could not established.

Exposure-Response Analysis for Adverse Event

• Lenvatinib AUC at steady state based on the starting dose was a significant predictor for the occurrence of any grade of decreased appetite. The occurrence of any grade of decreased appetite increased with higher lenvatinib AUC. No covariates tested in this analysis affected the exposure-response relationship for the occurrence of decreased appetite.

• For hypertension, proteinuria, weight decreased, fatigue, vomiting, thrombocytopenia, platelet count decreased, diarrhoea, palmar-plantar erythrodysaesthesia syndrome and hepatic encephalopathy, no significant relationship between lenvatinib exposure and these AEs was detected within the exposure range of study 304.

• Lenvatinib AUC at steady state based on the starting dose was a significant predictor for the occurrence of AEs leading to lenvatinib dose reduction or interruption. The occurrence of AEs leading to lenvatinib dose reduction or interruption increased with higher lenvatinib AUC.

• Lower baseline AFP level was a significant predictor for the occurrence of AEs leading to lenvatinib dose reduction or interruption. Lower baseline AFP level was also associated with longer treatment duration confounding any interpretation of AFP levels and dose reductions or interruptions.

• For AEs leading to lenvatinib treatment withdrawal, no significant relationship between lenvatinib exposure and these AEs was detected within the exposure range of study 304.

Exposure-Response Analysis for Blood Pressure

• Systolic and diastolic blood pressure (BP) data were best described by an indirect response model with lenvatinib AUC at BP assessment affecting input rate constant for BP resulting in increased BP.

• No covariates tested in this analysis affected the exposure-response relationship for blood pressure.

• The model predicted increase in BP was small and not considered clinically important in the therapeutic exposure range for subjects with HCC.

2.3.5. Discussion on clinical pharmacology

Data from 21 studies were used to characterize the pharmacokinetics (PK) of lenvatinib. These included a Phase 1/2 dose finding study for subjects with HCC (Study E7080-J081-202) and an HCC Phase 3 safety and efficacy study (Study E7080-G000-304). The understanding of the pharmacokinetics of lenvatinib is broadened by the secondary objectives defined in the clinical studies 202 and 304, especially by means of the accompanying POP PK analysis provided.

From study 304, it was observed that subjects with HCC had a 13.2% lower lenvatinib oral clearance than subjects with other cancer types, including DTC. Lenvatinib PK parameters were affected by body weight

with both clearance and volume parameters increasing with increasing body weight. This was associated with an increase in lenvatinib exposure in subjects with low body weight. Lenvatinib exposure was comparable between the 8-mg starting dose group with body weight <60 kg and the 12-mg dose group with body weight ≥60 kg. The 8-mg and 12-mg starting doses used in the lower and higher weight groups in Study 304 are supported from a PK perspective.

In HCC studies 202 and 304, subjects with Child-Pugh class A and B were included. In study 202, no relationship between CP score and the PK of lenvatinib was observed and the exposure is significantly decreased in moderate impaired patients with 8 mg QD compared to the exposure of mild and moderate impaired patients with 12 mg QD. In study 304, no PK analysis has been made with the subjects with child-Pugh B (score 7 or 8) since the enrolment of these subject was in fact a protocol deviation (n=3).
Patients ⩾75 years, of white race or female sex or those with worse baseline hepatic impairment (Child-Pugh A score of 6 compared to score of 5) appear to have reduced tolerability to lenvatinib.
The available data are insufficient to allow for a dosing recommendation for HCC patients with moderate hepatic impairment (Child-Pugh B). Lenvatinib has not been studied in patients with severe hepatic imparement (Child-Pugh C) and is not recommended for use in these patients.
From a non-clinical/clinical perspective, the 4 additional pharmacokinetics studies that have been completed (peaks in monkey plasma, protein binding in HLMs, reversibility of covalently bound lenvatinib-related components and MATE inhibition and substrate) are adequately performed and address questions raised during the review of the original marketing application. Lenvatinib is not a substrate for MATE1 and MATE2-K and showed minimal or no inhibitory effect on MATE2-K and weakly inhibits MATE1.

In addition to the population PK (PopPK) and PK/PD analyses performed for the original lenvatinib submissions (reported in CPMS-E7080-007R) and the population PK and PK/PD analyses performed for the RCC submission (reported in CPMS-E7080- 008R), an analysis supporting the HCC submission was performed.

No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. The available data do not allow for a dosing recommendation for patients with HCC and severe renal impairment (see SmPC section 4.2).

The level of lenvatinib protein binding is yet not considered to be known while the assessment of severe renal and hepatic impairment should be based on free fraction. To reply to this question, study 010 entitled "A Multicenter Phase 0 Study In Healthy Subjects As Well As Subjects With Either Hepatic Or Renal Impairment To Obtain Plasma To Assess In Vitro Lenvatinib Protein Binding" will be submitted according to the timeline and is included in the RMP. Study 109 entitled “drug-drug interaction to investigate the potential of lenvatinib for CYP3A4 inhibition/induction” is included in the RMP and should be submitted according to the timelines.

Based on the results of study E7080-A001-009, the lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed (see section 4.2 of the SmPC).

2.3.6. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of lenvatinib is appropriately described. No major issues have been identified. However, for the time being, it is not clearly demonstrated that the exposure in patients with moderate hepatic impairment is sufficiently high with a starting dose of 8 mg, especially for patients with > 60 kg. The SmPc should be adapted accordingly.

Lenvatinib is not a substrate for MATE1 and MATE2-K and showed minimal or no inhibitory effect on MATE2-K and weakly inhibits MATE1.

Study 010 entitled "A Multicenter Phase 0 Study In Healthy Subjects As Well As Subjects With Either Hepatic Or Renal Impairment To Obtain Plasma To Assess In Vitro Lenvatinib Protein Binding" and study 109 entitled “drug-drug interaction to investigate the potential of lenvatinib for CYP3A4 inhibition/induction” are included in the RMP and should be submitted according to the timelines.

The analyses of biomarkers in a subset of patients enrolled in the study did allow to make definitive conclusion or indicate a particular biomarker for selection of patients.

<The CHMP considers the following measures necessary to address the issues related to pharmacology:>

2.4. Clinical efficacy

Initial evidence for the efficacy and safety of lenvatinib in HCC was obtained from Study E7080-J081-202 (hereafter referred as Study 202), which was a multicenter, open-label, Phase 1/2 study of lenvatinib consisting of a Dose Escalation Component (Phase 1) and an Expansion Component (Phase 2) in subjects with advanced HCC for whom standard therapy or other appropriate therapy was not available. This study was conducted with tablet formulation of lenvatinib.

The primary basis for establishing the efficacy and safety of lenvatinib in HCC is the Phase 3 Study E7080-G000-304 (hereafter referred as Study 304), a randomized, controlled, open-label, multi-center, non-inferiority trial versus sorafenib. This study was conducted with an approved capsule formulation of lenvatinib.

A tabular listing of the lenvatinib studies contributing efficacy data in HCC is provided in table below.

Table 28 : **Clinical efficacy studies contributing to the evaluation of efficacy in hepatocellular carcinoma**

Study ID	Number of Study Centers (Locations)	Study Start/ Clinical Cutoff Date	Study Design / Indication	Study Treatment(s): Dose, Route & Regimen	No. Subjects Planned/ Treated/ Ongoing[a]	Treated Subjects Sex (M/F); Median age, y (Range)	Efficacy Endpoints
Pivotal Phase 3 Study							
E7080-G000-304	183 sites: Asia (China, Japan, Republic of Korea, Singapore, Taiwan, Hong Kong, Thailand, Philippines, Malaysia), North America, the EU, Russia, Israel	01 Mar 2013 (1st subject signed ICF) 13 Nov 2016 (clinical cutoff for primary analysis)	Randomized (1:1), open-label, noninferiority of lenvatinib vs sorafenib in subjects with unresectable, BCLC stage B or C HCC and CP class A	Lenvatinib QD: 8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) oral capsules Sorafenib 400 mg BID oral tablets	Planned: Total N = 940 Treated/Ongoing: [b] Lenvatinib: 478/27 Sorafenib: 476/25	Lenvatinib: 405M/73F 63.0 y (20, 88) Sorafenib: 401M/75F 62.0 y (22, 88)	Primary: OS Secondary (sequential analysis): PFS, TTP, ORR Exploratory: DCR, CBR, HRQoL
Supportive Study							
E7080-J081-202	Phase 1: Japan (2 sites) Phase 2: Japan (12 sites), Korea (2 sites)	24 Jul 2009 (1st subject signed ICF) 15 Jun 2014 (clinical cutoff for primary analysis) 13 Aug 2015: (cutoff date for final analysis)	Phase 1/2, nonrandomized, multicenter, multidose, open-label study with a dose-escalation component (Phase 1) and an expansion component at the RP2 dose (Phase 2) in subjects with advanced HCC	Lenvatinib QD: Phase 1: 8, 12, or 16 mg Phase 2: 12 mg (RP2 dose) oral tablets	Phase 1: Group 1 (CP score 5-6): Planned: 12-18/ Actual: 9; Group 2 (CP score 7-8): Planned: 6-18/ Actual: 11 Ongoing: 0 (Groups 1+2) Phase 2: (CP score 5-6) 46/46/0	Phase 1: 17M/3F 63.5 y (47, 74) Phase 2: 33M/13F 66.5 y (37, 80)	Phase 1: Primary: NA[c] Secondary: BOR Phase 2: Primary: TTP Secondary: BOR, ORR, DCR, OS

BCLC = Barcelona Clinic Liver Cancer; BID = twice daily; BOR = best overall response; BW = body weight; CBR = clinical benefit rate; CP = Child-Pugh; CSR = Clinical Study Report; DCR = disease control rate; EU = European Union; F = female; HCC = hepatocellular carcinoma; HRQoL = health-related quality of life; ICF = informed consent form; M = male; NA = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QD = once daily; RP2 = recommended Phase 2 (dose); TTP = time to progression.

2.4.1. Dose response study(ies)

Study E7080-J081-202: A Phase 1/2 Study of E7080 in Patients With Advanced Hepatocellular Carcinoma (HCC)

This study was a multicenter, open-label, Phase 1/2, dose-finding study of lenvatinib that evaluated the safety, activity, and pharmacokinetic (PK)/pharmacodynamic relationships of lenvatinib in subjects with advanced HCC for whom standard therapy or other appropriate therapy was not available. Lenvatinib was given as tablet formulation once daily (QD) for 4 weeks per cycle with no break. The study was conducted in Japan and Korea. The first patient enrolled 24 July 2009 and the data cut-off date for the primary analysis was 15 June 2014. The study completed 13 August 2015. The data cut-off for the interim analysis occurred on 23 Dec 2011 when all subjects completed at least 6 months of study therapy or discontinued study treatment.

Study 202 consisted of (1) a Dose-escalation component (Phase 1) designed to determine the maximum tolerated dose of lenvatinib in HCC based on dose-limiting toxicity (DLT) and identify a dose for Phase 2 of the study, and (2) an Expansion component (Phase 2) designed to evaluate the efficacy and safety of lenvatinib at the recommended Phase 2 dose (12 mg QD).

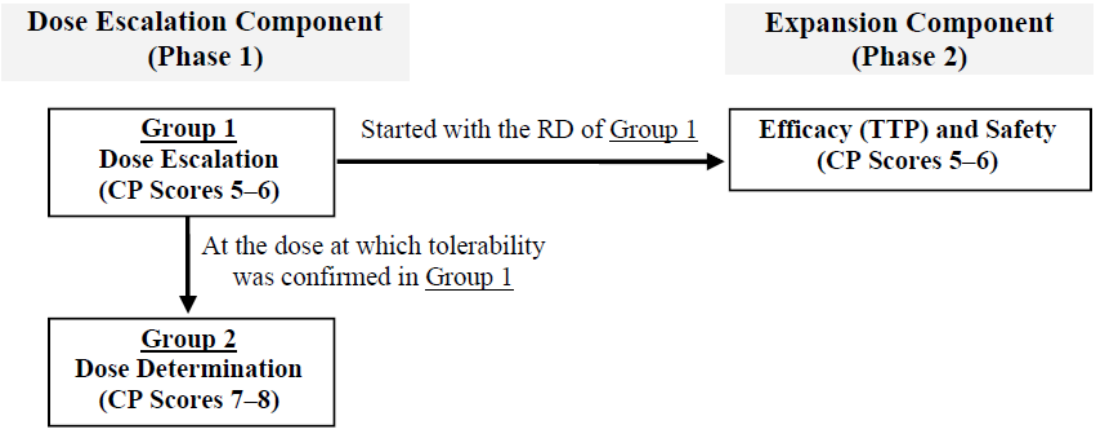


Figure 11: Study design of Phase1/2 study 202

In the dose-escalation component (Phase1), lenvatinib doses of 12 mg (6 subjects) and 16 mg (3 subjects) QD were tested in subjects with advanced HCC and hepatic function of Child-Pugh (CP) scores of 5–6 (Group 1) and lenvatinib dose of 8 mg (6 subjects) and 12 mg (5 subjects) QD in subjects with advanced HCC and hepatic function of Child-Pugh (CP) scores of 7–8 (Group 2). The dose-escalation component was designed primarily to determine the maximum tolerated dose based on DLT. The MTD was defined as the highest dose at which no more than 1 of 6 patients had a DLT. The Enrolled Analysis Set comprised 20 subjects (9 in Group 1 and 11 in Group 2) that received study treatment and completed the study (i.e. experienced DLT or completed tolerability assessment without DLT until Day 28 of Cycle 1).

In Group 1 (CP scores of 5–6), 1 DLT (fever and vomiting, resulting in less than 75% of the prescribed number of doses) was observed in the 6 subjects dosed at 12-mg QD and 2 DLTs (liver dysfunction and hepatic encephalopathy; proteinuria) were observed in the 3 subjects dosed at 16-mg QD, establishing 12 mg QD as the MTD for Group 1.

In Group 2 (CP scores of 7–8), 2 DLTs (hepatic encephalopathy; AST increased, hyperbilirubinaemia, creatinine increased resulting in less than 75% of the prescribed number of doses) were observed in the 5 subjects dosed at 12-mg QD and no DLT was observed in 6 subjects dosed at 8-mg QD, establishing 8 mg QD as the MTD for Group 2.

The 12-mg QD dose, determined to be the MTD in subjects with a Child-Pugh score of 5 or 6 (Class A

[CP-A]), was the recommended dose for the Phase 2 portion of the study.

Tumour assessments were performed using RECIST 1.1. Based on investigator assessment, the ORR was 15.0% (95% CI: 3.2, 37.9) and the DCR was 65.0% (95% CI: 40.8, 84.6). Three subjects (15.0%) had a BOR of PR, and 10 subjects (50.0%) had a BOR of SD, while 6 subjects (30.0%) had PD. One subject was declared NE. No subject had a BOR of CR. Median TTP was 3.60 months (95% CI: 1.90, 7.50).

However, approximately 74% of subjects with HCC treated with lenvatinib 12 mg QD required dose reduction to 8 mg. A PopPK analysis including Study 202 showed that both clearance and volume increased with increasing body weight (please refer to the PK section). Consequently, lenvatinib AUC increased as body weight decreased in subjects with HCC. Subjects with a low body weight (<60 kg) had a higher lenvatinib AUC, which appears to have led to the high rate of dose reductions and discontinuations in these subjects in Cycle 1 in Study 202.

Based on these results, a 2-tier dosing strategy based on body weight was proposed in future HCC trials both to achieve comparable lenvatinib exposures and to manage toxicity: 12 mg QD for subjects weighing 60 kg and over, and 8 mg QD for subjects weighing less than 60 kg. This 2-tier dosing strategy was used in HCC Study 304. The final PopPK model including data from Study 304 confirmed that lenvatinib PK was affected by body weight in subjects with HCC (Report CPMS-E7080-011R). The effect of changes in body weight was more pronounced in HCC than in previously studied tumour types (RR-DTC, RCC). In other tumour types, the effect of body weight on lenvatinib PK was small, not clinically relevant, and did not warrant any dose adjustment (CPMS-E7080-007R; CPMS-E7080-008R). These data supported the use of the 2-tier dosing strategy based on body weight in HCC. (see relevant clinical pharmacology sections)

2.4.2. Main study

Study E7080-G000-304: A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma

Methods

Study E7080-G000-304 (Study 304) was a multi-center, randomized, open-label, non-inferiority Phase 3 study of lenvatinib versus sorafenib.

The study consisted of 3 phases, the Pre-randomization, the Randomization, and the Extension Phase. The Pre-randomization phase comprised 2 periods, Screening and Baseline. The Randomization and the Extension phases each comprised 2 periods, the Treatment Period and Follow-up Period.

The Randomization Phase of the study ended at the date of data cut-off for the primary analysis of OS (13 Nov 2016), which occurred when the target number of events (700 deaths) among the 2 treatment groups was observed. All subjects who were still on study treatment or in follow-up at that time entered the Extension Phase. Ongoing subjects continued to be followed for survival and all subsequent anticancer treatments received were recorded.

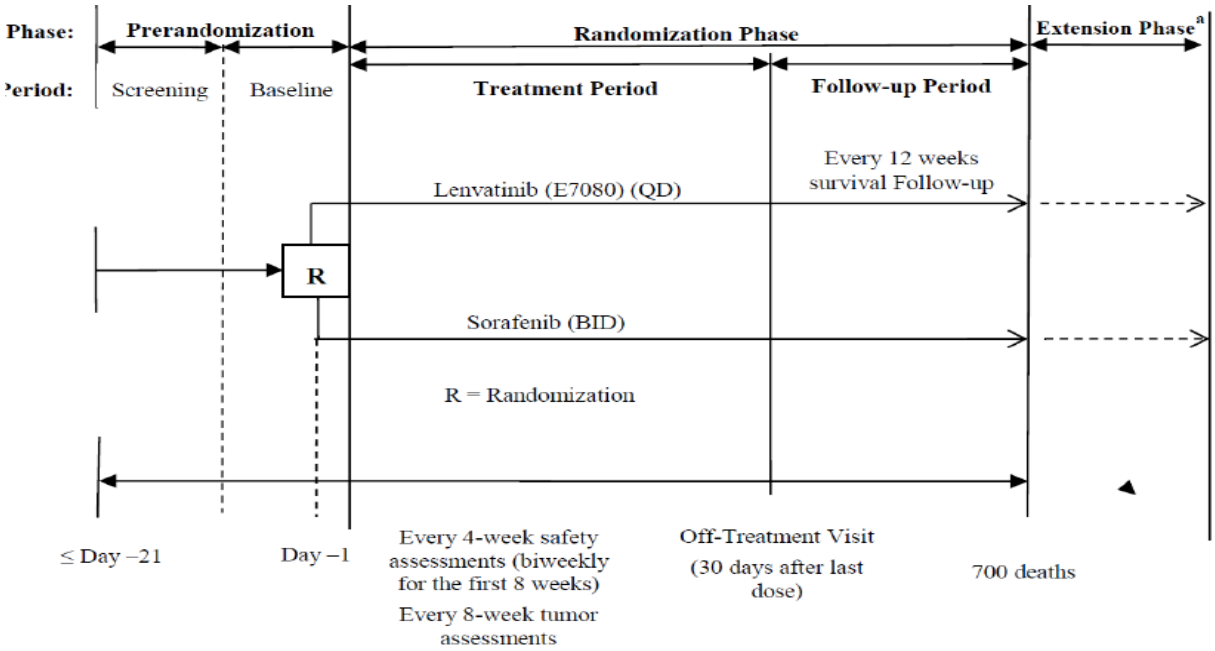


Figure 12: Flow-chart of study design for Phase 3 Study 304

a: Extension Phase also included a Treatment Period and Follow-up Period. All subjects still on treatment at the end of the Randomization Phase entered the Extension Phase and continued the same study treatment they received in the Randomization Phase.

Study participants

Main inclusion criteria

- ✓ Adult subjects (≥18 years of age) with a histologically or cytologically confirmed diagnosis of unresectable HCC, or a clinically confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria, including cirrhosis of any etiology, or with chronic hepatitis B or C infection were eligible.

- ✓ Subjects had at least 1 measureable target hepatic or non-hepatic lesion according to mRECIST, and adequate liver, bone marrow, blood coagulation, renal, and pancreatic function as defined in the protocol.
- ✓ Female subjects of childbearing potential could not be pregnant or lactating.
- ✓ Subjects categorized to stage B (not applicable for transarterial chemoembolization) or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging system.
- ✓ Adequately controlled blood pressure (BP) with up to 3 antihypertensive agents, defined as BP ⩽ 150/90 mm Hg at Screening and no change in antihypertensive agents within 1 week prior to Cycle 1/Day 1.
- ✓ Child-Pugh score A (score 5 or 6).
- ✓ ECOG PS 0 or 1.
- ✓ Survival expectation of 12 weeks or longer after starting study drug.

Main exclusion criteria

- ✓ Subjects were not eligible to participate in the study if they had any previous systemic anticancer therapy or any systemic investigational anticancer agents, including lenvatinib, for advanced/unresectable HCC.
- ✓ Subjects were excluded if they had imaging findings that indicated HCC with ⩾50% liver occupation, clear invasion into the bile duct or main portal branch invasion (Vp4), or any blood-enhancing treatment within 28 days of randomization.
- ✓ Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment at Screening
- ✓ Prolongation of QTc interval to >480 ms
- ✓ Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic international normalized ratio (INR) monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin and factor X inhibitors which did not require INR monitoring was permitted. Antiplatelet agents were prohibited throughout the study.
- ✓ Gastrointestinal bleeding event or active hemoptysis (bright red blood of at least 0.5 teaspoon) within 28 days prior to randomization
- ✓ Gastric or esophageal varices that required active interventional treatment within 28 days prior to randomization. Prophylaxis with pharmacologic therapy (eg, nonselective beta-blocker) was permitted.
- ✓ Subjects whose only target lesion was in bone.
- ✓ Subjects with a urine protein ⩾1 g/24 hours
- ✓ Female subjects of childbearing potential could not be pregnant or lactating.

Subjects who were taking herbal or Traditional Chinese Medicines (TCMs) approved for use in advanced HCC in China were eligible for enrolment although a letter was sent to investigators on 21 Nov 2014 instructing them to consider TCMs as prohibited concomitant medications; use of concomitant TCMs was classified as a minor protocol deviation.

Treatments

Lenvatinib capsules were taken orally, QD in continuous 28-day cycles. The lenvatinib dose was based on the subject's baseline body weight (BW):

- Lenvatinib 12 mg QD for subjects with baseline BW ⩾60 kg
- Lenvatinib 8 mg QD for subjects with baseline BW <60 kg

Capsules were taken in a fasting state or after a meal.

No dose adjustments were required on the basis of hepatic function in those patients who had mild hepatic impairment (Child-Pugh A).

Sorafenib tablets were taken orally at the approved dose for HCC (400 mg BID, Nexavar SmPC).

Table 29: **Treatments administered**

Drug Name	Baseline Body Weight	Strength	Oral Dose Form	Number Dispensed and Frequency
Lenvatinib	≥60 kg	12 mg	capsule	3 × 4-mg capsules, once daily at the same time each day
	<60 kg	8 mg	capsule	2 × 4-mg capsules, once daily at the same time each day
Sorafenib	N/A	400 mg	tablet	2 × 200-mg tablets, twice daily

N/A = not applicable.

Sorafenib was selected as comparator as this is the only approved systemic therapy for advanced HCC in the first-line setting and is regarded as standard of care.

Toxicity for both treatment arms was managed by a combination of treatment interruption, dose reduction, or treatment discontinuation. Dose modifications for sorafenib related toxicity followed the approved prescribing information for each country/region.

Objectives

Primary objective

- to compare OS in subjects treated with lenvatinib versus sorafenib as a first-line treatment in subjects with unresectable HCC.

Secondary objectives

- To compare progression-free survival (PFS), time-to progression (TTP), and objective response rate (ORR) of subjects treated with lenvatinib versus sorafenib using modified Response Evaluation Criteria in Solid Tumours (mRECIST)
- To compare the impact of treatment on generic Health Related Quality of Life (HRQoL) of subjects treated with lenvatinib versus sorafenib using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and HCC-specific EORTC QLQ-HCC18 questionnaire
- To compare safety and tolerability of subjects treated with lenvatinib versus sorafenib
- To characterize the pharmacokinetics (PK) of lenvatinib using the population approach
- To assess the PK/pharmacodynamic (PD) relationship between exposure and efficacy/safety.

Exploratory objectives

- To compare disease control rate (DCR) of subjects treated with lenvatinib versus sorafenib using mRECIST
- To compare the clinical benefit rate (CBR) of subjects treated with lenvatinib versus sorafenib

- To compare the impact of treatment on generic HRQoL factors for subjects treated with lenvatinib versus sorafenib using the European Quality of Life questionnaire
- To explore blood and tumour biomarkers which may correlate with clinical outcomes-related endpoints.

Outcomes / endpoints

Primary Efficacy Endpoint

- Overall survival (OS), measured from the date of randomization until the date of death from any cause. Subjects who were lost to follow-up were censored at the last date the subject was known to be alive, and subjects who remained alive were censored at the time of data cut-off.

Secondary Efficacy Endpoints

- Progression-free survival, defined as the time from the date of randomization to the date of first documentation of disease progression, or the date of death, whichever occurred first. Progression-free survival censoring rules were defined in the statistical analysis plan (SAP) and followed United States Food and Drug Administration (US FDA) guidance.
- Time to progression (TTP), defined as the time from the date of randomization to the date of the first documentation of disease progression. Time to progression censoring rules were defined in the SAP.
- Objective response rate, defined as the proportion of subjects who had a best overall response (BOR) of complete response (CR) or partial response (PR).
- HRQoL assessed using EORTC QLQ-C30, the HCC-specific questionnaire (HCC-18), and a generic instrument EQ-5D-3L.
- Plasma PK lenvatinib exposure parameters.

Exploratory endpoints

- Disease control rate, defined as the proportion of subjects with a BOR of CR or PR, or stable disease (SD). Best overall response of SD must have occurred at least 7 weeks after randomization (within a 1-week window of the protocol-specified 8-week time point for the first post-baseline tumour scan).
- Clinical benefit rate, defined as the proportion of subjects who had a BOR of CR or PR or durable SD (duration of SD ≥23 weeks after randomization).
- Exploratory biomarker analysis, defined as baseline and/or change from Baseline of exploratory soluble, tissue and/or genetic biomarkers and their correlations with clinical outcomes were assessed. Correlative data will be presented in a separate Biomarker Analysis Report.

Assessments

Tumour assessments were performed every 8 weeks from the date of randomization, or as clinically indicated, until disease progression. Subjects discontinued study treatment at the time of objectively documented disease progression, development of unacceptable toxicity, subject request or withdrawal of consent. Subjects were followed every 12 weeks for survival.

Time-to-event efficacy endpoints were based on investigator assessment of tumour response as determined using the mRECIST for hepatic lesions and RECIST v1.1 for non-hepatic lesions.

Investigators were trained in the application of mRECIST and early feedback on quality of tumour assessment was provided to sites by an independent mRECIST expert. All tumour assessment scans were sent to PAREXEL for quality assessment and archiving. A blinded, retrospective IIR of tumour assessment scans was performed by experienced radiologists using both mRECIST and RECIST 1.1.

Sample size

Sample size determination was based primarily on the required number of target events to detect the noninferiority and superiority of lenvatinib to sorafenib in the comparison of the OS. The required number of target events was estimated based on the following assumptions:

- Exponential distribution was assumed for OS. The estimated median OS of sorafenib is approximately 10 months, and an improvement of 2.5 months was derived from the underlying objective of achieving a hazard ratio (HR) of 0.8, which would be of marked clinical benefit.

- Using a noninferiority test by the 95% confidence interval (CI) lower limit method on log HR for OS with assumed true HR of 0.80 and noninferiority margin of 1.08 (corresponding to 60% retention of sorafenib effect versus placebo), the power of the study to declare noninferiority was approximately 97%.

- The power of the study to declare superiority of lenvatinib to sorafenib was approximately 82% using the superiority test with assumed true HR of 0.80. The overall false positive rate was set at 2-sided 0.05.

Based on these assumptions, the required number of events was estimated to be approximately 666 events (deaths) based on PPS. Assuming approximately 5% of subjects with major protocol deviations would be excluded from PPS, approximately 700 events (deaths) based on the FAS would be required at the time of primary analysis. Two interim analyses for futility (1 at approximately 30%, and a second at approximately 70% of the target number of events) were taken into account for the estimation. It was estimated that approximately 940 subjects were to be randomized to observe this number of events, which for a randomization ratio of 1:1 is a minimum of 470 per treatment group.

Randomisation

After the Baseline period, subjects were randomised 1:1 to lenvatinib (12mg if baseline BW ≥60kg or 8mg if baseline BW <60kg) QD oral dosing or sorafenib 400mg BID oral dosing. Allocation of randomization numbers was performed using an interactive voice/web response system (IxRS®) based on the following stratification factors:

- Region: Region 1 (Asia-Pacific); Region 2 (Western - EU, North America, other)
- Macroscopic portal vein invasion (MPVI) or extrahepatic spread or both: Yes; No
- Eastern Cooperative Oncology Group performance status (ECOG PS): PS = 0; PS = 1
- BW: <60 kg; ⩾60 kg

Blinding (masking)

The study was open-label.

Statistical methods

Definition of Analysis Sets

Full Analysis Set (Intent to Treat Analysis Set) included all subjects who were randomized. This was the primary analysis set for all efficacy evaluations. Subjects were analysed according to their randomized treatment group.

Per Protocol Analysis Set (PPS) included subjects who were randomized and received at least 1 dose of the assigned study drug and had no major protocol deviations. Criteria for exclusion from the PPS analysis set were determined before the data lock for the primary analysis of OS. This was the secondary analysis set for all efficacy evaluations.

Safety Analysis Set included subjects who received at least 1 dose of the study treatment. Subjects who received any dose of lenvatinib during the treatment period were grouped into the lenvatinib treatment group. Subjects who received sorafenib only during the treatment period were grouped into the sorafenib treatment group. This was the analysis set for all safety evaluations.

Pharmacokinetic Analysis Set included subjects who received at least 1 dose of lenvatinib, had evaluable dose data, and had at least 1 quantifiable lenvatinib concentration.

Pharmacodynamic Analysis Set included subjects who received at least 1 dose of study drug and had evaluable PD data.

Statistical Methodology

Primary efficacy analysis

The primary endpoint for this study was overall survival (OS).

A non-inferiority test of OS between lenvatinib and sorafenib was performed based on the FAS as the primary analysis set and the PPS as the secondary analysis set. Noninferiority of OS between lenvatinib and sorafenib was tested using a 2-sided 95% CI of HR (lenvatinib: sorafenib) estimated using a Cox proportional hazard model with treatment group as a factor, stratified by the randomization (IxRS) stratification factors (region, presence or absence MPVI or extrahepatic spread or both, ECOG PS, and BW). Noninferiority was declared if the upper limit of the 2-sided 95% CI for HR was <1.08 at the final analysis.The non-inferiority margin of 1.08 was calculated based on the sorafenib SHARP trial and Asia-Pacific trial data. Using the 95% CI lower limit method on log HR as described in Rothmann etal. (2003), the non-inferiority margin corresponding to lenvatinib preserving at least 60% of sorafenib effect versus placebo was calculated as 1.08. If at the final analysis the upper limit of the 2-sided 95% CI for the HR (lenvatinib/sorafenib) was less than 1.08, non-inferiority of lenvatinib to sorafenib would be inferred and >60% retention of sorafenib treatment effect by lenvatinib would be demonstrated. Using a margin of 1.08 and an assumed true HR of 0.8, the power of the study to declare NI was approximately 97%.

If noninferiority was declared for OS, then superiority (corresponding to $\delta = 1$) was to be tested for OS using a stratified log-rank test with the randomization (IxRS) stratification factors. Superiority would be declared if the 2-sided P value was <0.05 using the stratified log-rank test at the final analysis. No multiplicity adjustments were needed for testing of the noninferiority and superiority of OS due to the closed testing principle.

In the SAP, all primary efficacy analyses were changed to be based on randomisation stratification factors per IxRS rather than per the CRF data (as stated in the protocol). The analysis with stratification factors based on CRF data were used for sensitivity analyses. Other sensitivity analyses were an unstratified log rank test and an unstratified Cox proportional hazards model.

The median OS and the cumulative probability of OS at selected time points were calculated for each treatment group and presented with 2-sided 95% CIs. The selected time points depended on the OS times that were observed during the study and were specified in the SAP. Kaplan-Meier estimates of OS for each treatment group were plotted over time.

Secondary efficacy analyses

For the secondary endpoints, PFS, TTP, ORR using mRECIST and impact on health-related Qol, the objective was to show superiority of lenvatinib to sorafenib.

The fixed sequence procedure was used to control the overall type I error rate of analyses for the secondary endpoints at α = 0.05 (2-sided) after the non-inferiority for primary efficacy endpoint, OS, was declared. The order of testing for secondary endpoints followed the order: PFS, TTP, ORR, and health-realted QoL. In the ordered sequence, each secondary endpoint was tested at the 5% level until the first nonsignificant outcome occurred. If a nonsignificant outcome occurred, then the results of the inferential analyses of the subsequent endpoints were presented for descriptive purposes only.

PFS: The test for a difference in PFS between lenvatinib and sorafenib was performed using a stratified log-rank test stratified by the randomization stratification factors. The corresponding estimate of HR was calculated from the Cox proportional hazard model with treatment group as a factor and stratified by the randomization stratification factors. Median PFS and the cumulative probability of PFS at selected time points was calculated for each treatment group, and presented with corresponding 2-sided 95% CIs. The selected time points depended on the PFS times that were observed during the study and were specified in the SAP. Kaplan–Meier estimates of PFS for each treatment group were plotted over time.

TTP: The difference in TTP between lenvatinib and sorafenib was evaluated using the same procedure as used for PFS, with the exception that death was censored.

ORR: Objective response rate was estimated by treatment group. The statistical significance of the difference in ORR between treatment groups was evaluated using the Cochran–Mantel–Haenszel chi-square test with the stratification factors as strata, tested at an alpha level of 0.05 (2-sided). The 2-sided 95% CIs for the odds ratio and the difference in ORR were calculated as well as 2-sided 95% CIs for the rate within treatment group.

HRQoL: For HRQoL, a simple, comparative, cross-sectional analysis was performed for each available PRO variable using the cross-sectional population (CSP). The EORTC QLQ-HCC18 and QLQ-C30 domains were tested hierarchically, guided by their relative importance to the condition being studied, with all EORTC QLQ-HCC18 domains tested prior to the EORTC QLQ-C30 domains. To estimate the effect of treatment assignment on change in domain scores from Baseline, mixed models were constructed among patients included in the longitudinal period population (LPP)-based on the Full Analysis Set. Sensitivity analyses were conducted on the LPP-based on the per protocol analysis set. If the sample size of LPP permitted, longitudinal modelling of the EQ-5D Health Utility Index (HUI), EQ-5D Visual Analogue Scale (VAS), EORTC QLQ-C30 summary scores, and the QoL/global health status were conducted to estimate the effect of treatment assignment (lenvatinib versus sorafenib) on change from Baseline. A two-sided test with p-value ≤ 0.05 (unadjusted for multiplicity) was considered statistically significant.

Interim analyses

Two interim analyses were planned with early stopping rules for futility based on non-inferiority. The first interim analysis was planned for when ~210 deaths (30% of the target) were observed, estimated around 16 months. The second interim analysis was planned for when ~ 490 deaths (70% of the target) were observed, estimated around 26 months.

Results

Participant flow

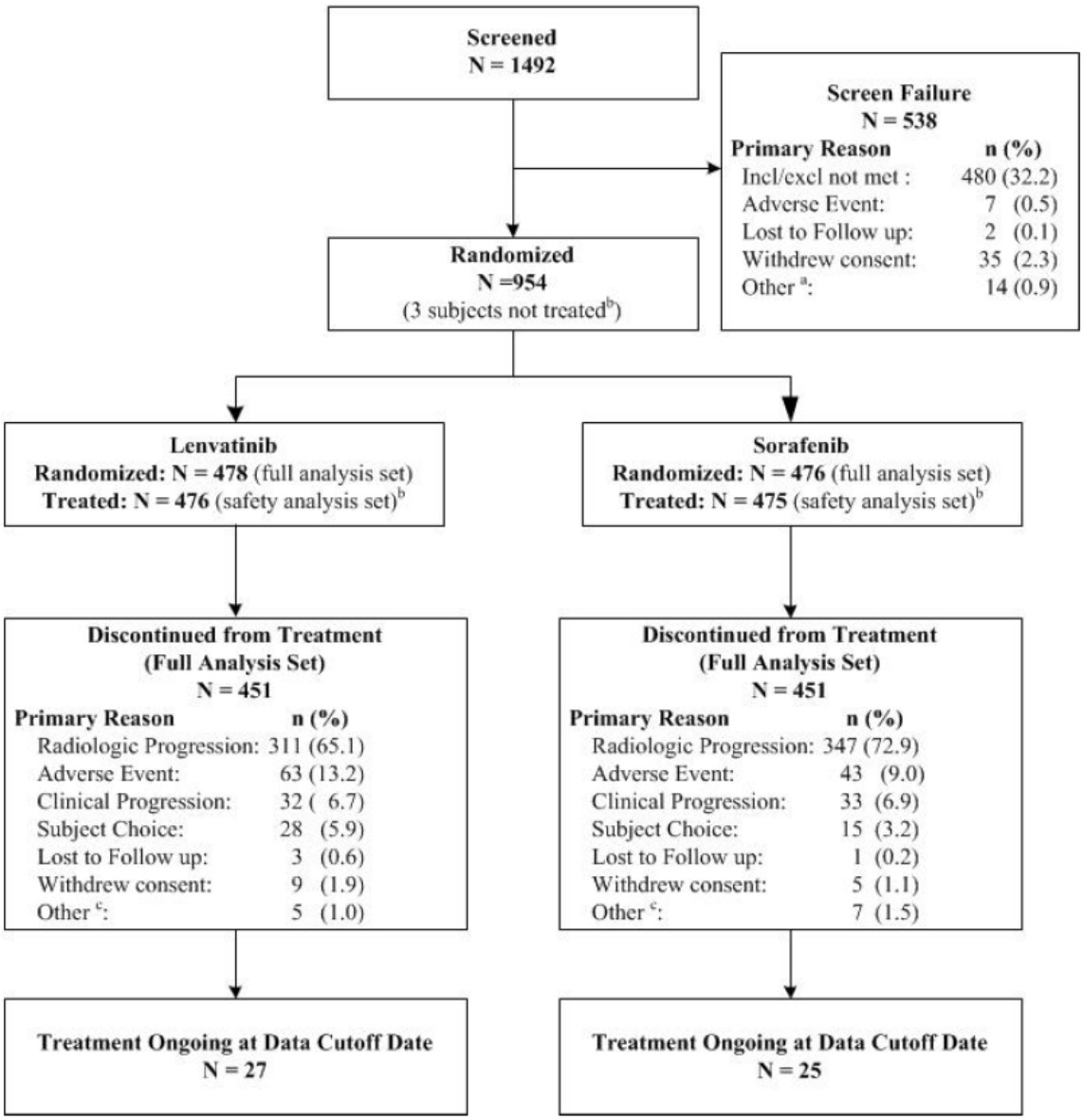


Figure 13: Subjects disposition in the randomization phase (Full Analysis Set)
Data cutoff date: 13 Nov 2016.
a: Other reasons for screening failure varied, with the most common reasons being expiration of the 21-day screening window (n=4) and worsening of the subject's condition (n=3).
b: Two subjects randomized to lenvatinib were not treated as they were randomized in error, and 1 subject randomized to sorafenib chose not to receive treatment; therefore the Safety Analysis Set includes 476 subjects in the lenvatinib arm and 475 subjects in the sorafenib arm.
c: "Other" reasons for discontinuation in the lenvatinib arm included randomization in error (n=2; not treated); subject required surgery (n=2) and investigator choice (n=1). In the sorafenib arm, "other" reasons included investigator choice (n=5); need for a prohibited medication (warfarin; 1 subject); and discontinuation to undergo liver transplantation (n=1).

Table 30: Status at the end of randomization phase (Full Analysis Set)

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)	Total (N=954) n (%)
On Study [a] Treatment ongoing at data cut-off	109 (22.8) 27 (5.6)	107 (22.5) 25 (5.3)	216 (22.6) 52 (5.5)
Off Study [b] – reason Death Lost to follow-up	369 (77.2) 351 (73.4) 5 (1.0)	369 (77.5) 350 (73.5) 11 (2.3)	738 (77.4) 701 (73.5) 16 (1.7)
Withdrawal of consent	13 (2.7)	8 (1.7)	21 (2.2)

Data cut-off date: 13 Nov 2016.
Percentages are based on the total number of subjects in FAS within the relevant treatment group.
a: On study refers to subjects who were still receiving study drug or who were in survival follow-up as of the cut-off date.
b: Off study refers to subjects who were no longer being followed for survival as of the cut-off date.

As of the 13 Nov 2016 data cut-off, median duration of treatment was 5.7 months in the lenvatinib arm and 3.7 months in the sorafenib arm.

Recruitment

Enrolment in Study 304 occurred between 01 March 2013 (first subject gave informed consent) and 30 July 2015 (last subject enrolled) . A total of 954 subjects were enrolled and assigned to treatment at 183 study sites (number of sites initiated) in Asia, North America, the European Union, Russia, and Israel. Per protocol, the planned number of subjects enrolled in China was limited to 200; in actuality, 213 subjects were randomly assigned to study treatment in China.

Conduct of the study

The data cut-off date for the primary analysis of OS was 13 November 2016, which occurred when the target number of events (700 deaths) was observed across the 2 treatment arms. All subjects who were still receiving study drug or who were in follow-up as of the cut-off date entered the Extension Phase of the study, whereby subjects continued to receive study drug at their assigned dose. Ongoing subjects continued to be followed for survival and all subsequent anticancer treatments received were recorded.

Interim Analyses and Data Monitoring

An independent DMC conducted 2 unblinded interim analyses. The interim analyses were performed by an independent statistical team and the study team was not given access to the summary of aggregated data by treatment group. Early stopping boundaries for futility at the interim analyses and success criteria at the final analyses are shown in Table below.

Table 31: Early Stopping Boundaries for Futility at the Interim Analyses and Noninferiority and Superior Efficacy Success Criteria at the Final Analysis

		Superior Efficacy	Futility for Noninferiority	Noninferiority
Analysis	No of Events: Planned/Actual	2-sided P-value Stratified Log-Rank Test	Bayesian Predictive Probability (%)	Upper Limit of 2-sided CI for HR (lenvatinib:sorafenib)
First Interim	210/249	NA	<5	NA
Second Interim	490/521	NA	<5	NA
Final	700/700	<0.05	NA	<1.08

CI = confidence interval, HR = hazard ratio, NA = not applicable.

The first interim analysis was performed when 249 deaths were reported, and the efficacy and key safety results were reviewed by the DMC on 13 May 2015. The second interim analysis was performed when 521 deaths were reported, and the results were reviewed on 3 Feb 2016. Both times, the DMC recommended continuation of the trial with no modifications.

Protocol amendments

The original protocol (v1.0) was approved on 16 Nov 2012. Three protocol amendments were made throughout the period covered by this study report.

Changes to planned analysis (SAP)s

A change to the planned analysed in the SAP before treatment unblinding was that all efficacy analyses had to be based on randomization factors per IxRS rather than per the CRF data (as stated in the protocol). The randomization factors based on CRF data were used for sensitivity analyses.

Protocol deviations

Overall, the rate of major protocol deviations was low (2.5%; 24 of 954 subjects; lenvatinib - 11 [2.3%] subjects; sorafenib- 13 [2.7%] subjects), and the incidence and nature of the protocol deviations were balanced across the treatment arms. (table below)

Most of the major protocol deviations in both the lenvatinib and sorafenib arms were eligibility criteria not met, mostly due to laboratory levels outside the acceptable range or Child-Pugh score of 7 or 8 (Class B).

Fifteen subjects, 8 (1.7%) in the lenvatinib and 7 (1.5%) in the sorafenib arm, were enrolled and did not meet eligibility criteria and 4 subjects, 2 (0.4%) in each arm, had a prohibited procedure. These prohibited procedures were:

Lenvatinib: TACE on Study Day 253 then discontinued study treatment 1 month later (subject 24151008) and radiotherapy of 1 target and 3 non-target lymph nodes on C1D1 plus baseline Child-Pugh of 8 [Class B], (subject 30031005).

Sorafenib: radiotherapy of lymph node target lesion on C1D7 (subject 30051009) and on C2D1 (subject 30051014).

One subject (14061009) in the lenvatinib arm took an overdose of study medication (single 120-mg dose on Study Day 1 rather than the assigned 12 mg).

Table 32: Major protocol deviations during the randomization phase (Full Analysis Set)

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)	Total (N=954) n (%)
No. of subjects with at least 1 major protocol deviation	11 (2.3)	13 (2.7)	24 (2.5)
Discontinuation criteria[a]	0 (0.0)	1 (0.2)	1 (0.1)
Eligibility criteria not met	8 (1.7)	7 (1.5)	15 (1.6)
Prohibited concomitant medication (warfarin)	0 (0.0)	1 (0.2)	1 (0.1)
Improper procedure[b]	0 (0.0)	1 (0.2)	1 (0.1)
Prohibited procedure	2 (0.4)	2 (0.4)	4 (0.4)
Screening/baseline assessment not done	0 (0.0)	1 (0.2)	1 (0.1)
Study drug dosing error/noncompliance	1 (0.2)	0 (0.0)	1 (0.1)

Data cutoff date: 13 Nov 2016.
Percentages are based on the total number of subjects within the relevant treatment group in the Full Analysis Set.
One sorafenib subject (Subject 17021001) had 2 major protocol deviations.
a: Subject developed a Grade 4 hemorrhage on study, but was not discontinued from study treatment by the investigator.
b: Subject's protocol deviation was mistakenly classified as "improper procedure" in the database. The subject did not meet Inclusion criterion #10 as the baseline Child-Pugh was 8 (Class B).

Baseline data

Demographic and Baseline Disease characteristics

Demographic and baseline characteristics of patients from the Study 304 in overall population are presented in the table below.

Table 33: Selected demographic and baseline characteristics, including some disease characteristics (Full Analysis set)

	Lenvatinib			Sorafenib (N = 476)	Total (N = 954)
	8 mg [a] (N = 151)	12 mg [a] (N = 327)	Total (N = 478)		
Age (years)					
Mean (SD)	63.1 (12.30)	60.4 (11.32)	61.3 (11.69)	61.2 (12.01)	61.3 (11.84)
Median	65.0	62.0	63.0	62.0	62.0
Min, Max	20, 86	24, 88	20, 88	22, 88	20, 88
Age group (yrs), n (%)					
<65	69 (45.7)	201 (61.5)	270 (56.5)	283 (59.5)	553 (58.0)
≥65 to <75	56 (37.1)	94 (28.7)	150 (31.4) 58	126 (26.5)	276 (28.9)
≥75	26 (17.2)	32 (9.8)	(12.1)	67 (14.1)	125 (13.1)
Sex, n (%)					
Male	106 (70.2)	299 (91.4)	405 (84.7)	401 (84.2)	806 (84.5)
Female	45 (29.8)	28 (8.6)	73 (15.3)	75 (15.8)	148 (15.5)
Region, n (%)					
Western [b]	21 (13.9)	136 (41.6)	157 (32.8)	157 (33.0)	314 (32.9)
Asia-Pacific [b]	130 (86.1)	191 (58.4)	321 (67.2)	319 (67.0)	640 (67.1)
Race, n (%)					
White	17 (11.3)	118 (36.1)	135 (28.2)	141 (29.6)	276 (28.9)
Black/Afr. American	0 (0.0)	7 (2.1)	7 (1.5)	6 (1.3)	13 (1.4)
Asian	134 (88.7)	200 (61.2)	334 (69.9)	326 (68.5)	660 (69.2)
Weight (kg)					
Mean (SD)	52.7 (4.90)	75.9 (14.40)	68.6 (16.32)	68.1 (13.90)	68.3 (15.16)
Median	53.0	72.0	66.2	67.0	66.9
Min, Max	39, 60	60, 142	39, 142	39, 123	39, 142
Body Weight Group					
<60 kg	151 (100.0)	2 (0.6)	153 (32.0)	146 (30.7)	299 (31.3)
≥60 kg	0 (0.0)	325 (99.4)	325 (68.0)	330 (69.3)	655 (68.7)
ECOG PS, n (%)					
0	93 (61.6)	211 (64.5)	304 (63.6)	301 (63.2)	605 (63.4)
1	58 (38.4)	116 (35.5)	174 (36.4)	175 (36.8)	349 (36.6)
Child-Pugh Score, n (%)					

5	111 (73.5)	257 (78.6)	368 (77.0)	357 (75.0)	725 (76.0)
6	40 (26.5)	67 (20.5)	107 (22.4)	114 (23.9)	221 (23.2)
7	0 (0.0)	3 (0.9)	3 (0.6)	4 (0.8)	7 (0.7)
8	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
MPVI, n (%)					
Yes	38 (25.2)	71 (21.7)	109 (22.8)	90 (18.9)	199 (20.9)
Extrahepatic spread, n (%)					
Yes	91 (60.3)	200 (61.2)	291 (60.9)	295 (62.0)	586 (61.4)
MPVI, extrahepatic spread or both, n (%)					
Yes	105 (69.5)	224 (68.5)	329 (68.8)	336 (70.6)	665 (69.7)
Cirrhosis, n (%) [c]					
Yes	75 (49.7)	168 (51.4)	243 (50.8)	231 (48.5)	474 (49.7)

Percentages based on the total number of subjects in the Full Analysis Set in the relevant treatment group.
ECOG = Eastern Cooperative Oncology Group; MPVI = Macroscopic Portal Vein Invasion
a: 8 mg and 12 mg were the lenvatinib starting doses based on body weight (<60 kg, ≥60 kg) at Baseline.
b: Western region consists of North America and Europe including Russia and Israel; Asia-Pacific region consists of China, Hong Kong, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand.
c: The proportion of subjects with underlying cirrhosis at Baseline was likely underestimated, as this information was collected on the CRF under medical history, and the presence or absence of cirrhosis was verified only if needed to confirm the clinical diagnosis of HCC.

Disease history and characteristics of patients from the Study 304 at study entry in the overall are presented in the table below.

Table 34: S**elected disease history and characteristics at study entry (Full Analysis Set)**

	Lenvatinib (N=478)	**Sorafenib (N=476)**	**Total (N=954)**
Time since First Diagnosis (months)			
Mean (SD)	21.1 (30.17)	23.3 (34.66)	22.2 (32.49)
Median	8.2	9.0	8.5
Q1, Q3	1.6, 27.3	2.0, 27.2	1.8, 27.2
Min, Max	0, 180	0, 250	0, 250
Barcelona Clinic Liver Cancer Stage, n (%)			
B: Intermediate stage	104 (21.8)	92 (19.3)	196 (20.5)
C: Advanced stage	374 (78.2)	384 (80.7)	758 (79.5)
Involved disease sites [a], n (%)			
Liver	441 (92.3)	430 (90.3)	871 (91.3)
Lung	163 (34.1)	144 (30.3)	307 (32.2)
Lymph nodes	127 (26.6)	141 (29.6)	268 (28.1)
Bone	51 (10.7)	43 (9.0)	94 (9.9)
Other	82 (17.2)	97 (20.4)	179 (18.8)
Involved disease sites per subject, n (%)			
1	207 (43.3)	207 (43.5)	414 (43.4)
2	167 (34.9)	183 (38.4)	350 (36.7)
≥3	103 (21.5)	86 (18.1)	189 (19.8)
Factor of carcinogenesis [b], n (%)			
Hepatitis B	251 (52.5)	228 (47.9)	479 (50.2)
Hepatitis C	91 (19.0)	126 (26.5)	217 (22.7)
Alcohol	36 (7.5)	21 (4.4)	57 (6.0)
Other	38 (7.9)	32 (6.7)	70 (7.3)
Unknown	62 (13.0)	69 (14.5)	131 (13.7)
Baseline Alpha-fetoprotein Level (ng/mL)			
Mean (SD)	17507.5 (105137.39)	16678.5 (94789.46)	17096.5 (100088.76)
Median	133.1	71.2	89.0
Q1, Q3	8.0, 3730.6	5.2, 1081.8	6.3, 2120.2
Min, Max	0, 1567470	0, 1446396	0, 1567470
Baseline Alpha-fetoprotein Group, n (%)			
<200 ng/mL	255 (53.3)	286 (60.1)	541 (56.7)
≥200 ng/mL	222 (46.4)	187 (39.3)	409 (42.9)
Missing	1 (0.2)	3 (0.6)	4 (0.4)
Ammonia level (µg/dL)			
Mean (SD)	38.2 (29.98)	36.7 (32.90)	37.5 (31.46)
Median	31.8	30.0	31.0
Min, Max	4, 246	4, 473	4, 473
Systemic Hepatitis B or C therapy, n (%)	163 (34.1)	149 (31.3)	312 (32.7)
Prior anticancer procedures, n (%)	327 (68.4)	344 (72.3)	671 (70.3)
Hepatic intra-arterial chemotherapy	22 (4.6)	35 (7.4)	
Transarterial [chemo] embolization	246 (51.5)	245 (51.5)	
Radiofrequency ablation	90 (18.8)	110 (23.1)	

Cryoablation	1 (0.2)	1 (0.2)	
Percutaneous ethanol injection	15 (3.1)	19 (4.0)	
Hepatectomy	124 (25.9)	144 (30.3)	
Other[c]	85 (17.8)	72 (15.1)	
End Recent Procedure to Randomization (months)			
Mean (SD)	6.5 (9.99)	6.7 (11.26)	
Median	3.8	3.7	
Q1, Q3	2.0, 6.7	2.1, 5.9	
Min, Max	0, 108	1, 106	
Radiotherapy, n (%)	49 (10.3)	60 (12.6)	109 (11.4)
Time Radiotherapy to Randomization (months)			
<3	22 (4.6)	28 (5.9)	
3 – 6	14 (2.9)	8 (1.7)	
>6	13 (2.7)	24 (5.0)	
Lesion Progressed Since Most Recent Radiotherapy			
Yes	18 (3.8)	20 (4.2)	
No	13 (2.7)	25 (5.3)	
Not Evaluated	18 (3.8)	15 (3.2)	

Percentages based on the total number of subjects within the relevant treatment group in the FAS
a: Subjects may be counted in more than 1 disease site.
b: Based on the combined data from HCC diagnosis and medical history. Subjects may be counted in more than 1 factor.
c: "Other" reported on the CRF by the investigator were varied, but were primarily hepatectomy, microwave therapy, biopsies or pulmonary resections.

Table 35: Demographic and Baseline Characteristics, disease history and characteristics at study entry by Region (Full Analysis Set)

	Lenvatinib		**Sorafenib**	
	Asia-Pacific (N=321)	**Western (N=157)**	**Asia-Pacific (N=319)**	**Western (N=157)**
Time since First Diagnosis (months)				
Mean (SD)	23.9 (31.70)	15.4 (25.93)	26.8 (37.61)	16.1 (26.40)
Median	10.3	5.6	11.4	5.3
Age at First Diagnosis (years)				
Mean (SD)	58.1 (11.45)	62.6 (11.26)	58.0 (11.23)	62.0 (11.72)
Median	59.0	63.0	59.0	63.0
HCC type, n (%)				
Trabecular	31 (9.7)	13 (8.3)	36 (11.3)	7 (4.5)
Moderately Differentiated	27 (8.4)	23 (14.6)	35 (11.0)	14 (8.9)
Poorly Differentiated	14 (4.4)	7 (4.5)	16 (5.0)	5 (3.2)
Well Differentiated	5 (1.6)	10 (6.4)	10 (3.1)	16 (10.2)
Biopsy Performed – HCC Type Unknown	61 (19.0)	50 (31.8)	57 (17.9)	42 (26.8)
Biopsy not Performed	160 (49.8)	35 (22.3)	140 (43.9)	49 (31.2)
Other	23 (7.2)	19 (12.1)	15 (4.7)	12 (7.6)
Barcelona Clinic Liver Cancer Stage, n(%)				
B: Intermediate stage	70 (21.8)	34 (21.7)	65 (20.4)	27 (17.2)
C: Advanced stage	251 (78.2)	123 (78.3)	254 (79.6)	130 (82.8)
Factor of carcinogenesis, n (%)				
Hepatitis B	212 (66.0)	39 (24.8)	197 (61.8)	31 (19.7)
Hepatitis C	50 (15.6)	41 (26.1)	70 (21.9)	56 (35.7)
Alcohol	17 (5.3)	19 (12.1)	8 (2.5)	13 (8.3)
Other	17 (5.3)	21 (13.4)	11 (3.4)	21 (13.4)
Unknown	25 (7.8)	37 (23.6)	33 (10.3)	36 (22.9)
Cirrhosis Present, n (%)				
Yes	180 (56.1)	63 (40.1)	169 (53.0)	62 (39.5)
Baseline Alpha-fetoprotein Level (ng/mL)				
Mean (SD)	10078.5 (39198.91)	32508.2 (173397.79)	16460.6 (77052.08)	17115.6 (123204.55)
Median	168.0	78.9	100.6	27.0
Q1, Q3	11.1, 4186.8	5.2, 3102.1	7.5, 1416.0	3.6, 622.0
Baseline Serum Alpha-fetoprotein Level Group, n (%)				
<200ng/mL	164 (51.1)	91 (58.0)	182 (57.1)	104 (66.2)
≥200ng/mL	157 (48.9)	65 (41.4)	137 (42.9)	50 (31.8)
Missing	0	1 (0.6)	0	3 (1.9)
Concomitant systemic antiviral therapy for Hep B or Hep C, n (%)	137 (42.7)	26 (16.6)	129 (40.4)	20 (12.7)
Prior Anticancer procedures n (%)	235 (73.2)	92 (58.6)	252 (79.0)	92 (58.6)
Prior Radiotherapy n (%)	42 (13.1)	7 (4.5)	55 (17.2)	5 (3.2)

Percentages are based on the total number of subjects in FAS within the relevant treatment group.

Prior therapy

Prior medication

Overall, 86.2% of lenvatinib subjects and 87.4% of sorafenib subjects received at least 1 prior medication (excluding anticancer therapies). The type and frequency of prior medications in the 2 treatment arms were comparable.

Table 36 : Antiviral therapy

Anatomical class (ATC Level 1) Pharmacological class (ATC Level 3) WHO Drug Name (Preferred Term)[a]	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
DIRECT ACTING ANTIVIRALS	163 (34.1)	149 (31.3)
ADEFOVIR	21 (4.4)	17 (3.6)
CLEVUDINE	1 (0.2)	1 (0.2)
DACLATASVIR	0 (0.0)	1 (0.2)
ENTECAVIR	93 (19.5)	89 (18.7)
LAMIVUDINE	23 (4.8)	21 (4.4)
SOFOSBUVIR	0 (0.0)	1 (0.2)
TELBIVUDINE	5 (1.0)	9 (1.9)
TENOFOVIR	33 (6.9)	25 (5.3)
THYMALFASIN	0 (0.0)	1 (0.2)

Prior anticancer therapy

Since Study 304 was designed to evaluate lenvatinib and sorafenib as first-line systemic treatment of subjects with advanced/unresectable HCC, **prior anticancer therapy** for this disease was not allowed, with two exceptions. Prior anticancer therapy was allowed only if given in the adjuvant setting or if administered locally, concurrently with a liver-directed procedure.

Three subjects in the lenvatinib arm received a prior anticancer medication; 2 as adjuvant HCC treatment (human telomerase reverse transcriptase peptide vaccine, approximately 30 months prior to randomization, and combination chemotherapy, approximately 3.5 years prior to randomization). The third subject received thalidomide for advanced HCC approximately 1.5 months prior to randomization; this was considered a major protocol deviation.

In the sorafenib arm, 2 subjects received adjuvant anticancer medication (an investigational drug, PI-88, sulfonated monophosphorylated mannose oligosaccharides) 3.9 months and 2.4 months, prior to randomization in this study.

Prior anticancer procedures

Table 37: Previous Anticancer Procedures and Radiotherapy – Full Analysis Set

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
Subjects with Any Previous Anticancer Procedure, n (%)	**327 (68.4)**	**344 (72.3)**
Number of Previous Procedures, n (%)		
1	144 (30.1)	149 (31.3)
2	118 (24.7)	119 (25.0)
3	44 (9.2)	56 (11.8)
4	14 (2.9)	15 (3.2)
≥5	7 (1.5)	5 (1.1)
Previous Procedure Name [a]		
Hepatic intra-arterial chemotherapy	22 (4.6)	35 (7.4)
Transarterial [chemo] embolization	246 (51.5)	245 (51.5)
Radiofrequency ablation	90 (18.8)	110 (23.1)
Cryoablation	1 (0.2)	1 (0.2)
Percutaneous ethanol injection	15 (3.1)	19 (4.0)
Hepatectomy	124 (25.9)	144 (30.3)
Other[b]	85 (17.8)	72 (15.1)
Time from End of Most Recent Procedure to Randomization (months)		
N	327	344
Mean (SD)	6.5 (9.99)	6.7 (11.26)
Median	3.8	3.7
Q1, Q3	2.0, 6.7	2.1, 5.9
Min, Max	0, 108	1, 106
No. of Subjects with any Previous Radiotherapy Treatment	**49 (10.3)**	**60 (12.6)**
Time from Most Recent Radiotherapy to Randomization (months)		
<3	22 (4.6)	28 (5.9)
3 – 6	14 (2.9)	8 (1.7)
>6	13 (2.7)	24 (5.0)

Percentages are based on the total number of subjects within the relevant treatment group in the Full Analysis Set. a: A subject may be counted in multiple categories. b: Previous anticancer procedures that were reported on the case report form by the investigator in the "other" category were varied, but were primarily hepatectomy, microwave therapy, biopsies, or pulmonary resections.

Concomitant therapy

Concomitant Medication: The proportion of subjects who received at least 1 concomitant medication was similar in the 2 treatment arms (>95%). A high proportion of patients took concomitant anti-hypertensive agents (72.8% and 67.6%, in the lenvatinib and sorafenib arms, respectively). Other concomitant medications were generally balanced between the 2 arms. Thyroid preparations were administered more often in the lenvatinib arm (levothyroxine 13.6% vs 4.6%, respectively). Loperamide was used by more sorafenib-treated subjects (15.9% of lenvatinib vs. 24.4% of sorafenib) and dermatological agents/ emollients were more common with sorafenib.

Concomitant Palliative Radiotherapy: A few subjects in both treatment arms received low dose, short duration, palliative radiotherapy during the study (15 patients, 3.1%, lenvatinib; 11 patients, 2.3%,

sorafenib). Most radiotherapy was to bone (13, 2.7% lenvatinib; 9 (1.9%) sorafenib) and was directed at a non-target lesion.

Anticancer Medications and Procedures during Survival Follow-up: In the overall population, slight imbalance between the treatment arms was seen in the proportion of subjects who received any posttreatment anticancer therapy (anticancer medications and procedures): 51.1% (243/476) in the sorafenib versus 43.1% (206/478) in the lenvatinib arm.

Posttreatment anticancer medication (not for a procedure), was given to 38.7% in the sorafenib 32.6% in the lenvatinib arm.

Table 38: Anticancer Medications (Not Given for Any Procedure) During Survival Follow-up – FAS

	Lenvatinib (N=478) n (%)	**Sorafenib (N=476) n (%)**
Subjects with Anticancer Medication during Survival Follow-up, n (%)	156 (32.6)	184 (38.7)
Number of Medications, n (%)		
1	100 (20.9)	98 (20.6)
2	20 (4.2)	50 (10.5)
3	19 (4.0)	22 (4.6)
4	9 (1.9)	8 (1.7)
≥5	8 (1.7)	6 (1.3)
Duration of First Posttreatment Anticancer Medication (Months)		
n	115	132
Mean (SD)	3.1 (4.90)	2.8 (2.95)
Median	1.6	1.7
Q1, Q3	0.5, 3.3	0.9, 3.6
Min, Max	0, 30	0, 16

Percentages are based on the total number of subjects within the relevant treatment group in the Full Analysis Set.
Source: Table 14.1.6.10. (and Table 20 of CSR)

Sorafenib was the most common anti-cancer agent, given to 121 (25.3%) of lenvatinib treated subjects, whilst 56 (11.8%) of patients in the sorafenib arm restarted or continued sorafenib during survival follow-up. A higher proportion of subjects in the sorafenib arm (9.5% [45] vs 3.1% [15]) received posttreatment anticancer therapy with investigational drugs, as many second-line trials targeted sorafenib failures and/or sorafenib-intolerant subjects.

Anticancer procedures were performed during survival follow-up in comparable proportions of subjects in the 2 treatment arms: 25.5%, lenvatinib and 27.3%, sorafenib. Transcatheter arterial chemoembolization (TACE) was most common (14.4% vs. 17.0% of subjects in the lenvatinib and sorafenib arm, respectively). Regional chemotherapy was given to 4.8% of lenvatinib and 5.3% of sorafenib patients. The figures for radiotherapy to bone were 5.0%, lenvatinib and 4.8%, sorafenib.

Numbers analysed

The analysis sets and number and percentage of subjects in each analysis set is summarised in table below.

Table 39: Analysis sets (Randomization Phase)

	Lenvatinib	Sorafenib	Total
Full Analysis Set [a]	478 (100.0)	476 (100.0)	954 (100.0)
Safety Analysis Set [b]	476 (99.6)	475 (99.8)	951 (99.7)
Per Protocol Analysis Set [c]	467 (97.7)	462 (97.1)	929 (97.4)
Pharmacokinetic Analysis Set [d]	468 (97.9)	0 (0.0)	468 (49.1)
Pharmacodynamic Analysis Set [e]	66 (13.8)	48 (10.1)	114 (11.9)

Data cutoff date: 13 Nov 2016.
Percentages are based on the number of subjects within the relevant treatment group in the Full Analysis Set.
a: Full Analysis Set includes all subjects who were randomized.
b: Safety Analysis Set includes all subjects who received at least 1 dose of study drug.
c: Per Protocol Analysis Set includes all subjects who were randomized, received at least 1 dose of the assigned study drug, and had no major protocol deviations. Eleven subjects in the lenvatinib arm had a major protocol deviation; 2 of these subjects did not receive study drug. Thirteen subjects in the sorafenib arm had a major protocol deviation, and 1 additional subject chose not to receive study treatment.
d: PK Analysis Set includes all subjects who have received at least 1 dose of lenvatinib and have at least 1 quantifiable lenvatinib concentration.
e: Pharmacodynamic Set includes all subjects who received at least 1 dose of study drug and have evaluable Pharmacodynamic data.

Outcomes and estimation

Primary efficacy endpoint of Overall Survival (OS)

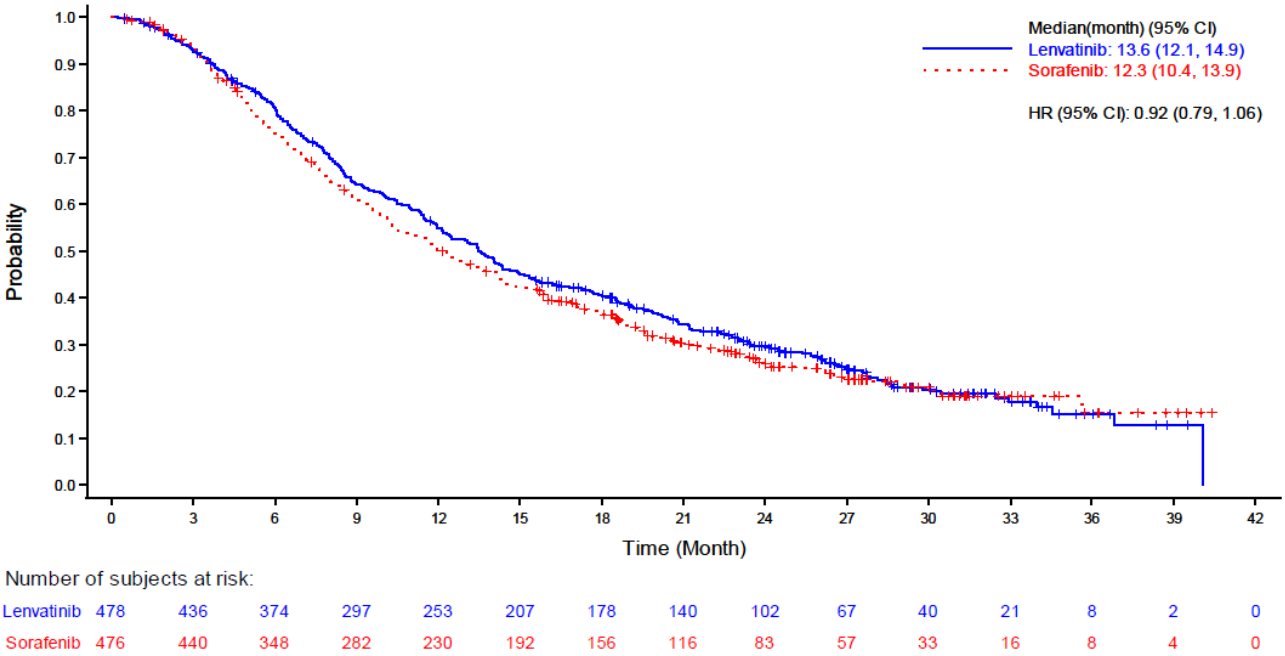
Primary analysis

Table 40: Overall Survival based on randomization stratification factors recorded in the IxRS (Full Analysis Set) – Cut-off date: 13 November 2016

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
Deaths, n (%)	351 (73.4)	350 (73.5)
Censored Subjects, n (%)	127 (26.6)	126 (26.5)
Lost to follow-up	5 (1.0)	11 (2.3)
Withdrawal of consent	13 (2.7)	8 (1.7)
Alive	109 (22.8)	107 (22.5)
Median Overall Survival (months)[a] (95% CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Overall Survival Rate (%) (95% CI) [b] at		
6 Months	80.8 (76.9, 84.1)	75.2 (71.0, 78.8)
12 Months	55.0 (50.4, 59.4)	50.0 (45.4, 54.5)
24 Months	29.9 (25.6, 34.2)	26.2 (22.1, 30.5)
Stratified Cox Model Hazard Ratio (95% CI) [c,d]	0.92 (0.79, 1.06)	

Data cutoff date: 13 Nov 2016.
Noninferiority margin for the HR of lenvatinib versus sorafenib is 1.08.
a: 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
b: OS rate & 95% CI calculated using Kaplan-Meier product-limit method and Greenwood Formula.
c: Hazard ratio is for lenvatinib vs. sorafenib, based on a Cox model including treatment group as a factor. Efron method was used for ties.
d: Stratified by region (Region 1: Asia-Pacific; Region 2: Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg).

Median duration of survival follow-up was 27.7 months (95% CI 26.4, 29.4) in the lenvatinib arm and 27.2 months (95% CI 25.9, 28.4) in the sorafenib arm.



Data cutoff date = 13 Nov 2016.
Noninferiority margin for hazard ratio (Lenvatinib vs. Sorafenib) is 1.08.
Median was estimated with the Kaplan-Meier method and the 95% confidence interval was constructed with a generalized Brookmeyer and Crowley method.
HR was estimated from the Cox proportional hazard model with treatment as independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.
+ = censored observations.

Figure 14: Kaplan-Meier curve and analysis of Overall Survival with stratification factors recorded in the IxRS – Full Analysis Set

Supportive analyses Per Protocol Population

Table 41: Overall Survival based on randomization stratification factors recorded in the IxRS (Per Protocol Analysis Set)

	Lenvatinib (N=467) n (%)	Sorafenib (N=462) n (%)
Deaths, n (%)	342 (73.2)	339 (73.4)
Censored Subjects, n (%)	125 (26.8)	123 (26.6)
Lost to follow-up	5 (1.1)	11 (2.4)
Withdrawal of consent	12 (2.6)	7 (1.5)
Alive	108 (23.1)	105 (22.7)
Overall Survival (months)[a]		
Median (95% CI)	13.7 (12.2, 15.1)	12.3 (10.6, 14.2)
Q1 (95% CI)	7.1 (6.3, 8.0)	6.2 (5.4, 7.0)
Q3 (95% CI)	27.2 (24.5, 30.1)	25.4 (22.3, 30.2)
Overall Survival Rate (%) (95% CI)[b] at		
6 Months	81.4 (77.5, 84.7)	75.5 (71.3, 79.2)
12 Months	55.3 (50.6, 59.8)	50.3 (45.6, 54.8)
18 Months	41.2 (36.7, 45.7)	36.8 (32.3, 41.3)
24 Months	30.3 (26.0, 34.7)	26.3 (22.1, 30.7)
Stratified Cox Model Hazard Ratio (95% CI)[c,d]	0.91 (0.78, 1.06)	
Duration of Survival Follow-up (months)[a,e]		
Median (95% CI)	27.7 (26.4, 29.3)	27.1 (25.9, 27.7)
Q1 (95% CI)	23.3 (22.3, 24.3)	22.6 (20.7, 23.8)
Q3 (95% CI)	33.1 (31.2, 34.2)	31.1 (29.4, 33.1)

Secondary efficacy endpoints

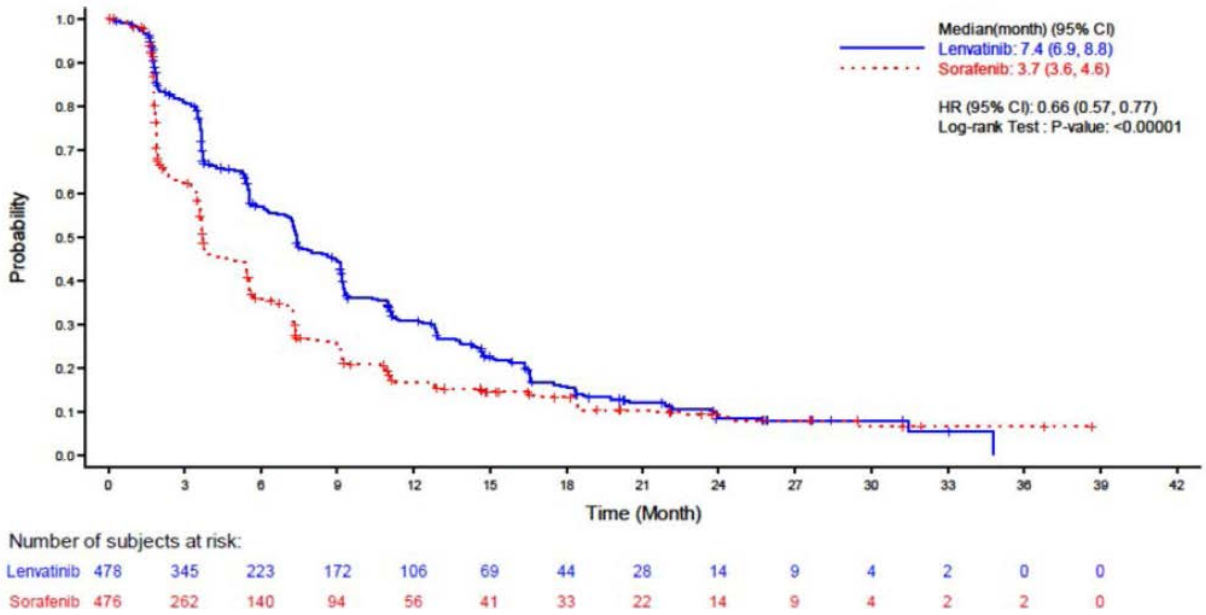
Progression-free Survival

Full Analysis Set

Table 42: Progression-free Survival based on randomization stratification factors recorded in IxRS (Full Analysis Set)

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
Subjects with Events, n (%)	349 (73.0)	367 (77.1)
Progressive Disease	308 (64.4)	343 (72.1)
Death	41 (8.6)	24 (5.0)
Censored Subjects, n (%)	129 (27.0)	109 (22.9)
No postbaseline tumor assessment	23 (4.8)	21 (4.4)
Death or Progression after more than 1 missing assessment	4 (0.8)	1 (0.2)
New anticancer treatment started	10 (2.1)	14 (2.9)
No progression at the time of data cutoff	26 (5.4)	24 (5.0)
No progression at the time of treatment discontinuation	66 (13.8)	49 (10.3)
Progression-free Survival (months) [a]		
Median (95% CI)	7.4 (6.9, 8.8)	3.7 (3.6, 4.6)
Q1 (95% CI)	3.6 (3.5, 3.7)	1.9 (1.8, 1.9)
Q3 (95% CI)	14.3 (12.8, 16.4)	9.1 (7.4, 9.4)
Progression-free Survival Rate (%) (95% CI) [b] at		
6 Months	56.8 (51.9, 61.4)	35.9 (31.3, 40.5)
12 Months	30.8 (26.3, 35.5)	16.7 (13.2, 20.7)
18 Months	15.7 (12.0, 19.7)	13.1 (9.9, 16.9)
24 Months	8.5 (5.5, 12.2)	9.3 (6.3, 12.9)
Stratified Cox Model Hazard Ratio (95% CI) [c,d]	0.66 (0.57, 0.77)	
Stratified Log-rank Test *P*-value [d]	<0.00001	
Follow-up Time for Progression-free Survival (months) [a,e]		
Median (95% CI)	20.3 (18.4, 23.9)	19.2 (15.2, 23.3)
Q1 (95% CI)	11.0 (9.1, 14.3)	10.8 (7.4, 14.6)
Q3 (95% CI)	25.9 (23.9, 29.5)	25.8 (23.3, 31.2)

P-value is for the superiority test of lenvatinib versus sorafenib
a: Quartiles are estimated by Kaplan-Meier method, and the 95% confidence intervals are estimated with a generalized Brookmeyer and Crowley method.
b: PFS rate and 95% CI were calculated using the Kaplan-Meier product-limit method and the Greenwood Formula.
c: Hazard ratio is for lenvatinib vs sorafenib, based on a Cox model including treatment group as a factor.
d: Stratified by region (Region 1: Asia-Pacific; Region 2: Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg).
e: Follow-up time for PFS was measured from date of randomization to date of the subject's last PFS follow-up, and it has same numeric value but opposite censoring indicator as compared to PFS.



Data cutoff date = 13 Nov 2016.
Median was estimated with the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
Hazard ratio is expressed as lenvatinib:sorafenib and was estimated from the Cox proportional hazard model with treatment as independent variable and stratified by IxRS stratification factors. The Efron method used for correction of tied events.
P-value was for superiority test (lenvatinib vs. sorafenib) and was calculated using log-rank test stratified by IxRS stratification factors.
+ = censored observations.
CI = confidence interval; HR = hazard ratio; IxRS = interactive voice/web response system.

Figure 15: Kaplan-Meier Curves and Analysis of Progression-free Survival With Stratification Factors Recorded in the IxRS (Full Analysis Set)

Per Protocol Analysis Set

Results of the PFS in the PFFs were consistent; the median PFS was 7.4 months for lenvatinib versus 3.7 months for sorafenib (HR = 0.66; 95% CI of 0.57, 0.77; P<0.00001).

Time to Progression

Table 43: Time to Progression based on randomization stratification factors recorded in IxRS (Full Analysis Set)

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
Subjects with Disease Progression, n (%)	308 (64.4)	343 (72.1)
Censored Subjects, n (%)	170 (35.6)	133 (27.9)
No postbaseline tumor assessment [a]	33 (6.9)	34 (7.1)
Progression after more than 1 missing assessment	4 (0.8)	1 (0.2)
New anticancer treatment started	10 (2.1)	14 (2.9)
No progression at the time of data cutoff	26 (5.4)	24 (5.0)
No progression at the time of treatment discontinuation	97 (20.3)	60 (12.6)
Time to Progression (months) [b]		
Median (95% CI)	8.9 (7.4, 9.2)	3.7 (3.6, 5.4)
Q1 (95% CI)	3.7 (3.6, 3.7)	1.9 (1.8, 1.9)
Q3 (95% CI)	15.8 (13.7, 16.6)	9.2 (7.4, 11.0)
Cumulative Progression Rate (%) (95% CI) [c] at		
6 Months	39.7 (35.0, 44.7)	61.9 (57.2, 66.7)
12 Months	65.2 (60.2, 70.1)	82.0 (77.9, 85.8)
18 Months	81.6 (76.9, 85.8)	85.6 (81.6, 89.1)
24 Months	89.5 (85.0, 93.1)	89.9 (86.0, 93.1)
Stratified Cox Model Hazard Ratio (95% CI) [d, e]	0.63 (0.53, 0.73)	
Stratified Log-rank Test *P*-value [d]	<0.00001	
Follow-up time for time to progression (months) [b, f]		
Median (95% CI)	16.7 (14.7, 20.3)	17.5 (14.7, 22.0)
Q1 (95% CI)	7.3 (5.5, 9.1)	7.3 (5.5, 10.8)
Q3 (95% CI)	25.7 (23.8, 27.7)	25.8 (22.1, 29.4)

P-value is for the superiority test of lenvatinib vs sorafenib.
Percentages are based on the total number of subjects within the relevant treatment group in the FAS.
a: Deaths were not counted as progression events in this analysis.
b: Quartiles are estimated by Kaplan-Meier method, and the 95% confidence intervals are estimated with a generalized Brookmeyer and Crowley method.
c: Cumulative progression rate was calculated using the Kaplan-Meier product-limit method and Greenwood Formula.
d: Hazard ratio is for lenvatinib vs sorafenib, based on a Cox model including treatment group as a factor. Efron method was used for ties.
e: Stratified by region (Region 1: Asia-Pacific; Region 2: Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg).
f: Follow-up time for TTP was measured from the date of randomization to the date of the subject's last follow-up, and it has same numeric value but opposite censoring indicator as compared to TTP.

Results for the TTP analysis based on the PPS were supportive: median TTP was 9.0 months for lenvatinib versus 3.7 months for sorafenib (HR = 0.63; 95% CI 0.53, 0.74; *P*<0.00001).

Objective Response Rate

A summary of the ORR for the FAS is presented in the table below.

Table 44: Summary of investigator assessment of Objective Response using mRECIST (Full Analysis Set)

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
Best Overall Response, n (%)		
Complete Response (CR)	6 (1.3)	2 (0.4)
Partial Response (PR)	109 (22.8)	42 (8.8)
Stable Disease (SD)	246 (51.5)	244 (51.3)
Durable Stable Disease (SD)	167 (34.9)	139 (29.2)
Progressive Disease (PD)	71 (14.9)	147 (30.9)
Unknown/Not Evaluable	46 (9.6)	41 (8.6)
No baseline tumour assessment	1 (0.2)	0 (0.0)
No postbaseline tumour assessment	39 (8.2)	34 (7.1)
1 or more lesions were not evaluable	2 (0.4)	1 (0.2)
Early SD (SD <7 Weeks)	4 (0.8)	6 (1.3)
Objective Response Rate (CR + PR), n (%)	115 (24.1)	44 (9.2)
95% CI [a]	(20.2, 27.9)	(6.6, 11.8)
Difference (%) (95% CI) [a]	14.8 (10.2, 19.4)	
Odds ratio (95% CI) [b] with stratification factors in IxRS	3.13 (2.15, 4.56)	
P-value [b]	<0.00001	
Odds ratio (95% CI) [b] with stratification factors in CRF	3.08 (2.12, 4.48)	
P-value [b]	<0.00001	
Time to First Objective Response (months)		
Subjects with objective response	n=115	n=44
Mean (standard deviation)	3.6 (3.45)	4.8 (4.95)
Median	1.9	1.9
Q1, Q3	2, 4	2, 6
Min, Max	1, 28	2, 26
Duration of Objective Response (months)		
Subjects with objective response	n=115	n=44
Median (95% CI) [c]	7.3 (5.6, 7.7)	11.2 (5.6, 16.6)
Q1 (95% CI)	3.7 (2.2, 3.7)	3.8 (1.9, 7.3)
Q3 (95% CI)	12.9 (9.6, 16.6)	20.5 (14.8, NE)

Data cut-off: 13 Nov 2016. Percentages are based on the total number of subjects within the relevant treatment group in the Full Analysis Set. Tumour assessment based on mRECIST

a: 95% CI was calculated using asymptotic normal approximation.

b: Odds ratio and *P*-value (for superiority test) were calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS or CRF stratification factors.

c: Median was estimated using the Kaplan-Meier product-limit method and 95% CI was estimated using a generalized Brookmeyer and Crowley method. SD must have occurred ≥7 weeks after randomization. Durable stable disease is a subset of SD, and is defined as SD with a duration of ≥23 weeks after randomization.

Time to first objective response (months) = (Date of first objective response – Date of Randomization + 1) *12/365.25, for subjects with a best overall response of CR or PR. Subjects without a best overall response of CR or PR were censored.

Duration of objective response (months) = (Date of progressive disease/Death – Date of first objective response) *12/365.25, for subjects with objective response.

The ORR analysis in the PPS was supportive; 24.4% in the lenvatinib compared with 9.3% in the sorafenib arm. The difference between the treatment arms was 15.1% (95% CI: 10.4, 19.8). The odds ratio was 3.19 (95% CI: 2.18, 4.66), which was statistically significant (P<0.00001) in favour of lenvatinib treatment.

Quality of Life

Assessments of HRQoL scores were performed using the generic cancer HRQoL instrument (EORTC QLQ-C30), the HCC-specific module (EORTC QLQ-HCC18), and the generic HRQoL instrument, EQ-5D.

During the Randomization Phase, the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D were administered at Baseline, Day 1 of each cycle after Cycle 1, and at the OTV. During the Extension Phase, the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D were administered on Day 1 of each treatment and during the OTV.

Missing data were evaluated at the score level for each patient at each cycle to assess the patterns of missing data within and between treatment arms for potential evaluation in subsequent statistical analyses if required or deemed to be appropriate. Patients missing baseline data were excluded from the longitudinal analyses. No imputation for missing PRO data were conducted.

Study compliance was high (>90%) for the patient outcome measures at baseline and throughout the Randomisation Phase, but interpretation was limited in later cycles due to the decline in patient numbers.

Under half of the total population was observed at Cycle 6 (48.6% and 48.1% in the CSP and LPP, respectively) and one quarter at Cycle 12 (23.2% and 22.6% in the CSP and LPP, respectively). Baseline scores for all domains in the EORTC QLQ-HCC18, EORTC QLQ-C30 and EQ-5D were similar between the lenvatinib and sorafenib treatment arms. The QoL scores declined with both treatments and there was no significant difference between the 2 arms for most domains.

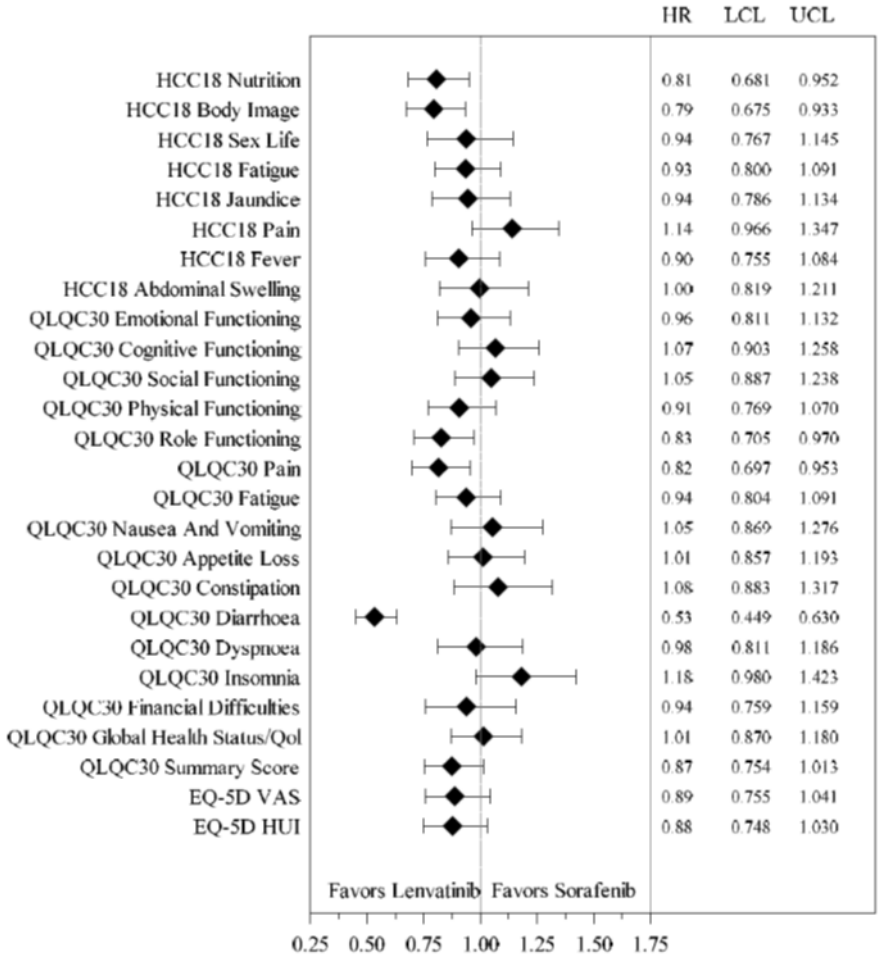


Figure 16: Hazard ratio of time to clinically meaningful worsening of EQ-5D, EORTC QLQ-C30 and EORTC QLQ-HCC18 domains

Ancillary analyses

Overall Survival

Sensitivity Analyses for OS based on stratification data in the CRF and without stratification factors

Data used for stratification for the primary analysis were obtained by the IxRS. Stratification factors were region (Asia-Pacific; Western), MPVI or extrahepatic spread or both, ECOG PS (PS = 0; 1), and body weight (<60 kg; ≥60 kg). When comparing the stratification - factors based on CRF-reported data to those based on the IxRS data, the factor 'MPVI, extrahepatic spread or both' had a discrepancy of 87 subjects, and the rest of the factors had no or few discrepancies (15 subjects for ECOG PS and 2 for body weight).

Results of a sensitivity analysis of OS for the FAS based on the stratification data recorded on the CRF [median OS 13.6 vs. 12.3 months, stratified HR 0.91 (0.79, 1.06)] were highly consistent with the results obtained with the primary analysis of OS. An analysis of OS without stratification factors for the FAS

confirmed the results based on the primary OS analysis [median OS 13.6 months (95% CI 12.1, 14.9) vs. 12.3 months (95% CI 10.4, 13.9), unstratified Cox Model HR 0.928 (95% CI 0.801, 1.077)].

OS Adjusted by Baseline Characteristics that may have impacted OS

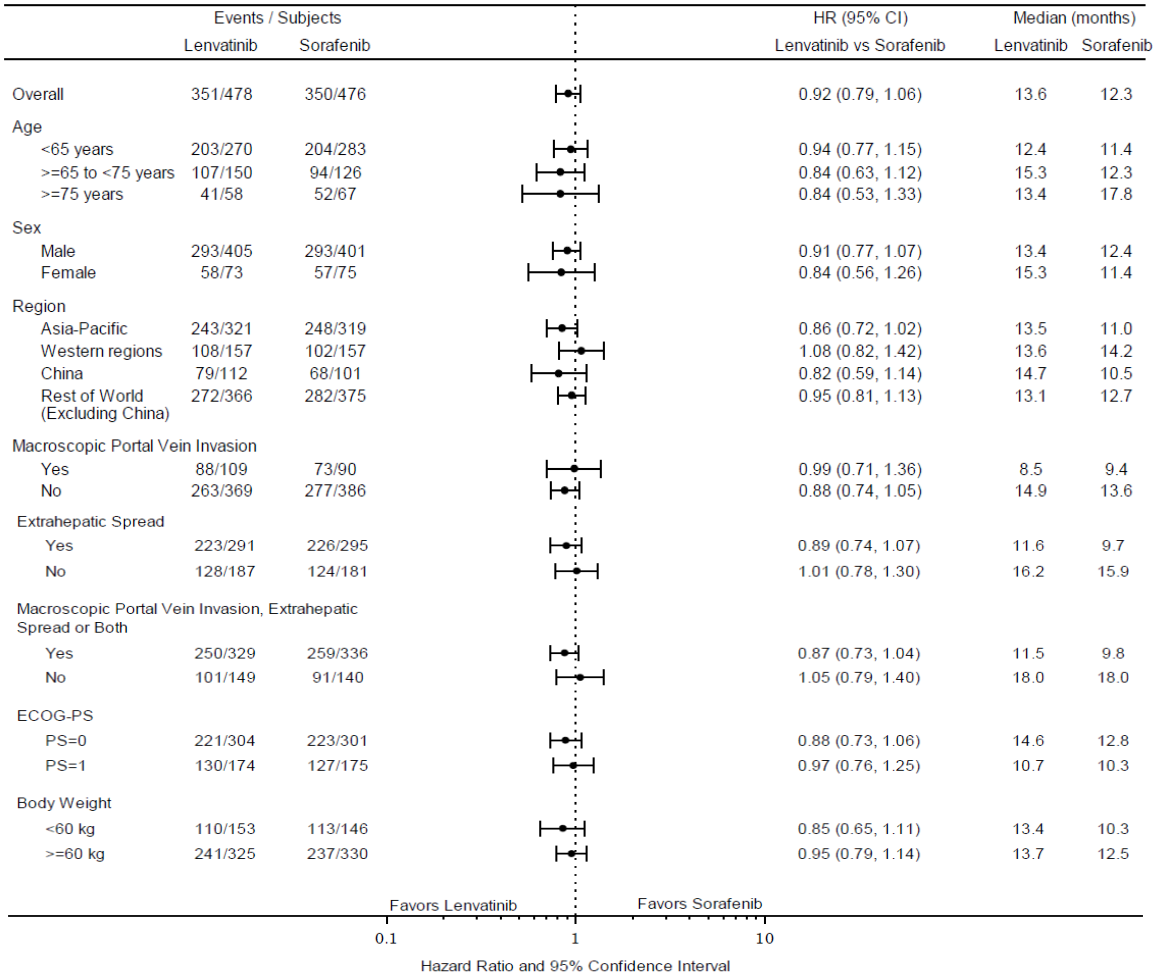
Table 45 : Overall Survival with Stratification Factors in IxRS, Adjusted by Baseline Characteristics (Full Analysis Set)

Baseline Characteristics	Hazard Ratio [a] (Lenvatinib: Sorafenib) (95% CI)
Overall	**0.916 (0.789, 1.064)**
Age (<65, ≥65 to <75, ≥75 yrs.)	0.919 (0.791, 1.067)
Sex (Male, Female)	0.916 (0.789, 1.064)
Region (Asia-Pacific, Western Region)	0.915 (0.789, 1.062)
Macroscopic Portal Vein Invasion (Yes, No)	0.910 (0.784, 1.057)
Extrahepatic Spread (Yes, No)	0.915 (0.788, 1.062)
Macroscopic Portal Vein Invasion, Extrahepatic Spread or Both (Yes, No)	0.908 (0.783, 1.054)
ECOG PS (0, ≥1)	0.923 (0.795, 1.071)
Body Weight (<60 kg, ≥60 kg)	0.923 (0.796, 1.071)
Alpha-fetoprotein level at Baseline (<200 ng/mL, ≥200 ng/mL)	0.856 (0.736, 0.995)
Ammonia level (≤ULN, >ULN)	0.920 (0.788, 1.073)
Antiviral Therapy for Hepatitis B or Hepatitis C (Yes, No)	0.912 (0.785, 1.059)
Child-Pugh Score (5, ≥6)	0.932 (0.802, 1.082)
No. of Disease Sites at Baseline (1, 2, ≥3)	0.878 (0.755, 1.020)
Etiology (HBV, HCV, Alcohol)	0.855 (0.721, 1.013)
Underlying Cirrhosis (Yes, No)	0.916 (0.789, 1.063)
BCLC Staging (Stage B, Stage C)	0.918 (0.791, 1.067)
Prior Procedure (Yes, No)	0.902 (0.777, 1.048)

If a stratification factor was same as the respective baseline characteristics, this stratification factor was excluded from stratified analysis. Aetiology was based on data from medical history. Prior procedure excluded prior radiotherapy.
a: Hazard ratio was based on a Cox regression model including treatment group and the respective baseline characteristics (not included for overall population) as factors. Efron method was used for ties.

For baseline AFP, the HR for lenvatinib: sorafenib was 0.856 (95% CI: 0.736, 0.995). Analysis of OS adjusted for baseline AFP category (<200 ng/mL, ≥200 ng/mL) was consistent with the primary analysis (4 subjects without baseline AFP values were excluded, 1 in the lenvatinib and 3 in the sorafenib arm). Median OS with baseline AFP as a factor was 13.6 months (12.2, 14.9) vs. 12.3 months (10.6, 14.1) for lenvatinib and sorafenib respectively.

Subgroup Analysis of OS


Events / Subjects
Lenvatinib
Sorafenib
HR (95% CI)
Lenvatinib vs Sorafenib
Median (months)
Lenvatinib
Sorafenib
Overall 351/478 350/476 0.92 (0.79, 1.06) 13.6 12.3
Age
<65 years 203/270 204/283 0.94 (0.77, 1.15) 12.4 11.4
>=65 to <75 years 107/150 94/126 0.84 (0.63, 1.12) 15.3 12.3
>=75 years 41/58 52/67 0.84 (0.53, 1.33) 13.4 17.8
Sex
Male 293/405 293/401 0.91 (0.77, 1.07) 13.4 12.4
Female 58/73 57/75 0.84 (0.56, 1.26) 15.3 11.4
Region
Asia-Pacific 243/321 248/319 0.86 (0.72, 1.02) 13.5 11.0
Western regions 108/157 102/157 1.08 (0.82, 1.42) 13.6 14.2
China 79/112 68/101 0.82 (0.59, 1.14) 14.7 10.5
Rest of World (Excluding China) 272/366 282/375 0.95 (0.81, 1.13) 13.1 12.7
Macroscopic Portal Vein Invasion
Yes 88/109 73/90 0.99 (0.71, 1.36) 8.5 9.4
No 263/369 277/386 0.88 (0.74, 1.05) 14.9 13.6
Extrahepatic Spread
Yes 223/291 226/295 0.89 (0.74, 1.07) 11.6 9.7
No 128/187 124/181 1.01 (0.78, 1.30) 16.2 15.9
Macroscopic Portal Vein Invasion, Extrahepatic Spread or Both
Yes 250/329 259/336 0.87 (0.73, 1.04) 11.5 9.8
No 101/149 91/140 1.05 (0.79, 1.40) 18.0 18.0
ECOG-PS
PS=0 221/304 223/301 0.88 (0.73, 1.06) 14.6 12.8
PS=1 130/174 127/175 0.97 (0.76, 1.25) 10.7 10.3
Body Weight
<60 kg 110/153 113/146 0.85 (0.65, 1.11) 13.4 10.3
>=60 kg 241/325 237/330 0.95 (0.79, 1.14) 13.7 12.5
Favors Lenvatinib
Favors Sorafenib
0.1
1
10
Hazard Ratio and 95% Confidence Interval

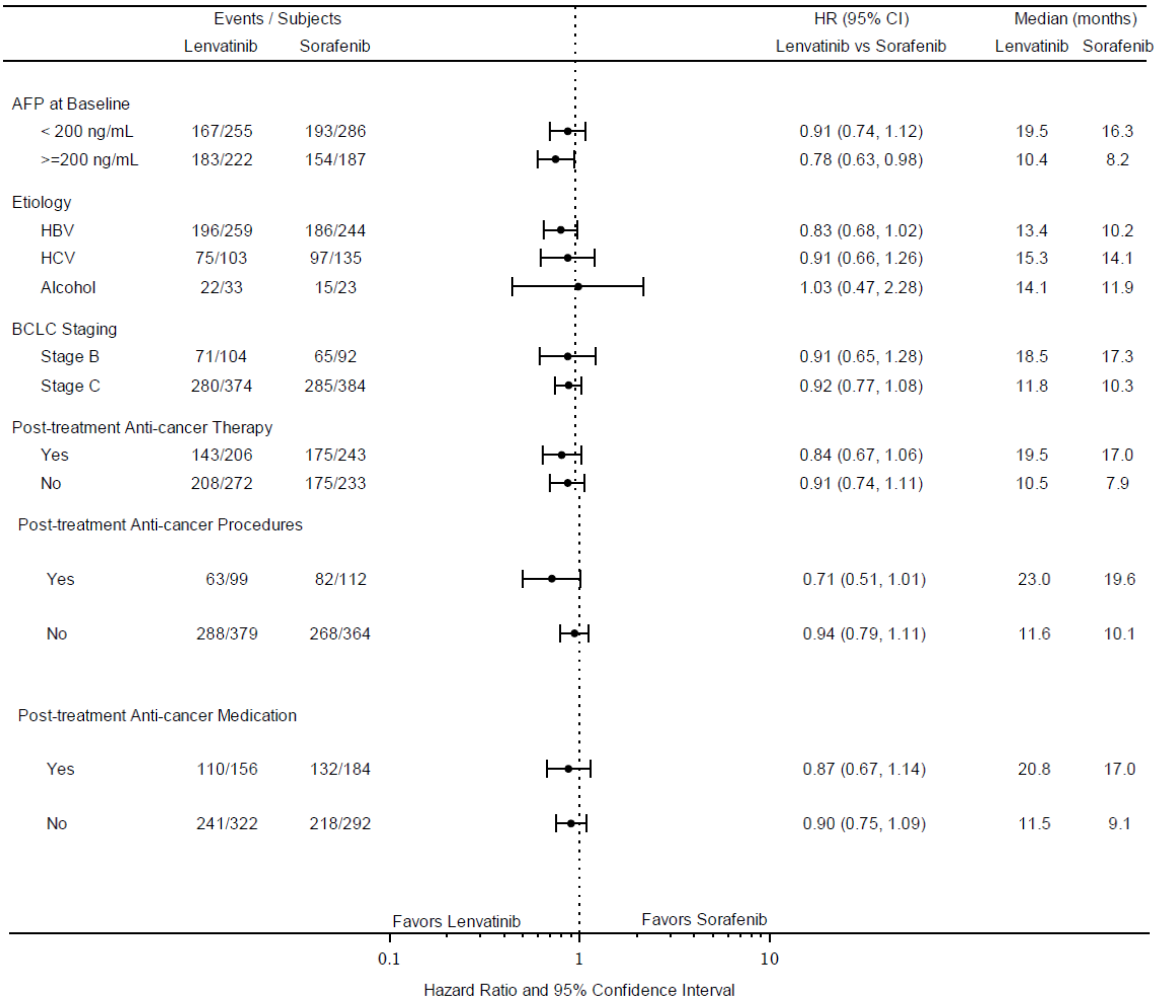


Figure 17: Forest Plot of Hazard Ratio for Lenvatinib vs Sorafenib in Overall Survival with Stratification Factors in IxRS (Full Analysis Set)

OS by Region and Subsequent Anti-Cancer Therapy (medication and procedures)

Analysis of OS by subgroup (see figure above) revealed that within each treatment, subjects who received posttreatment anticancer therapy during survival follow-up had longer median OS than those who did not.

Table 46: Post-treatment Anticancer Therapy during Survival Follow-up by Region (Full Analysis Set)

	Lenvatinib		Sorafenib	
	Asia-Pacific (N=321)	**Western (N=157)**	**Asia-Pacific (N=319)**	**Western (N=157)**
Received any anticancer therapy [a] during survival follow-up, n (%)	162 (50.5)	44 (28.0)	172 (53.9)	71 (45.2)
Underwent any anticancer procedure [b] during survival follow-up, n (%)	111 (34.6)	11 (7.0)	112 (35.1)	18 (11.5)
Received any anticancer medication [c] (not given for procedure) during survival follow-up, n (%)	115 (35.8)	41 (26.1)	123 (38.6)	61 (38.9)
Fluorouracil	18 (5.6)	2 (1.3)	25 (7.8)	1 (0.6)
Doxorubicin	5 (1.6)	2 (1.3)	8 (2.5)	11 (7.0)
Cisplatin	17 (5.3)	1 (0.6)	21 (6.6)	2 (1.3)
Sorafenib	84 (26.2)	37 (23.6)	43 (13.5)	13 (8.3)
Investigational drug	11 (3.4)	4 (2.5)	25 (7.8)	20 (12.7)

Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.
a: Posttreatment anticancer therapy includes both posttreatment anticancer procedures and posttreatment anticancer medications during survival follow-up.
b: Subject with 2 or more procedures reported in the same system organ class or preferred term were only counted once. Anticancer procedures were coded using MedDRA version 19.1.

c: Subjects with 2 or more medications within a class level and drug name were counted only once within that class level and drug name. WHODD MAR2016 HD B2 was used to code posttreatment anticancer medications not given for any procedure.
Selected anticancer medications presented when frequency in any region >5%

Subject health status, including hepatic function, at the end of treatment visit was comparable between the lenvatinib and sorafenib arms in the Western region except for an imbalance in AFP concentration (median AFP: 124.6 ng/mL [Q1, Q3: 7.7, 3848 ng/mL] in the lenvatinib arm vs 45.9 ng/mL [Q1, Q3: 4.7, 986.2 ng/mL] in the sorafenib arm). This reflected the imbalance between the arms at Baseline and the change from Baseline in AFP concentration was similar in both arms.

Median OS was approximately 9 months longer in subjects who received post-treatment anticancer therapy than in those who did not. In the lenvatinib arm, median OS was 19.5 months (95% CI: 15.7, 23.0) for subjects who received post-treatment anticancer therapy (43%) and 10.5 months (95% CI: 8.6, 12.2) for those who did not. In the sorafenib arm, median OS was 17.0 months (95% CI: 14.2, 18.8) for subjects who received posttreatment anticancer therapy (51%) and 7.9 months (95% CI: 6.6, 9.7) for those who did not. Median OS was longer by approximately 2.5 months in the lenvatinib compared with the sorafenib arm in both subsets of subjects (with or without post-treatment anticancer therapy).

When adjusted for post-treatment anticancer therapy, the HR for OS favoured lenvatinib in both regions (table below).

Table 47: Overall Survival adjusted by use of post-treatment anticancer treatment, overall and by region (Full Analysis Set)

	Stratified Cox Model Hazard Ratio (95% CI)[a]	
	Without Adjustment	With Adjustment[b]
Overall	0.92 (0.79, 1.06)	0.87 (0.75, 1.01)
Region		
Asia-Pacific	0.86 (0.72, 1.02)	0.83 (0.70, 1.00)
Western	1.08 (0.82, 1.42)	0.93 (0.70, 1.23)

For the Asia-Pacific and Western regions, the stratification factor of "region" was not included.
a: Hazard ratio is for lenvatinib: sorafenib, based on a Cox model including treatment group as a factor. The Efron method used for correction of tied events. Stratified by region (Region 1: Asia-Pacific; Region 2: Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1), and body weight (<60 kg, ≥60 kg).
b: Status of posttreatment anticancer therapy (yes/no) was used as an additional covariate factor.

Progression-free Survival

Sensitivity Analysis for PFS

A stratified analysis of PFS using all disease progression and death events was done as a sensitivity analysis using the FAS.

PFS by subgroup

Forest plots of the HRs (lenvatinib:sorafenib) in PFS for selected stratification factors in the IxRS is presented in the figure below.

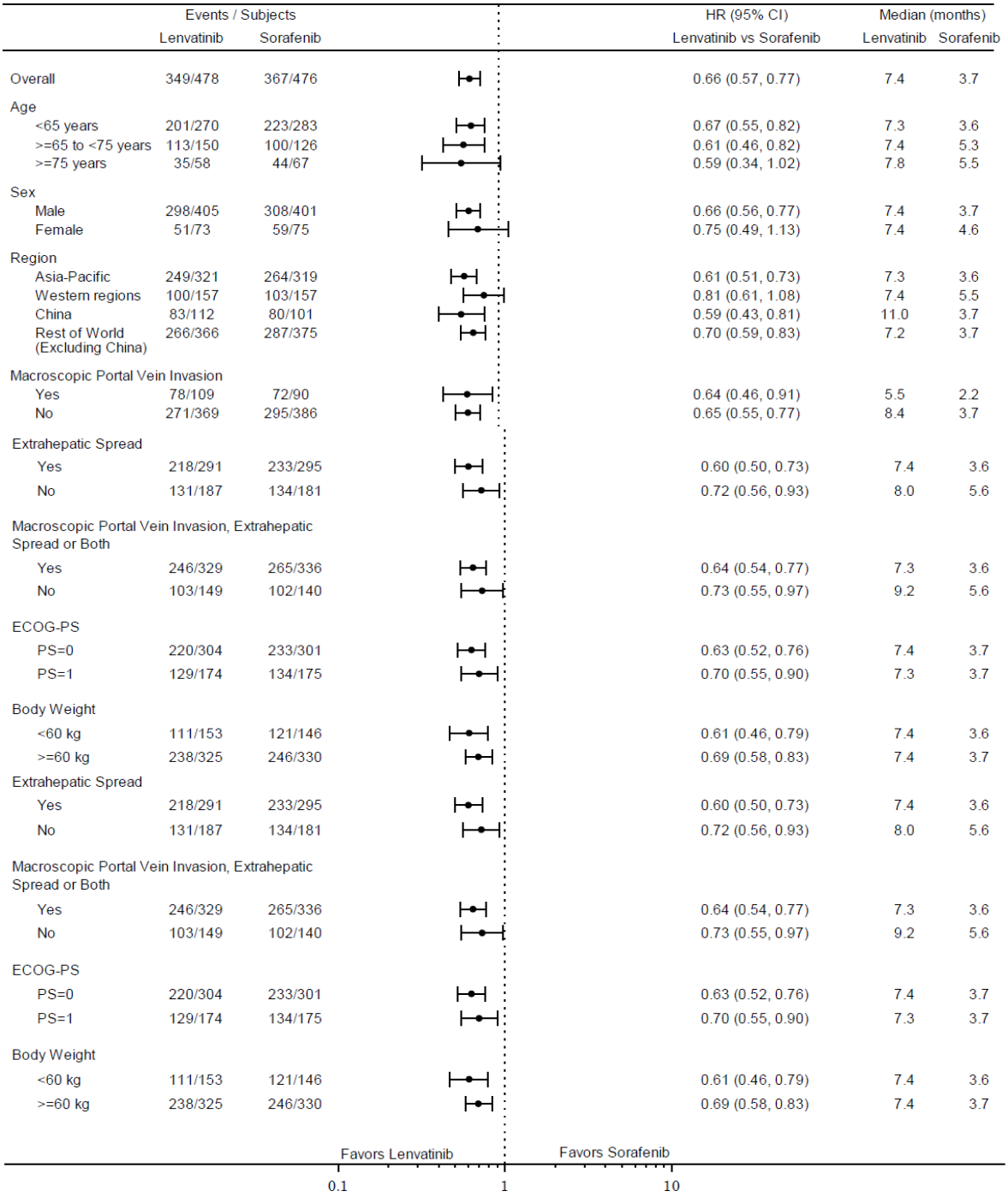


Figure 18: Forest Plot of Hazard Ratio for Lenvatinib vs Sorafenib in Progression Free Survival with Stratification Factors in IxRS Full Analysis Set

Time to Progression

Sensitivity Analyses for TTP

A stratified analysis of TTP using all disease progression events (subjects were not censored for missing assessments, new anticancer therapy or treatment discontinuation for reasons other than PD) was consistent with the initial results. Median TTP was 7.6 months for lenvatinib compared with 3.7 months for sorafenib with an HR = 0.62, 95% CI of 0.54, 0.73, and $P<0.00001$.

Subgroup analysis of TTP

As seen in the overall population, median TTP with stratification factors in the IxRS was longer with lenvatinib than sorafenib, with HR <1 in each of the subgroups tested.

Objective Response Rate

Subgroup analysis of ORR

The ORR was consistently higher in the lenvatinib arm than in the sorafenib arm in each of the subgroups tested, with the exception of alcohol use, for which the number of subjects was small.

The ORR with lenvatinib in the Western region (21.0%, 95% CI: 14.6, 27.4) was consistent with that observed for the Asia-Pacific region (25.5%, (95% CI: 20.8, 30.3) and for the overall population (24.1%, 95% CI: 20.2, 27.9). The odds ratios were 2.18 (1.15, 4.11) for the Western region, 3.77 (95% CI: 2.36, 6.04) for the Asia-Pacific region, and 3.13 (95% CI: 2.15, 4.56) for the overall population.

Post-hoc retrospective independent imaging review

A post hoc, blinded IIR was conducted per an Independent Review Charter (IRC).

At screening all but 5 subjects (4 lenvatinib, 1 sorafenib) had disease as identified by the IIR. In regard to target lesions at baseline, 33 patients by mRECIST (18 lenvatinib, 15 sorafenib) and 21 patients by RECIST 1.1 (12 lenvatinib, 9 sorafenib) did not have lesions meeting requirement for a target lesion at baseline.

Although the proportion of subjects with cirrhosis was underreported based on CRF data (49.7%), further post-hoc analysis of screening scans using non-invasive imaging confirmed diagnosis of HCC in 74.5% for lenvatinib arm and 76.5% for sorafenib arm.

A side-by-side summary of key efficacy results for both treatment arms, obtained using the investigator assessment (primary comparison) and the confirmatory blinded IIR using mRECIST, is presented in table below.

Table 48: Summary of key efficacy results obtained with the investigator or blinded independent review using mRECIST – Randomization Phase (Full Analysis Set)

	Investigator Assessment		Independent Imaging Assessment	
	Lenvatinib	**Sorafenib**	**Lenvatinib**	**Sorafenib**
Progression-free Survival – Primary Analysis				
Median (mo) (95% CI) [a]	7.4 (6.9, 8.8)	3.7 (3.6, 4.6)	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
Hazard Ratio (95% CI) [b, c]	0.66 (90.57, 0.77) *P*<0.00001		0.64 (0.55, 0.75) *P*<0.00001	
Progression-free Survival – Sensitivity Analysis				
Median (mo) (95% CI)[a]	7.3 (5.8, 7.5)	3.7 (3.6, 4.7)	6.6 (5.5, 7.4)	3.7 (3.6, 5.1)
Hazard Ratio (95% CI) *P* value [b, c]	0.72 (0.63, 0.83) *P*<0.00001		0.82 (0.71, 0.94) *P*=0.0047	
Time to Progression				
Median (mo) (95% CI) [a]	8.9 (7.4, 9.2)	3.7 (3.6, 5.4)	7.4 (7.2, 9.1)	3.7 (3.6, 3.9)
Hazard Ratio (95% CI) *P* value [b, c]	0.63 (0.53, 0.73) *P*<0.00001		0.60 (0.51, 0.71) *P*<0.00001	
Objective Response Rate				
ORR (CR+ PR), % [d] (95% CI) [e]	24.1% (20.2, 27.9)	9.2% (6.6, 11.8)	40.6% (36.2, 45.0)	12.4% (9.4, 15.4)
Difference (%) (95% CI) [e]	14.8 (10.2, 19.4)		28.2 (22.9, 33.5)	
Odds Ratio (95% CI) with stratification factors from IxRS; *P* value [f]	3.13 (2.15, 4.56) *P*<0.00001		5.01 (3.59, 7.01) *P*<0.00001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel CR = complete response; CRF = case report form; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IxRS = Interactive Voice/Web Response System; ORR – objective response rate; PR = partial response.

a: 95% CIs were estimated with a generalized Brookmeyer and Crowley method.

b: Hazard ratio is for lenvatinib vs sorafenib, based on a Cox model including treatment group as a factor. Efron method is used for ties.

c: Stratified by region (Region 1: Asia-Pacific; Region 2: Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg).

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

e: 95% CI was calculated using asymptotic normal approximation.

f: Odds ratio and *P*-value (for superiority test) were calculated using the CMH method, stratified by IxRS or CRF stratification factors.

PFS

Table 49: Progression-Free Survival Based on Randomization Stratification Factors Recorded in the IxRS – Independent Imaging Review Using mRECIST (Full Analysis Set)

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
Subjects with Events, n (%)	**311 (65.1)**	**323 (67.9)**
Progressive Disease	278 (58.2)	307 (64.5)
Death	33 (6.9)	16 (3.4)
Censored Subjects, n (%)	**167 (34.9)**	**153 (32.1)**
No baseline tumor assessment	3 (0.6)	1 (0.2)
No postbaseline tumor assessment	23 (4.8)	22 (4.6)
New anticancer treatment started	43 (9.0)	31 (6.5)
No progression at the time of data cutoff	16 (3.3)	13 (2.7)
No progression at the time of treatment discontinuation	82 (17.2)	86 (18.1)
Progression-Free Survival (months)[a]		
Median (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
Q1 (95% CI)	3.5 (2.3, 3.6)	1.9 (1.8, 1.9)
Q3 (95% CI)	11.2 (11.0, 12.9)	7.3 (5.6, 9.2)
Progression-Free Survival Rate (%) (95% CI)[b] at		
6 Months	53.7 (48.6, 58.5)	27.4 (22.8, 32.2)
12 Months	24.4 (19.8, 29.2)	15.4 (11.5, 19.8)
18 Months	12.6 (8.9, 16.9)	11.7 (8.1, 16.0)
24 Months	8.4 (5.1, 12.6)	8.5 (5.1, 13.0)
Stratified Cox Model Hazard Ratio (95% CI)[c,d]	**0.64 (0.55, 0.75)**	
Stratified Log-Rank Test *P* value[d]	<0.00001	
Follow-Up Time for Progression-Free Survival (months)[a,e]		
Median (95% CI)	14.7 (11.3, 17.5)	11.0 (7.6, 14.7)
Q1 (95% CI)	5.5 (3.7, 7.3)	3.6 (2.1, 5.4)
Q3 (95% CI)	23.8 (21.7, 26.6)	23.9 (18.4, 27.6)

Data cutoff date: 13 Nov 2016. *P* value is for the superiority test of lenvatinib versus sorafenib. Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment arm.
a: Quartiles estimated by Kaplan-Meier method; 95% CIs estimated with a generalized Brookmeyer and Crowley method
b: PFS rate and 95% CI calculated using Kaplan-Meier product-limit method and Greenwood Formula.
c: Hazard ratio is for lenvatinib vs sorafenib, based on a Cox model including treatment arm as a factor. Efron method was used for ties.
d: Stratified by region (Region 1: Asia-Pacific; Region 2: Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1), and body weight (<60 kg, ≥60 kg).
e: Follow-up time for PFS measured from the date of randomization to the date of the subject's last PFS follow-up, and had same numeric value but opposite censoring indicator as compared to PFS.

A sensitivity analysis using all PD and deaths as events was consistent with the primary PFS analysis; median PFS was 6.6 months for lenvatinib compared with 3.7 months for sorafenib with an HR of 0.82 (95% CI: 0.71, 0.94) and *P*=0.0047.

TTP - Similarly, median TTP as assessed by blinded IIR using mRECIST was consistent with the median TTP obtained using the investigator assessment.

Table 50: Time to Progression Based on Randomization Stratification Factors Recorded in the IxRS – Independent Imaging Review Using mRECIST (Full Analysis Set)

	Lenvatinib (N=478) n (%)	Sorafenib (N=476) n (%)
Subjects with Disease Progression, n (%)	**278 (58.2)**	**307 (64.5)**
Censored Subjects, n (%)	**200 (41.8)**	**169 (35.5)**
No baseline tumor assessment	3 (0.6)	1 (0.2)
No postbaseline tumor assessment	33 (6.9)	34 (7.1)
New anticancer treatment started	43 (9.0)	31 (6.5)
No progression at the time of data cutoff	16 (3.3)	13 (2.7)
No progression at the time of treatment discontinuation	105 (22.0)	90 (18.9)
Time to Progression (months)[a]		
Median (95% CI)	7.4 (7.2, 9.1)	3.7 (3.6, 3.9)
Q1 (95% CI)	3.6 (3.5, 3.7)	1.9 (1.8, 1.9)
Q3 (95% CI)	12.9 (11.0, 14.7)	7.4 (5.7, 9.2)
Cumulative Progression Rate (%) (95% CI)[b] at		
6 Months	42.9 (38.1, 48.1)	71.4 (66.5, 76.1)
12 Months	72.5 (67.2, 77.6)	83.9 (79.4, 88.0)
18 Months	85.5 (80.7, 89.7)	87.8 (83.3, 91.6)
24 Months	90.0 (85.0, 93.8)	91.1 (86.4, 94.7)
Stratified Cox Model Hazard Ratio (95% CI)[c,d]	**0.60 (0.51, 0.71)**	
Stratified Log-rank Test *P* value[d]	<0.00001	
Follow-Up Time for TTP (months)[a,e]		
Median (95% CI)	11.3 (9.2, 14.7)	11.0 (7.4, 13.0)
Q1 (95% CI)	3.7 (3.6, 5.5)	3.4 (1.9, 3.7)
Q3 (95% CI)	22.2 (20.1, 25.9)	23.3 (16.7, 25.8)

Results of a TTP sensitivity analysis using all PD events were consistent with the results obtained with the primary TTP analysis.

ORR

Table 51: Summary of Tumour Response per Investigator Assessment and Independent Imaging Review per mRECIST (Full Analysis Set)

	Investigator Assessment		Independent Review	
	Lenvatinib (N=478) n (%)	**Sorafenib (N=476) n (%)**	**Lenvatinib (N=478) n (%)**	**Sorafenib (N=476) n (%)**
Complete Response (CR) Partial	6 (1.3)	2 (0.4)	10 (2.1)	4 (0.8)
Response (PR) Stable Disease	109 (22.8)	42 (8.8)	184 (38.5)	55 (11.6)
(SD) Durable SD	246 (51.5)	244 (51.3)	159 (33.3)	219 (46.0)
Progressive Disease (PD) Not	167 (34.9)	139 (29.2)	84 (17.6)	90 (18.9)
Evaluable/Unknown	71 (14.9)	147 (30.9)	79 (16.5)	152 (31.9)
	46 (9.6)	41 (8.6)	46 (9.6)	46 (9.7)

Mean time to first objective response for responders was shorter by IIR than Ix assessment (2.7 months for lenvatinib and 3.4 months for sorafenib by IIR vs. 3.6 and 4.8 months by Ix). For responders, median duration of response was 7.3 months for lenvatinib-treated subjects (n=194) and 6.2 months for sorafenib-treated subjects (n=59) by IIR compared to 7.3 months (n=115) and 11.2 months (n=44) by Ix assessment.

Overall, agreement on best overall response (BOR) between the independent and investigator assessments was 62.6%. Agreement was higher for sorafenib (70.0%; 333/476) than lenvatinib (55.2%; 264/478), driven by the high agreement on BOR of SD and PD in the sorafenib arm. Independent

reviewers assessed more instances of PR when investigators assessed SD, especially for subjects treated with lenvatinib (103 [21.5%]) as compared with sorafenib (29 [6.1%]).

Table 52: Summary of Progression Assessed by Investigator and Independent Review Using mRECIST (Full Analysis Set)

		Independent Review	
	Investigator Review	PD n (%)	Non PD n (%)
Overall (N=954)	PD	538 (56.4)	165 (17.3)
	Non PD	77 (8.1)	174 (18.2)
Lenvatinib (N=478)	PD	249 (52.1)	80 (16.7)
	Non PD	45 (9.4)	104 (21.8)
Sorafenib (N=476)	PD	289 (60.7)	85 (17.9)
	Non PD	32 (6.7)	70 (14.7)

Table 53: Agreement on timing of progression assessed by investigator and IRR using mRECIST

	Agreement on Timing of PD[a]	
Subjects With PD by Both Investigator Review and IIR	Yes n (%)	No n (%)
Overall (N=538)	274 (50.9)	264 (49.1)
Lenvatinib (N=249)	115 (46.2)	134 (53.8)
Sorafenib (N=289)	159 (55.0)	130 (45.0)

IIR = Independent Imaging Review; mRECIST = modified Response Evaluation Criteria in Solid Tumors; PD = progressive disease.
Percentages are based on the total number of randomized subjects with PD by both Investigator and Independent Reviewer in the relevant treatment arm.
a: If both Investigator and Independent Reviewer identified PD for a subject on the same date, they were considered as agreed on timing of PD; if the PDs of the subject were on different dates, they were considered as not agreed on timing.
Source: IIR Summary Table 7.

Table 54 : Comparison of Timing of Progression Assessed per mRECIST by Investigator and Independent Review (Full Analysis Set)

	Lenvatinib (N=478)	Sorafenib (N=476)	Differential Discordance for Lenvatinib vs Sorafenib	Overall (N=954)
Early Discordance Rate (EDR, %)	28.3	26.2	2.1	27.2
Late Discordance Rate (LDR, %)	64.1	60.3	3.8	62.3

EDR (Early Discordance Rate) = (number of subjects with INV PD earlier than IIR PD + number of subjects with INV PD and without IIR PD) / number of subjects with INV PD.
LDR (Late Discordance Rate) = (number of subjects with INV PD later than IIR PD + number of subjects without INV PD but with IIR PD)/ (number of subjects with INV PD earlier than IIR PD + number of subjects with INV PD later than IIR PD + number of subjects without INV PD but with IIR PD + number of subjects with INV PD and without IIR PD).
Differential discordance for EDR = Difference among EDR between 2 treatment arms.
Differential discordance for LDR = Difference among LDR between 2 treatment arms.

Discordance rates on timing of progression (EDR and LDR) were similar in the 2 arms (EDR: 28.3% in the lenvatinib arm vs 26.2% in the sorafenib arm; LDR: 64.1% in the lenvatinib arm vs 60.3% in the sorafenib arm), showing that there was no meaningful bias in the investigator results.

IRR using RECIST 1.1

Independent review of tumour assessments using RECIST 1.1 yielded similar results for both PFS (median 7.3 months lenvatinib vs 3.6 months sorafenib; HR=0.65 [95% CI: 0.56, 0.77; p<0.00001]) and TTP (median 7.4 months vs. 3.7 months; HR=0.61 [95% CI: 0.51, 0.72; p<0.00001]) as with mRECIST. As expected, the response rates for both arms were lower when using RECIST 1.1 (18.8% for lenvatinib vs

6.5% for sorafenib) than with mRECIST, but the relative benefit of lenvatinib treatment compared with sorafenib by mRECIST was maintained (Odds ratio 3.34; 95% CI: 2.17, 5.14; p<0.00001).

The duration of objective response was longer in sorafenib arm than in lenvatinib arm: 15.8 (5.9, NE) months vs 7.4 (5.6, 9.2) months, respectively.

Efficacy results by dose of lenvatinib

Efficacy by Lenvatinib Starting Dose (Body Weight Category)

At the request of the CHMP, the MAH reviewed the efficacy data by starting dose of lenvatinib.

Starting dose was based on body weight. The number of subjects who received lenvatinib by starting dose (8 mg, n=151; 12 mg, n=327) was nearly identical to the number of subjects in the body weight subgroups (<60 kg, n=153; ≥60 kg, n=325). The efficacy of lenvatinib by starting dose was based on the analysis by body weight category, as already presented in the subgroup analyses. Body weight was not a randomization factor; these were not planned analyses.

Table 55 : Efficacy by Lenvatinib starting dose (BW category)

Lenvatinib results	**BW<60kg (8mg starting dose)**	**BW ≥60kg (12mg starting dose)**
Median OS months (95% CI) HR lenvatinib: sorafenib	13.4 (10.5, 15.7) 0.85 (0.65, 1.11)	13.7 (12.0, 15.6) 0.95 (0.79, 1.14)
Median PFS months (95% CI) HR lenvatinib: sorafenib	7.4 (5.4, 9.2) 0.61 (0.46, 0.79)	7.4 (6.9, 9.0) 0.69 (0.58, 0.83)
Median TTP months (95% CI) HR lenvatinib: sorafenib	9.0 (5.6, 9.2) 0.61 (0.46, 0.80)	8.8 (7.3, 9.2) 0.64 (0.53, 0.77)
ORR % (95% CI) Odds ratio lenvatinib: sorafenib	22.2 (15.6, 28.8) 3.16 (1.56, 6.41)	24.9 (20.2, 29.6) 3.11 (2.00, 4.85)

Summary of main study(ies)

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

Table 56: Summary of Efficacy for trial 304

Title: A Multicenter, Randomised, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma		
Study identifier	E7080-G000-304	
Design	- Phase III - randomised (1:1), open-label, multi-centre, non-inferiority study - comparator-controlled (sorafenib)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Until target 700 deaths (~3 years 8 months) 01 March 2013 – 13 November 2016 ~21 days (screening + baseline) ongoing
Hypothesis	Non-inferiority (NI margin for HR lenvatinib vs sorafenib = 1.08)	
Treatments groups	lenvatinib	8 mg QD (BW<60kg), N=151 12 mg AQD (BW≥60kg), N=327 TOTAL N=478
	sorafenib	400 mg BID, N=476

Endpoints and definitions	Primary endpoint	Overall Survival (OS)	The time from the date of randomisation until death due to any cause
	Secondary endpoints	Progression -free Survival (PFS)	The time from the date of randomisation to the date of first documentation of radiologic disease progression (investigator assessed by mRECIST), or date of death, whichever occurs first
		Time-to-Progression (TPP)	The time from the date of randomisation to the date of first documentation of radiologic disease progression (investigator assessed by mRECIST)
		Objective Response Rate (ORR)	The proportion of subjects who have best overall response of complete response (CR) or partial response (PR).
		HRQoL	EORTC QLQ-C30, HC-18 and EQ-5D-3L.
Database lock	Data cut-off date for primary analysis: 13 November 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) i.e. ITT – all randomised subjects analysed per their randomised treatment, based on randomisation stratification factors per IxRS		
Descriptive statistics and estimate variability	Treatment group	Lenvatinib	Sorafenib
	Number of subjects	478	476
	Number of deaths	351 (73.4%)	350 (73.5%)
	OS (months) median	13.6	12.3
	95% CI	(12.1;14.9)	(10.4;13.9)
	PFS (months) median	7.4	3.7
	95% CI	(6.9;8.8)	(3.6;4.6)
	TTP (months) median	8.9	3.7
	95% CI	(7.4;9.2)	(3.6;5.4)
	ORR (%)	24.1	9.2
	95% CI	(20.2;27.9)	(6.6;11.8)

Effect estimate per comparison	Primary endpoint OS	Comparison groups	Lenvatinib - Sorafenib
		Stratified HR	0.92
		95% CI	(0.79;1.06)
		P-value	-
	Secondary endpoint PFS	Comparison groups	Lenvatinib - Sorafenib
		Stratified HR	0.66
		95% CI	(0.57;077)

		P-value	<0.00001
	Secondary endpoint TTP	Comparison groups	Lenvatinib - Sorafenib
		Stratified HR	0.63
		95% CI	(0.53;0.73)
		P-value	<0.00001
	Secondary endpoint ORR	Comparison groups	Lenvatinib - Sorafenib
		Odds ratio (IxRS stratified)	3.13
		95% CI	(2.15;4.56)
		P-value	<0.00001
Analysis description	**Secondary analysis**		
Analysis population and time point description	Per Protocol Analysis Set (PPS) consisted of subjects who were randomised and received at least 1 dose of the assigned drug, and had no major protocol deviations		
Descriptive statistics and estimate variability	Treatment group	Lenvatinib	Sorafenib
	Number of subjects	467	462
	OS (months) median	13.7	12.3
	95% CI	(12.2;15.1)	(10.6;14.2)
	PFS (months) median	7.4	3.7
	95% CI	(7.2;8.9)	(3.6;4.6)
	TTP (months) median	9.0	3.7
	95% CI	(7.4;9.2)	(3.6;5.4)
	ORR (%)	24.4	9.3
	95% CI	(20.5;28.3)	(6.7;12.0)
sEffect estimate per comparison	Primary endpoint OS	Comparison groups	Lenvatinib - Sorafenib
		Stratified HR	0.91
		95% CI	(0.78;1.06)
		P-value	-
	Secondary endpoint PFS	Comparison groups	Lenvatinib - Sorafenib
		Stratified HR	0.66
		95% CI	(0.57;0.77)
		P-value	<0.00001
	Secondary endpoint TTP	Comparison groups	Lenvatinib - Sorafenib
		Stratified HR	0.63
		95% CI	(0.53;0.74)
		P-value	<0.00001
	Secondary endpoint ORR	Comparison groups	Lenvatinib - Sorafenib
		Odds ratio (IxRS stratified)	3.19
		95% CI	(2.18;4.66)
		P-value	<0.00001

Analysis description	**Ancillary analysis:** *Retrospective analysis of key secondary endpoints using **mRECIST** and per **blinded independent review***		
Analysis population and time point description	Full Analysis Set (FAS) i.e. ITT – all randomised subjects analysed per their randomised treatment, based on randomisation stratification factors per IxRS		
Descriptive statistics and estimate variability	Treatment group	Lenvatinib	Sorafenib
	Number of subject	478	476
	PFS (months) median	7.3	3.6
	95% CI	(5.6;7.5)	(3.6;3.7)
	TTP (months) median	7.4	3.7
	95% CI	(7.2;9.1)	(3.6;3.9)
	ORR (%)	40.6	12.4
	95% CI	(36.2;45.0)	(9.4;15.4)
Effect estimate per comparison	Secondary endpoint PFS	Comparison groups	Lenvatinib - Sorafenib
		Stratified HR	0.64
		95% CI	(0.55;0.75)
		P-value	<0.00001
	Secondary endpoint TTP	Comparison groups	Lenvatinib - Sorafenib
		HR	0.60
		95% CI	(0.51;0.71)
		P-value	<0.00001
	Secondary endpoint ORR	Comparison groups	Lenvatinib - Sorafenib
		Odds ratio (IxRS stratified)	5.01
		95% CI	(3.59;7.01)
		P-value	<0.00001

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

Comparison with historical studies of sorafenib (SHARP & Asia -Pacific)

The MAH provided Study E7080-G000-304 Constancy Report (10 July 2017). To evaluate the validity of the constancy assumption, key study features were compared among Study 304 and the 2 previous sorafenib studies (SHARP and Asia-Pacific). These features included characteristics of the patient population, inclusion/exclusion (entry) criteria, concomitant treatments allowed, sorafenib dose, and analytic approach for determination of treatment effect (study endpoints). In addition, the use of posttreatment anticancer therapy among the 3 studies was also considered.

Table : Baseline Disease Characteristics – Study 304 and Previous Sorafenib Trials

	SHARP Sorafenib (N=299)	Asia-Pacific Sorafenib (N=150)	Study 304 Sorafenib (N=476)	Study 304 Sorafenib Western Region (N=157)	Study 304 Sorafenib Asia-Pacific Region (N=319)
Disease Etiology					
Hepatitis B virus	56 (19)	106 (70.7)	228 (47.9)	31 (19.7)	197 (61.8)
Hepatitis C virus	87 (29)	16 (10.7)	126 (26.5)	56 (35.7)	70 (21.9)
Alcohol	79 (26)	NA	21 (4.4)	13 (8.3)	8 (2.5)
Other	28 (9)	NA	32 (6.7)	21 (13.4)	11 (3.4)
Unknown	49 (16)	NA	69 (14.5)	36 (22.9)	33 (10.3)
ECOG PS					
0	161 (54)	38 (25.3)	301 (63.2)	97 (61.8)	204 (63.9)
1	114 (38)	104 (69.3)	175 (36.8)	60 (38.2)	115 (36.1)
2	24 (8)	8 (5.3)	0	0	0
BCLC stage					
B (intermediate)	54 (18)	NA	92 (19.3)	27 (17.2)	65 (20.4)
C (advanced)	244 (82)	143 (95.3)	384 (80.7)	130 (82.8)	254 (79.6)
MPVI, EHS, or Both					
Present	209 (70)	118 (79.7)	336 (70.6)	115 (73.2)	221 (69.3)
Absent	90 (30)	32 (20.3)	140 (29.4)	42 (26.8)	98 (30.7)
MPVI	108 (36)	54 (36.0)	90 (18.9)	26 (16.6)	64 (20.1)
Extrahepatic spread	159 (53)	103 (68.7)	295 (62.0)	102 (65.0)	193 (60.5)
Lymph nodes	89 (30)	46 (30.7)	141 (29.6)	58 (36.9)	83 (26.0)
Lung	67 (22)	78 (52.0)	144 (30.3)	34 (21.7)	110 (34.5)
Child–Pugh					
A	284 (95)	146 (97.3)	471 (98.9)	152 (96.8)	319 (100.0)
B	14 (5)	4 (2.7)	5 (1.1)	5 (3.2)	0
Alpha-fetoprotein (ng/mL)					
Median	44.3	NA	71.2	27.0	100.6
Min–Max	0–208×10^4	NA	0–145×10^4	0–145×10^4	1–93×10^4
< 40 ng/mL	NA	28 (18.7)	215 (45.2)	86 (54.8)	129 (40.4)
≥ 40 ng/mL	NA	114 (76.0)	258 (54.2)	68 (43.3)	190 (59.6)
< 200 ng/mL	NA	NA	286 (60.1)	104 (66.2)	182 (57.1)
≥ 200 ng/mL	NA	NA	187 (39.3)	50 (31.8)	137 (42.9)
≤ ULN	111 (37.1)	NA	124 (26.1)	55 (35.0)	69 (21.6)
ULN - ≤ 400 ng/mL	78 (26.1)	NA	184 (38.7)	58 (36.9)	126 (39.5)
> 400 ng/mL	93 (31.1)	NA	165 (34.7)	41 (26.1)	124 (38.9)
Previous therapy					
Surgical resection	57 (19)	49 (32.7)	144 (30.3)	24 (15.3)	120 (37.6)
Transarterial chemoembolization	86 (29)	61 (40.7)	245 (51.5)	60 (38.2)	185 (58.0)
Percutaneous ethanol injection	28 (9)	NA	19 (4.0)	4 (2.5)	15 (4.7)
Radiofrequency ablation	17 (6)	NA	110 (23.1)	20 (12.7)	90 (28.2)
Radiotherapy	13 (4)	NA	60 (12.6)	5 (3.2)	55 (17.2)

BCLC = Barcelona Clinic Liver Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; EHS = extrahepatic spread; MPVI = macroscopic portal invasion; ULN = upper limit of normal.

Table : Outcomes in Historical Sorafenib Studies and Study 304

Parameter	SHARP Sorafenib (N=299)	Asia-Pacific Sorafenib (N=150)	Study 304 Sorafenib (N=476)	Study 304 Sorafenib Western Region (N=157)	Study 304 Sorafenib Asia-Pacific Region (N=319)
OS (months)					
Median	10.7	6.5	12.3	14.2	11.0
95% CI	9.4–13.3	5.56–7.56	10.4–13.9	11.9–18.0	9.6–12.5
% at 6 months	NA	53.5	75.2	78.8	73.3
% at 12 months	44	NA	50.0	57.6	46.2
P value vs Placebo	< 0.001	0.014	NA	NA	NA
HR (95% CI)	0.69 (0.55–0.87) (sorafenib:placebo)	0.68 (0.50–0.93) sorafenib:placebo	0.92 (0.79, 1.06) lenvatinib:sorafenib	1.08 (0.82, 1.42) lenvatinib:sorafenib	0.86 (0.72, 1.02) lenvatinib: sorafenib
TTP (months)					
Median	5.5	2.8	3.7	5.6	3.6
95% CI	4.1–6.9	2.63–3.58	3.6–5.4	3.9–7.9	3.5–3.8
ORR (%)			9.2	10.8	8.5
CR	0	0	0.4	0.6	0.3
PR	2	3.3	8.8	10.2	8.2
SD	71	54.0	51.3	56.7	48.6
PD	NA	30.7	30.9	22.3	35.1

Clinical studies in special populations

N/A

Supportive study

Study E7080-J081-202: A Phase 1/2 Study of E7080 in patients with advanced hepatocellular carcinoma (HCC)

In the expansion component (Phase 2), the lenvatinib 12 mg dose (recommended Phase 2 dose) was tested in subjects with advanced HCC and hepatic function of CP scores of 5–6.

In total 46 subjects were enrolled. Subjects were permitted to receive up to 1 prior systemic therapy, including targeted therapy or transarterial infusion chemotherapy.

The expansion component was primarily designed to evaluate the efficacy (TTP based on independent review assessments using mRECIST in Per Protocol Population) and safety of lenvatinib at the recommended dose. Secondary efficacy endpoints included ORR, DCR, OS, and PFS based on mRECIST.

The Safety Analysis Set, FAS, PK Analysis Set and the PD Analysis Set were identical (N= 46). The PPS (N=41) excluded 5 subjects; 1 subject did not meet inclusion criterion #3 (baseline haematology and renal laboratory values), 3 subjects discontinued during the 2 cycles and 1 subject did not show ⩾75%

cumulative treatment compliance without regard to study drug interruption due to toxicity.

Table 57: Efficacy Results for Study 202 Phase 2 – Child Pugh Score 5 or 6, lenvatinib 12mg OD

Efficacy endpoint	Independent review	95% CI	Investigator assessment	95% CI
Median TTP by mRECIST in PPS Probability of progression at 6 months	7.4 months 44%	5.5, 9.4 30, 61	12.8 months 30.9%	7.2, 14.7 18.8, 48.0
Median TTP by mRECIST in FAS Probability of progression at 6 months	7.4 months 45.2%	5.5, 9.4 31.3, 61.9	12.8 months 32.2%	7.2, 14.7 20.1, 49.0
ORR in FAS DCR in FAS (CR, PR + SD≥8 weeks)	37.7% 78.3%	23.2, 52.5 63.6, 89.1	37.7% 82.6%	23.2,52.5 68.6,92.2
Median PFS for FAS	7.4 months	5.5, 9.4	12.8 months	7.2,14.0
Median OS for PPS 12-month OS rate	18.3 months 68.3%	12.7, 25.1 51.7, 80.2		
Median OS for FAS 12-month OS rate	18.65 months 67.4%	12.7, 25.1 51.9, 78.9		

PPS, N=41; FAS, N=46

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The main study E7080-G000-304 (REFLECT or Study 304) was a multi-centre, randomized, open-label, non-inferiority Phase 3 study to compare the efficacy and safety of lenvatinib versus sorafenib as a first-line systemic treatment in subjects with unresectable HCC.

For the main Study 304, sorafenib as comparator is acceptable in the first line treatment for advanced disease since it is the only medicine approved in this setting for systemic treatment and is considered as a standard of care.

The primary endpoint of OS is supported as the most relevant and unbiased measure of efficacy.

In view of non-inferiority design, several critical aspects were highlighted at the time of CHMP scientific advice, like internal validity, internal consistency and external validity. The enrolment of an adequate number of patients from EU population was advised.

The trial was well–conducted. Very few randomised subjects were not treated (3 in total) and the rate of major protocol deviations was low (2.5%) and balanced across the treatment arms.

Still, the trial was open-label, which always introduces the possibility of investigator bias in terms of adjudication of progression. Most subjects in both treatment arms received study drug until PD as stipulated in the protocol, but more had no progression at the time of treatment discontinuation in the lenvatinib than the sorafenib arm (97 vs. 60 in the TTP analysis, 66 vs 49 in the PFS analysis). This may be due to safety concerns as discussed later.

Patients were to have advanced/unresectable HCC suitable for palliative treatment but very advanced disease was excluded. Patients had stage BCLC B (multiple liver tumours) or BCLC C (portal vein invasion/ extrahepatic spread) HCC but with liver function adequately maintained – CP A (score of 5 or 6) and PS 0-1. Patients with very heavy liver involvement (≥50% occupation), clear invasion into the main

portal vein or bile duct, or any blood-enhancing treatment within 28 days of randomization were excluded. Patients could have received prior local therapy but not systemic therapy alone for advanced disease.

The comparability of the patient populations among Study 304 and the historical trials was evaluated. The geographical patient pool of the SHARP and the Asia-Pacific trials are comparable to the Western and the Asia-Pacific regions of the Study 304, respectively.

The overall patient populations of Study 304 and the historical SHARP and Asia Pacific trials were similar with regard to demographic and key disease characteristics.

The baseline demographics and disease characteristics of Study 304 were reasonably well matched between the 2 treatment groups for the overall population, except a greater proportion with baseline AFP >200 ng/ml in the lenvatinib arm and more subjects with underlying hepatitis C in the sorafenib arm.

With a higher threshold, the proportion of subjects with a baseline AFP concentration of ⩾400 ng/mL was 40.8% (195 subjects) in the lenvatinib arm and 34.7% (165 subjects) in the sorafenib arm. Both imbalances might favour the sorafenib arm.

The aetiology, course and prognosis of HCC differ by regions, with epidemiologic risk factors varying greatly. At the time of scientific advice the Applicant was requested to enrol at least one third of patients in the Western region.

In both the Asia-Pacific and Western regions, the proportion of subjects with baseline AFP levels ⩾200 ng/mL was greater in the lenvatinib than in the sorafenib arm, although the difference was greatest in the Western region: 48.9% vs 42.9%, respectively, for the Asia-Pacific, and 41.4% vs 31.8% for the Western region. Regarding the proportion of subjects with baseline hepatitis C, for lenvatinib vs. sorafenib this was 26.1% vs. 35.7% in the West (15.6% vs 21.9% Asia Pacific).

Still, other factors such as BCLC stage of disease were well balanced between the regions; BCLC C (advanced stage) was 78.3% vs. 82.8% for lenvatinib vs. sorafenib in the West and 78.2% vs. 79.6% for lenvatinib vs. sorafenib in the Asia-Pacific. The proportion with MVPI/ extrahepatic spread, one of the stratification factors, was requested by treatment group by region. MPVI/ EHS were shown to be well balanced between the treatment arms although a lower proportion of sorafenib compared with lenvatinib treated subjects had MPVI alone in the Western region. Subjects with MVPI/ EHS had a shorter median OS regardless of the treatment arm. Non-inferiority of lenvatinib vs. sorafenib was maintained for all subgroups of MVPI/ EHS.

The baseline characteristics of patients in the sorafenib arm were sufficiently similar to those of the historical sorafenib trials to allow cross-study comparison in terms of sorafenib efficacy to support the evaluation of non-inferiority in the current study.

Efficacy data and additional analyses

Efficacy results – primary endpoint

Non-inferiority of lenvatinib to sorafenib for OS, the primary endpoint of the study, has been convincingly demonstrated. The OS data are sufficiently mature (about 75%). However, superiority could not be shown (median OS 13.6 vs. 12.3 months for lenvatinib vs. sorafenib). The per protocol analysis was similar to the FAS, as were sensitivity analyses based on stratification factors in the CRF (rather than IxRS) and without stratification factors.

Subjects who were lost to follow-up were censored at the last date the subject was known to be alive, and subjects who remained alive were censored at the time of data cut-off.

The MAH indicated imbalances in the use of posttreatment anticancer therapy, as well as imbalances in some baseline factors (ie, AFP, HCV aetiology) in the sorafenib arm overall, appeared to have favoured sorafenib for OS, which resulted in a higher hazard ratio in the Western region.

At the end of study treatment, subjects on the sorafenib arm were naturally eligible for potential second-line trials specifically requiring enrollment of sorafenib failures and/or sorafenib-intolerant patients, while lenvatinib patients would be typically ineligible for such trials. Consequently, a higher proportion of subjects received post-study treatment with investigational anticancer drugs in the sorafenib arm (9.5%) vs lenvatinib (3.1%). These factors might favour the sorafenib arm, but no definitive conclusions can be made to this regard. Subgroup analyses for OS revealed that the effect of lenvatinib and sorafenib on OS was generally consistent across subgroups. Amongst the subgroup analyses, the only exception was the Western Region where the median OS for lenvatinib was 13.6 months compared to 14.2 months for sorafenib, resulting in an HR of 1.08 (95% CI: 0.82, 1.42). Still, this HR does not deviate far from 1.00 and the median OS difference is only 0.6 months.

Median OS for sorafenib in the Western region in Study 304 was higher than that in the full sorafenib trial population (12.3 months) and higher than the median OS in the historic SHARP trial (10.7 months), which was conducted in Western countries. Furthermore, the median OS of sorafenib in the Asia-Pacific region (11.0 months) in Study 304 was higher than the median OS of sorafenib in the historic Asia-Pacific trial (6.5 months; 95% CI: 5.6, 7.6). The possible reason for the higher OS of sorafenib in Study 304 compared to historical sorafenib studies may be the greater use of posttreatment anticancer therapies, as explained by the MAH.

Overall, the KM curves and HR are consistent with non-inferiority in OS for lenvatinib vs sorafenib in patients $\geqslant$ 75 years. The secondary efficacy endpoints favoured lenvatinib in this subgroup.

Efficacy results – secondary endpoints

The results of secondary analyses support those reported for primary analyses, however statistically significant differences in secondary endpoints do not appear to translate into the OS benefit, with potential underlying reasons discussed above.

Lenvatinib treatment resulted in improvement over sorafenib for PFS (median PFS, 7.4 vs 3.7 months, respectively; HR=0.66; 95% CI of 0.57, 0.77, P<0.00001) for this population of patients. Median follow-up time was 20.3 and 19.2 months for the lenvatinib and sorafenib arms, respectively. Median TTP with lenvatinib was longer than that of sorafenib: 8.9 months for lenvatinib versus 3.7 months for sorafenib (HR = 0.63; P<0.00001).

Taken together, PFS and TTP were the same for sorafenib but the benefit on progression was greater for lenvatinib in the TTP analysis (8.9 vs 3.7 months) where deaths before progression were not considered as an event compared to the PFS results (7.4 vs. 3.7 months).

Lenvatinib treatment significantly prolonged TTP compared to sorafenib. However, neither PFS benefit nor TTP benefit translated to OS improvement. The observed TTP in the lenvatinib arm was longer than the duration of treatment (5.7 months), while it was similar to the duration of treatment in the sorafenib arm (3.7 months).

The ORR by investigator assessment was increased for lenvatinib compared with sorafenib (24.1% vs. 9.2%) mainly due to an increase in the proportion of lenvatinib patients with PR (22.8 vs. 8.8%). This result included all responses; there was no consideration of confirmed responses, as tumour assessments were conducted every 8 weeks. The duration of response in responders was longer for sorafenib (11.2 vs. 7.3 months), albeit with overlapping 95% confidence intervals, whilst the proportion with durable stable disease (≥23 weeks) was higher for lenvatinib (34.9% vs. 29.2%). By IRR, the duration of objective response was 7.4 (5.6, 9.2) months in the lenvatinib arm and 15.8 (5.9, NE) months in the sorafenib

arm.

The ORR with lenvatinib in the Western region (21.0%, 95% CI: 14.6, 27.4) was consistent with that observed for the Asia-Pacific region (25.5%, (95% CI: 20.8, 30.3) and for the overall population (24.1%, 95% CI: 20.2, 27.9). The odds ratios were 2.18 (1.15, 4.11) for the Western region, 3.77 (95% CI: 2.36, 6.04) for the Asia-Pacific region, and 3.13 (95% CI: 2.15, 4.56) for the overall population.

The results of IIR using mRECIST or RECIST 1.1 both supported the results of the investigator-based assessments.

The PFS and TTP subgroup analysis consistently favoured lenvatinib. The only ORR subgroup that favoured sorafenib was alcohol but this involved a small number of patients with wide confidence intervals and PFS/ TTP still favoured lenvatinib.

The primary endpoint and key secondary endpoint results were similar in the lenvatinib arm per the 2 starting doses, as assessed based on body weight category (<60kg vs. ≥60kg). Lenvatinib dose was not adjusted based on change in body weight during treatment. Lenvatinib dose adjustments were performed only for individual subjects who experienced lenvatinib-related toxicity as pre-specified in the dose-modification section of the protocol.

PFS on sorafenib post lenvatinib in comparison to the other post lenvatinib therapies was investigated to assess whether sorafenib remains a useful option in this patient population (data not shown). There was no difference in PFS2 (based on the surrogate duration of next line therapy) between patients who received sorafenib compared with another therapy post progression on lenvatinib.

2.4.4. Conclusions on the clinical efficacy

The non-inferiority in terms of OS over sorafenib has been demonstrated for lenvatinib monotherapy. Secondary endpoints support the primary analysis.

2.5. Clinical safety

Introduction

The safety data for the new HCC indication are taken from Study 304 and from Study 202. Two sets are defined: The HCC randomized safety data coming from study 304, a randomized, sorafenib controlled trial and the All HCC Lenvatinib Safety Set that contain the data of 20 additional patients (4% of this last database). In absence of a placebo control arm, a third set of non HCC patients (monotherapy) is also used to contrast safety issues more likely linked to the disease and/or the patient condition.

The "HCC Randomized Safety Set" (N = 476)

This set corresponds to the study 304 safety data. In this study subjects with advanced/unresectable HCC were randomized and treated with either lenvatinib (476 patients; 12 mg or 8 mg QD by oral dosing) or sorafenib (475 patients; 400 mg BID by oral dosing) in a 1:1 ratio. The starting dose of lenvatinib was based on baseline BW: 12 mg QD for subjects with a BW of ⩾60 kg (325 pts) and 8 mg QD for subjects with a BW of <60 kg (151 pts). The cutoff date for the study 304 safety data was 13 Nov 2016.

The "All HCC Lenvatinib Safety Set" (N = 496)

This set corresponds to the data of study 304 (HCC Randomized Safety Set) to which have been added the safety data of 20 patients of study 202.

In Study 202, the maximum tolerated (MTD) was determined in subjects with Child-Pugh (CP) Class A (CP score of 5 to 6) and CP Class B. The MTD found for subjects with Child-Pugh Class A was 12 mg QD

and in an extension Phase 2, all subjects (CP Class A) were treated with this 12 mg dose of lenvatinib. However, only the safety data for the 20 subjects in Phase 2 who had baseline BW ⩾60 kg and received at least 1 dose of lenvatinib 12 mg QD (ie the dosing matching the recommendations for the sough indication) were included in the "All HCC Lenvatinib Safety Set". Safety information for the additional 26 subjects in Study 202 who took lenvatinib 12 mg QD but weighed <60 kg is presented in the Study 202 CSR.

The "Non-HCC Lenvatinib Monotherapy Safety Set" (N=1327)

This set includes all subjects who received at least 1 dose of lenvatinib monotherapy in the following 14 studies that evaluated various tumour types (including DTC and RCC): E7080-G000-201, -203, -204, -205 (only monotherapy arm), -206, 209, -303 (both Randomized and optional open-label) and -398; E7080-J081-105 and – 208; E7080-A001-102; E7080-E044-101 and -104; E7080-703.

In this safety set, 1130/1327 (85%) subjects received a lenvatinib starting dose of 24 mg QD and an additional 7 subjects received a total daily dose of 24 mg (12 mg BID); the remaining subjects were enrolled in dose-finding studies and received a range of lenvatinib starting doses of 0.2 to 32 mg daily (Appendix 1). The safety data cutoff date was 01 Sep 2016 for ongoing studies; for studies completed before 01 Sep 2016, their respective completion dates were used.

Table 58: Number of HCC patients exposed

	HCC Patients enrolled	HCC Patients exposed	HCC Patients exposed to 8 - 12 mg lenvatinib	HCC Patients with ≥ 1 year safety data
Placebo-controlled	-	-	-	-
Active -controlled ("HCC randomized safety set")	478	476	476	109
Open studies	ND	66	20 (*)	7 (*)
Post marketing		2208		
Compassionate use		ND		
total ("All HCC Lenvatinib Safety Set")			496	116 (**)

(*) overall 63 HCC patients were exposed to 8 or 12 mg in study 20. However only 20 fitted the inclusion criterions for body weight and Child-Plough score of A and were included in the safety analysis. Sources: table 2.7.4-4 of SCS.

Patient exposure

In the Study 304, 51% of the subjects on the 8 mg lenvatinib dose and 36% of those on the 12 mg lenvatinib dose received 100% of their planned starting dosage (overall 41% of subjects in the lenvatinib arm). In addition 24% of patients on the 8 mg lenvatinib dose and 30% of patients on the 12 dose received at least 80% of the planned dosing (overall 27.7% for the lenvatinib arm). Thus 75% (8 mg group) and 66% (12 mg group) of patients received at least 80% of the planned dose. Three subjects received accidentally higher than planned doses (2 patients received once 24 mg of lenvatinib and one patient received one dose of 120 mg).

In the sorafenib arm, 33.9% of subjects received 100% of their planned dosage; an additional 31.2% received at least 80% of the planned dosage. Overall 65 % of the patients received at least 80% of the planned dosage but more patients received less than 60% of the planned dosage than in the lenvatinib arm.

Regarding dose intensity, the patients received on 'average' 87.5% of the planned dose in the lenvatinib arm and 83% of the planned dose in the sorafenib arm. In both treatment arms, exposure (ie, dose intensity) versus planned dose was high, and the percentage of planned dose received was similar between the 2 arms or slightly higher for lenvatinib.

Table 59: Study Drug Extent of Exposure – HCC Randomized, All HCC Lenvatinib, and Non-HCC Lenvatinib Monotherapy Safety Sets

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
	Lenvatinib 8 or 12 mg (N=476) n (%)	Sorafenib 800 mg (N=475) n (%)	Lenvatinib 8 or 12 mg (N=496) n (%)	(N=1327) n (%)
Duration of Treatment[a] (months)				
n	476	475	496	1327
Mean (SD)	8.2 (7.04)	6.0 (6.47)	8.2 (6.99)	**11.3** (14.10)
Median	5.7	3.7	5.9	5.5
Q1, Q3	2.9, 11.1	1.8, 7.4	3.0, 11.2	1.9, 14.5
Min, Max	0.0, 35.0	0.1, 38.7	0.0, 35.0	0.0, 125.1
Duration of Treatment (months), n (%)				
0 - <1	39 (8.2)	31 (6.5)	41 (8.3)	163 (12.3)
1 - <2	50 (10.5)	124 (26.1)	51 (10.3)	208 (15.7)
2 - <4	94 (19.7)	114 (24.0)	95 (19.2)	206 (15.5)
4 - <6	59 (12.4)	53 (11.2)	62 (12.5)	153 (11.5)
6 - <8	46 (9.7)	47 (9.9)	47 (9.5)	81 (6.1)
8 - <12	79 (16.6)	45 (9.5)	84 (16.9)	140 (10.6)
12 - <18	58 (12.2)	28 (5.9)	64 (12.9)	96 (7.2)
>=18	51 (10.7)	33 (6.9)	52 (10.5)	280 (21.1)
No. of Subject-Years[b]	324.2	239.1	340.0	1244.7
Total Dose (mg) Per Subject				
n	476	475	496	1327
Mean (SD)	2282.5 (2167.04)	121396.0 (142550.76)	2305.6 (2167.92)	5301.9 (6541.03)
Median	1578.0	66200.0	1616.0	2764.0
Q1, Q3	679.0, 3254.0	42000, 148000	680.0, 3303.0	1128, 6672
Min, Max	24.0, 11964.0	1400, 916800	24, 11964	1.6, 44905.5
Dose Intensity (mg/day/Subject)				
n	476	475	496	1327
Mean (SD)	9.4 (5.71)	663.8 (173.15)	9.4 (5.62)	17.9 (5.76)
Median	8.9	771.4	8.9	19.1
Q1, Q3	7.9, 12.0	514.6, 800.0	7.9, 12.0	13.5, 24.0
Min, Max	1.7, 120.0	126.3, 800.0	1.7, 120.0	0.2, 32.0
Received Dose as Percentage of Planned Starting Dose				
n	476	475	496	1327
Mean (SD)	87.5 (46.40)	83.0 (21.64)	87.2 (45.64)	78.3 (21.77)
Median	98.2	96.4	97.7	84.1
Q1, Q3	73.5, 100	64.3, 100.0	72.8, 100.0	60.5, 100.0
Min, Max	14.4, 1000	15.8, 100.0	14.4, 1000	2.8, 106.2
<60%	59 (12.4)	106 (22.3)	62 (12.5)	320 (24.1)
60% - <70%	42 (8.8)	24 (5.1)	47 (9.5)	141 (10.6)
70% - <80%	45 (9.5)	36 (7.6)	48 (9.7)	127 (9.6)
80% - <90%	41 (8.6)	30 (6.3)	42 (8.5)	185 (13.9)
90% - <100%	91 (19.1)	118 (24.8)	94 (19.0)	172 (13.0)
=100%	195 (41.0)	161 (33.9)	200 (40.3)	374 (28.2)
>100%	3 (0.6)	0 (0.0)	3 (0.6)	8 (0.6)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies).

HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; max = maximum; min = minimum; Q1, Q3 = first, third quartiles; QD = once daily; SD = standard deviation.

a: Duration of treatment (months) = (Date of last dose of study drug -Date of first dose of study drug + 1)/30.4375.
b: Number of subject-years = Sum of all years received by all subjects based on treatment duration.

Table 60: Subject Exposure by Subgroup – HCC Randomized, All HCC Lenvatinib, and Non-HCC Lenvatinib Monotherapy Safety Set

	HCC Randomized Safety Set				All HCC Lenvatinib Safety Set		Non-HCC Lenvatinib Monotherapy Safety Set	
	Lenvatinib 8 or 12 mg (N=476) n (%)		Sorafenib 800 mg (N=475) n (%)		Lenvatinib 8 or 12 mg (N=496) n (%)		Lenvatinib (N=1327) n (%)	
Subgroup	Number of Subjects n	Median Duration Months (a*)	Number of Subjects n	Median Duration Months (a*)	Number of Subjects n (%)	Median Duration Months (a*)	Number of Subjects n (%)	Median Duration Months (a*)
Total, n (%)	476	5.7	475	3.7	496	5.9	1327	5.5
Sex								
Male	403	6.0	400	3.7	423 (85%)	6.4	666 (50%)	5.5
Female	73	5.6	75	3.9	73 (15%)	5.6	661 (50%)	5.4
Age								
<65 years	269	6.0	282	3.6	283 (57%)	6.5	833 (63%)	5.6
≥65 -<75 years	150	5.7	126	4.0	155 (31%)	5.7	379 (29%)	5.3
≥75 years	57	5.6	67	3.7	58 (12%)	5.6	115 (9%)	3.5
Region								
Asia-Pacific	321	5.7	319	3.5	341 (69%)	5.7	237 (18%)	8.9
Western regions	155	6.2	156	4.6	155 (31%)	6.2	1090 (82%)	4.7
Race Group								
Asian	333	5.7	325	3.6	353 (71%)	5.7	188 (14%)	7.4
White	134	6.5	141	4.7	134 (27%)	6.5	1088 (82%)	5.0
Black or African American	7	2.9	6	2.9	7 (1%)	2.9	27 (2%)	6.2
American Indian or Alaska Native	1	7.4	0	-	1 (0%)	7.4	2 (0%)	11.9
Native Hawaiian or Other Pacific Islander	0	-	1	4.0	0	-	4 (0%)	7.0
Other	1	3.4	2	2.5	1 (0%)	3.4	18 (1%)	3.3
ECOG PS								
0	304	6.5	301	3.7	320 (65%)	6.9	542 (41%)	8.3
≥1	172	5.5	174	3.7	176 (35%)	5.5	556 (42%)	5.5

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD.

Percentages are based on total number of subjects in the corresponding safety set within the relevant treatment group. ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; PS = performance status; QD = once daily.

a: Duration of treatment (months) = (Date of last dose of study drug - Date of first dose of study drug + 1)/30.4375.

Table 61: Study 304 Extent of Exposure to Study Treatment including by lenvatinib dose

	Lenvatinib			Sorafenib
	8 mg [a] (N = 151)	12 mg [a] (N = 325)	Total (N = 476)	400 mg bd (N = 475)
Duration of Treatment [b] (months)				
Mean (SD)	7.6 (6.47)	8.5 (7.27)	8.2 (7.04)	6.0 (6.47)
Median	5.6	6.3	**5.7**	3.7
Q1, Q3	2.4, 11.0	3.2, 12.0	2.9, 11.1	1.8, 7.4
Min, Max	0.1, 33.7	0.0, 35.0	0.0, 35.0	0.1, 38
Duration of Treatment (months), n (%)				
0 -<1	15 (9.9)	24 (7.4)	39 (8.2)	31 (6.5)
1 -<2	15 (9.9)	35 (10.8)	50 (10.5)	**124 (26.1)**
2 -<4	34 (22.5)	60 (18.5)	94 (19.7)	114 (24.0)
4 -<6	17 (11.3)	42 (12.9)	59 (12.4)	53 (11.2)
6 -<8	10 (6.6)	36 (11.1)	46 (9.7)	47 (9.9)
8 -<12	29 (19.2)	50 (15.4)	**79 (16.6)**	45 (9.5)
12 -<18	19 (12.6)	39 (12.0)	**58 (12.2)**	28 (5.9)
≥18	12 (7.9)	39 (12.0)	**51 (10.7)**	33 (6.9)
No. of subject months[c]	1141.3	2748.9	3890.2	2869.1
Total Dose (mg) per Subject				
Mean	1609.5	2595.2	2282.5	121396.0
(SD)	(1497.01)	(2353.30)	(2167.04)	(142550.76)
Median	1012.0	1812.0	1578.0	66200.0
Q1	496.0,	768.0,	679.0,	42000.0,
Q3	2256.0	3648.0	3254.0	148000.0
Min, Max	24.0, 8208.0	48.0, 11964.0	24.0, 11964.0	1400.0, 916800
Dose Intensity (mg/day/subject)				
Mean (SD)	7.0 (1.59)	10.5 (6.54)	9.4 (5.71)	663.8 (173.1)
Median	8.0	11.5	8.9	771.4
Q1, Q3	6.3, 8.0	8.7, 12.0	7.9, 12.0	514.6, 800.0
Min, Max	2.1, 8.0	1.7, 120.0	1.7, 120.0	126.3, 800.0
Percentage of Planned Starting Dose Received [d]				
Mean (SD)	87.7(19.84)	87.5 (54.53)	87.5 (46.40)	83.0 (21.64)
Median	100.0	96.0	98.2	96.4
Q1, Q3	78.6, 100.0	72.7, 100.0	73.5, 100.0	64.3, 100.0
Min, Max	25.8, 100.0	14.4, 1000.0[e]	14.4, 1000.0[e]	15.8, 100.0
<60%	21 (13.9)	38 (11.7)	59 (12.4)	**106 (22.3)**
60% -<70%	8 (5.3)	34 (10.5)	42 (8.8)	24 (5.1)
70% -<80%	9 (6.0)	36 (11.1)	45 (9.5)	36 (7.6)
80% -<90%	10 (6.6)	31 (9.5)	41 (8.6)	30 (6.3)
90% -<100%	26 (17.2)	65 (20.0)	91 (19.1)	**118 (24.8)**
100%	**77 (51.0)**	118 (36.3)	**195 (41.0)**	161 (33.9)
>100%	0 (0.0)	3 (0.9)	3 (0.6)	0 (0.0)

Percentages are based on the total number of subjects within the relevant treatment group in the Safety Analysis Set.
Dose Intensity = Total dose received during the study/(Date of last dose of study drug -Date of first dose of study drug + 1).
Max = maximum; Min = minimum; Q1, Q3 = first quartile, third quartile; SD = standard deviation.

a: 8 mg and 12 mg were the starting doses of lenvatinib based on the subjects' body weight (<60 kg, ≥60 kg) at Baseline
b: Duration of treatment (months) = (Date of last dose of study drug -Date of first dose of study drug + 1) ÷ 30.4375.
c: Number of subject-months = Sum of all months that all subjects received study drug based on treatment duration.
d: Defined as the actual dose received as a percentage of planned starting dose (without interruption or reduction). Calculated as cumulative total dose divided by (planned starting daily dose × treatment duration in days).
e: One lenvatinib-treated subject mistakenly took a single 120-mg dose rather than 12 mg on Day 1.

Adverse events

Table 62: Overview of Treatment-emergent Adverse Events – Study 304 Safety Analysis Set

	Lenvatinib			Sorafenib
	8 mg [a] (N = 151)	12 mg [a] (N = 325)	Total (N = 476)	(N = 475)
Subject with Any TEAE	151 (100.0)	319 (98.2)	470 (98.7)	472 (99.4)
Subject with Any Related TEAE	143 (94.7)	304 (93.5)	447 (93.9)	452 (95.2)

Number of Subjects with TEAE with Worst CTCAE Grade [b] of				
≥3	100 (66.2)	257 (**79.1**)	357 (**75.0**)	316 (66.5)
3	74 (49.0)	186 (57.2)	260 (54.6)	248 (52.2)
4	12 (7.9)	24 (7.4)	36 (7.6)	32 (6.7)
5	14 (9.3)	47 (14.5)	61 (**12.8**)	36 (7.6)
Number of Subjects with Related TEAE with Worst CTCAE Grade [b] of				
≥3	70 (46.4)	200 (**61.5**)	270 (**56.7**)	231 (48.6)
3	61 (40.4)	178 (**54.8**)	239 (50.2)	209 (44.0)
4	6 (4.0)	14 (4.3)	20 (4.2)	18 (3.8)
5	3 (2.0)	8 (2.5)	11 (2.3)	4 (0.8)
Number of Subjects with Any Serious AE [c]	58 (38.4)	147 (45.2)	205 (**43.1**)	144 (30.3)
Number of Subjects with Any Fatal SAE [d]	14 (9.3)	47 (14.5)	61 (**12.8**)	36 (7.6)
Number of Subjects with Nonfatal SAEs	54 (35.8)	135 (41.5)	189 (**39.7**)	128 (26.9)
Number of Subjects with [c]				
TEAEs Leading to Study Drug Withdrawal	33 (21.9)	61 (18.8)	94 (**19.7**)	69 (14.5)
TEAEs Leading to Study Drug Dose Reduction	43 (28.5)	141 (**43.4**)	184 (38.7)	185 (38.9)
TEAEs Leading to Study Drug Interruption	72 (47.7)	176 (54.2)	248 (**52.1**)	193 (40.6)
TEAEs Leading to Study Drug Dose Reduction or Interruption	81 (53.6)	213 (**65.5**)	294 (61.8)	264 (55.6)

Data cutoff date: 13 Nov 2016. Percentages are based on the total number of subjects within the relevant treatment group in the Safety Analysis Set. For each row category, subjects with 2 or more TEAEs in that category were counted only once.

Related TEAEs include TEAEs that were considered by the investigator to be possibly or probably related to study drug or TEAEs with a missing causality. AE = adverse event; CTCAE = Common Terminology Criteria for AEs; TEAE = treatment-emergent AE.

a: 8 mg and 12 mg were the lenvatinib starting doses based on the subjects' body weight (<60 kg, ≥60 kg) at Baseline.

b: Adverse events were graded using CTCAE version 4.0.

c: Subjects may be counted in more than 1 subcategory.

d: Category includes 70 subjects who had a TEAE ongoing at the time of death due to disease progression or whose cause of death was unknown.

Exposure was 1.5-times longer with lenvatinib than with sorafenib. Therefore, TEAEs have also been adjusted by treatment duration. As shown in the table below the rate of TEAE episodes adjusted for treatment duration was 18.89 episodes/SY and 19.73 episodes/SY for the lenvatinib and sorafenib arms, respectively.

Table 63: Overview of Treatment-emergent Adverse Events Adjusted by Treatment Duration – Study 304 Safety Set

	Lenvatinib			Sorafenib
	8 mg[a] (N = 151) Total Duration= 95.1 years n (AE Rate)	12 mg[a] (N = 325) Total Duration= 229.1 years n (AE Rate)	Total (N = 476) Total Duration= 324.2 years n (AE Rate)	(N = 475) Total Duration= 239.1 years n (AE Rate)
Any TEAE Episodes Adjusted by SY	1737(18.26)	4387 (19.15)	6124 (18.89)	4718 (19.73)
Related TEAE Episodes Adjusted by SY	974 (10.24)	2572 (11.23)	3546 (10.94)	2865 (11.98)
Grade 3, 4 or 5 TEAE Episodes Adjusted by SY	278 (2.92)	745 (3.25)	1023 (3.16)	795 (3.33)
Related Grade 3, 4 or 5 TEAE Episodes Adjusted by SY	126 (1.32)	391 (1.71)	517 (1.59)	430 (1.80)
Any Serious AE Episodes Adjusted by SY	113 (1.19)	296 (1.29)	409 (1.26)	232 (0.97)
Fatal SAE Episodes Adjusted by SY: [b]	14 (0.15)	47 (0.21)	61 (0.19)	36 (0.15)
Fatal SAE not Related to PD	4 (0.04)	15 (0.07)	19 (0.06)	8 (0.03)
Fatal SAE Related to PD [c]	10 (0.11)	32 (0.14)	42 (0.13)	28 (0.12)
Nonfatal SAE Episodes Adjusted by SY	108 (1.14)	271 (1.18)	379 (1.17)	207 (0.87)

Data cutoff date: 13 Nov 2016. Related TEAEs include TEAEs that were considered by the investigator to be possibly or probably related to study drug or TEAEs with a missing causality. Adverse events were graded using CTCAE version 4.0. An AE episode was based on MedDRA LLT. A single episode was defined from onset through resolution or, if ongoing, to the end of reporting period. Subjects with fatal SAEs may also have reported nonfatal SAEs.

Total Duration = sum of treatment time (in years) for all subjects in each treatment group (including dose interruption). AE Rate (episode/subject-year) = total occurrence of AE episode (n) divided by total duration in each treatment group. AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; LLT = low level term; MedDRA = Medical Dictionary for Regulatory Activities; PD = disease progression; SAE = serious adverse events; SY = subject-year; TEAE = treatment-emergent adverse event.

a: 8 mg and 12 mg were the lenvatinib starting doses based on the subjects' body weight (<60 kg, ≥60 kg) at Baseline.

b: Fatal AE episodes are counted only once per subject, if more than 1 fatal AE was reported for the same subject.

c: Includes all subjects who had a TEAE ongoing at the time of death due to disease progression.

Common AEs

Table 64: TEAEs Occurring in ≥10% of Subjects in the HCC Safety Sets by MedDRA SOC and PT – HCC Randomized, All HCC Lenvatinib, and Non-HCC Lenvatinib Monotherapy Safety Sets

	Subject Incidence			
	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
MedDRA System Organ Class Preferred Term	Lenvatinib 8 or 12 mg (N=476) n (%)	Sorafenib 800 mg (N=475) n (%)	Lenvatinib 8 or 12 mg (N=496) n (%)	Lenvatinib (N=1327) n (%)
Subjects with Any TEAEs	*470 (98.7)*	*472 (99.4)*	*490 (98.8)*	*1316 (99.2)*
Endocrine disorders	84 (17.6)	12 (2.5)	86 (17.3)	193 (14.5)
Hypothyroidism	78 (16.4)	8 (1.7)	79 (15.9)	162 (12.2)
Gastrointestinal disorders	371 (77.9)	357 (75.2)	390 (78.6)	1137 (85.7)
Diarrhoea	184 (38.7)	220 (46.3)	189 (38.1)	684 (51.5)
Nausea	93 (19.5)	68 (14.3)	103 (20.8)	568 (42.8)
Abdominal pain	81 (17.0)	87 (18.3)	85 (17.1)	281 (21.2)
Vomiting	77 (16.2)	36 (7.6)	82 (16.5)	443 (33.4)
Constipation	76 (16.0)	52 (10.9)	84 (16.9)	360 (27.1)
Ascites	68 (14.3)	44 (9.3)	71 (14.3)	11 (0.8)
Abdominal pain upper	58 (12.2)	40 (8.4)	59 (11.9)	195 (14.7)
Stomatitis	45 (9.5)	56 (11.8)	50 (10.1)	371 (28.0)
General disorders and administration site conditions	284 (59.7)	243 (51.2)	300 (60.5)	1009 (76.0)
Fatigue	141 (29.6)	119 (25.1)	152 (30.6)	631 (47.6)
Pyrexia	69 (14.5)	63 (13.3)	71 (14.3)	164 (12.4)
Oedema peripheral	66 (13.9)	33 (6.9)	72 (14.5)	220 (16.6)
Asthenia	54 (11.3)	48 (10.1)	54 (10.9)	212 (16.0)
Investigations	304 (63.9)	255 (53.7)	320 (64.5)	742 (55.9)
Weight decreased	147 (30.9)	106 (22.3)	151 (30.4)	451 (34.0)
Platelet count decreased	87 (18.3)	58 (12.2)	90 (18.1)	62 (4.7)
Blood bilirubin increased	71 (14.9)	63 (13.3)	71 (14.3)	34 (2.6)
Aspartate aminotransferase increased	65 (13.7)	80 (16.8)	68 (13.7)	100 (7.5)
Alanine aminotransferase increased	53 (11.1)	52 (10.9)	55 (11.1)	106 (8.0)
Metabolism and nutrition disorders	220 (46.2)	196 (41.3)	235 (47.4)	818 (61.6)
Decreased appetite	162 (34.0)	127 (26.7)	173 (34.9)	583 (43.9)
Musculoskeletal and connective tissue disorders	180 (37.8)	132 (27.8)	190 (38.3)	829 (62.5)
Back pain	50 (10.5)	31 (6.5)	53 (10.7)	240 (18.1)
Nervous system disorders	163 (34.2)	106 (22.3)	172 (34.7)	768 (57.9)
Headache	46 (9.7)	38 (8.0)	51 (10.3)	420 (31.7)
Renal and urinary disorders	151 (31.7)	84 (17.7)	162 (32.7)	588 (44.3)
Proteinuria	117 (24.6)	54 (11.4)	128 (25.8)	463 (34.9)
Respiratory, thoracic and mediastinal disorders	213 (44.7)	148 (31.2)	225 (45.4)	858 (64.7)
Dysphonia	113 (23.7)	57 (12.0)	121 (24.4)	412 (31.0)
Skin and subcutaneous tissue disorders	237 (49.8)	353 (74.3)	257 (51.8)	744 (56.1)
PPE	128 (26.9)	249 (52.4)	144 (29.0)	259 (19.5)
Rash	46 (9.7)	76 (16.0)	51 (10.3)	186 (14.0)
Alopecia	14 (2.9)	119 (25.1)	16 (3.2)	106 (8.0)
Vascular disorders	214 (45.0)	152 (32.0)	231 (46.6)	854 (64.4)
Hypertension	201 (42.2)	144 (30.3)	218 (44.0)	775 (58.4)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Display is in decreasing order of AE rate of PTs in the lenvatinib group of the HCC Randomized Safety Set. Adverse event terms were coded using MedDRA version 19.1. Subject Incidence: Subjects with 2 or more TEAEs reported in the same SOC or PT were counted only once. Percentages are based on the total number of subjects in the corresponding safety set within the relevant treatment group. Treatment Exposure-adjusted Rate: AE episode is based on MedDRA LLT. A single episode is defined from onset through resolution or, if ongoing, to the end of reporting period. (*) PPE: Palmar-plantar erythrodysaesthesia syndrome AE = adverse event; HCC = hepatocellular carcinoma; PPE = Palmar-plantar erythrodysaesthesia syndrome;

ISS = Integrated Summary of Safety; LLT = low level term; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SOC = system organ class.

Table 65: TEAEs Occurring in ≥ 10% of Subjects in Either Treatment Arm of study 304, by PT

Preferred Term	Lenvatinib (N = 476)	Sorafenib (N = 475)
Subjects with Any TEAEs	*470 (98.7)*	*472 (99.4)*
Hypertension	201 (**42.2**)	144 (30.3)
Diarrhoea	184 (38.7)	220 (**46.3**)
Decreased appetite	162 (**34.0**)	127 (26.7)
Weight decreased	147 (**30.9**)	106 (22.3)
Fatigue	141 (29.6)	119 (25.1)
Palmar-plantar erythrodysaesthesia syndrome	128 (26.9)	249 (**52.4**)
Proteinuria	117 (**24.6**)	54 (11.4)
Dysphonia	113 (**23.7**)	57 (12.0)
Nausea	93 (**19.5**)	68 (14.3)
Platelet count decreased	87 (**18.3**)	58 (12.2)
Abdominal pain	81 (17.0)	87 (18.3)
Hypothyroidism	78 (**16.4**)	8 (1.7)
Vomiting	77 (**16.2**)	36 (7.6)
Constipation	76 (**16.0**)	52 (10.9)
Blood bilirubin increased	71 (14.9)	63 (13.3)
Pyrexia	69 (14.5)	63 (13.3)
Ascites	68 (**14.3**)	44 (9.3)
Oedema peripheral	66 (**13.9**)	33 (6.9)
Aspartate aminotransferase increased	65 (13.7)	80 (16.8)
Abdominal pain upper	58 (12.2)	40 (8.4)
Asthenia	54 (11.3)	48 (10.1)
Alanine aminotransferase increased	53 (11.1)	52 (10.9)
Back pain	50 (**10.5**)	31 (6.5)
Rash	46 (9.7)	76 (**16.0**)
Stomatitis	45 (9.5)	56 (11.8)
Alopecia	14 (2.9)	119 (**25.1**)

Data cutoff date: 13 Nov 2016. Percentages are based on the total number of subjects within the relevant treatment group in the Safety Analysis Set. Display is in decreasing order of frequency of TEAEs in the lenvatinib total group. Subjects with 2 or more TEAEs in the same preferred term were counted only once. Adverse Event terms were coded using MedDRA version 19.1. MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event. a: 8 mg and 12 mg were the lenvatinib starting doses based on the subjects' body weight (<60 kg, ≥60 kg) at Baseline.

Severe (Grade 3 and 4) TEAEs

A summary of CTCAE grade 3 or 4 TEAEs occurring in ⩾1% of subjects in any group of the safety sets is presented in the Table 66 below.

Grade 3 or higher TEAEs occurred in 357 subjects (75%) in the lenvatinib arm and 316 subjects (66.5%) in the sorafenib arm.

Adjusted by treatment duration, the rate of Grade ⩾3 TEAEs in the lenvatinib and sorafenib arms was 3.16 and 3.33 episodes/SY, respectively.

There were higher incidences of Grade 3 WBC (2.4% vs 0.2%) and neutrophil (2.6% vs 0.2%) decreased counts in the All HCC than in the Non-HCC Safety Set.

Table 66: Grade 3 or 4 TEAEs That Occurred in ≥1% of Subjects in any Group in the HCC Safety Sets Adjusted by Treatment Exposure, by Preferred Term

	HCC Randomized Safety Set (Study 304)				All HCC Lenvatinib Safety Set			Non-HCC Monotherapy Safety Set
	Lenvatinib 8 or 12 mg (N=476) Total Exposure = 324.2 years n (AE Rate)		Sorafenib 800 mg (N=475) Total Exposure = 239.1 years n (AE Rate)		Lenvatinib 8 or 12 mg (N=496) Total Exposure = 340 years n (AE Rate)			Lenvatinib (N=1327) Total Exposure = 1244.7 years n (AE Rate)
Preferred Term	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Subjects with Any Grade 3 or 4 TEAEs	887 (2.74)	64 (0.20)	704 (2.94)	53 (0.22)	935 (2.75)	64 (0.19)	2874 (2.31)	198 (0.16)
Hypertension	124 (0.38)	0	74 (0.31)	0	138 (0.41)	0	509 (0.41)	6 (<0.01)
Weight decreased	37 (0.11)	0	14 (0.06)	0	38 (0.11)	0	93 (0.07)	0
Hepatic encephalopathy	**29 (0.09)**	2 (<0.01)	8 (0.03)	0	33 (0.10)	2 (<0.01)	0	0
Platelet count decreased	29 (0.09)	0	14 (0.06)	2 (<0.01)	35 (0.10)	0	5 (<0.01)	0
Proteinuria	**28 (0.09**)	0	8 (0.03)	0	33 (0.10)	0	140 (0.11)	1 (<0.01)
Blood bilirubin increased	27 (0.08)	**7 (0.02)**	22 (0.09)	2 (<0.01)	27 (0.08)	7 (0.02)	4 (<0.01)	0
Decreased appetite	**24 (0.07)**	0	6 (0.03)	0	24 (0.07)	0	50 (0.04)	0
Diarrhoea	24 (0.07)	0	24 (0.10)	0	25 (0.07)	0	117 (0.09)	0
Aspartate aminotransferase increased	22 (0.07)	3 (<0.01)	**36 (0.15)**	**6 (0.03)**	22 (0.06)	3 (<0.01)	11 (<0.01)	1 (<0.01)
Gamma-glutamyltransferase increased	21 (0.06)	**6 (0.02)**	16 (0.07)	**4 (0.02)**	21 (0.06)	6 (0.02)	9 (<0.01)	0
Hyponatraemia	**20 (0.06)**	3 (<0.01)	8 (0.03)	1 (<0.01)	21 (0.06)	3 (<0.01)	41 (0.03)	9 (<0.01)
Ascites	18 (0.06)	0	15 (0.06)	0	18 (0.05)	0	5 (<0.01)	0
Fatigue	18 (0.06)	0	17 (0.07)	0	18 (0.05)	0	137 (0.11)	2 (<0.01)
Neutrophil count decreased	**18 (0.06)**	3 (<0.01)	8 (0.03)	3 (0.01)	19 (0.06)	3 (<0.01)	2 (<0.01)	0
Anaemia	17 (0.05)	0	17 (0.07)	0	17 (0.05)	0	30 (0.02)	0
Alanine aminotransferase increased	16 (0.05)	0	12 (0.05)	4 (0.02)	16 (0.05)	0	15 (0.01)	0
Asthenia	15 (0.05)	0	11 (0.05)	0	15 (0.04)	0	65 (0.05)	1 (<0.01)
Palmar-plantar erythrodysaesthesia syndrome	15 (0.05)	0	**63 (0.26)**	0	16 (0.05)	0	28 (0.02)	0
Lymphocyte count decreased	13 (0.04)	1 (<0.01)	6 (0.03)	0	13 (0.04)	1 (<0.01)	9 (<0.01)	1 (<0.01)
White blood cell count decreased	13 (0.04)	0	10 (0.04)	1 (<0.01)	13 (0.04)	0	4 (<0.01)	0
Blood alkaline phosphatase increased	11 (0.03)	0	7 (0.03)	0	11 (0.03)	0	9 (<0.01)	0
Lipase increased	10 (0.03)	4 (0.01)	8 (0.03)	3 (0.01)	10 (0.03)	4 (0.01)	23 (0.02)	6 (<0.01)
Abdominal pain upper	9 (0.03)	0	6 (0.03)	0	9 (0.03)	0	9 (<0.01)	0
Thrombocytopenia	9 (0.03)	1 (<0.01)	6 (0.03)	0	18 (0.05)	1 (<0.01)	20 (0.02)	4 (<0.01)

Abdominal pain	8 (0.02)	0	**14 (0.06)**	0	8 (0.02)	0	40 (0.03)	3 (<0.01)
Dyspnoea	8 (0.02)	0	3 (0.01)	0	8 (0.02)	0	38 (0.03)	2 (<0.01)
Hepatic function abnormal	8 (0.02)	0	**9 (0.04)**	0	8 (0.02)	0	7 (<0.01)	0
Neutropenia	7 (0.02)	0	0	0	7 (0.02)	0	15 (0.01)	1 (<0.01)
Oesophageal varices haemorrhage	7 (0.02)	1 (<0.01)	4 (0.02)	0	7 (0.02)	1 (<0.01)	0	0
Hyperkalaemia	6 (0.02)	0	1 (<0.01)	1 (<0.01)	6 (0.02)	0	8 (<0.01)	2 (<0.01)
Vomiting	6 (0.02)	0	5 (0.02)	0	6 (0.02)	0	36 (0.03)	1 (<0.01)
Electrocardiogram QT prolonged	5 (0.02)	0	7 (0.03)	0	5 (0.01)	0	14 (0.01)	0
Hyperbilirubinaemia	5 (0.02)	1 (<0.01)	1 (<0.01)	0	5 (0.01)	1 (<0.01)	4 (<0.01)	0
Jaundice cholestatic	5 (0.02)	3 (<0.01)	2 (<0.01)	1 (<0.01)	5 (0.01)	3 (<0.01)	0	0
Cancer pain	4 (0.01)	0	6 (0.03)	0	5 (0.01)	0	11 (<0.01)	0
Hepatic failure	4 (0.01)	1 (<0.01)	**9 (0.04)**	1 (<0.01)	4 (0.01)	1 (<0.01)	1 (<0.01)	0
Hypokalaemia	4 (0.01)	1 (<0.01)	**13 (0.05)**	0	4 (0.01)	1 (<0.01)	22 (0.02)	7 (<0.01)
Back pain	1 (<0.01)	0	5 (0.02)	0	1 (<0.01)	0	18 (0.01)	0
Jaundice	1 (<0.01)	0	5 (0.02)	0	1 (<0.01)	0	1 (<0.01)	0

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Display is in decreasing order of Grade 3 AE rate in the lenvatinib group of the HCC Randomized Safety Set. AE episode is based on MedDRA LLT. A single episode is defined from onset through resolution or, if ongoing, to the end of reporting period. Adverse Event terms were coded using MedDRA version 19.1. Total Exposure (SY) = sum of treatment duration (in years) for all subjects in each treatment group (including dose interruption). AE Rate (episode/SY) = total occurrence of TEAE episodes (n) divided by the total exposure (SY) for the specified treatment group. AE = adverse event; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; LLT = low level term; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SY = subject year; TEAE = treatment-emergent adverse event.

Table 67: TEAEs that Occurred in at Least 10% of Subjects in Either Treatment Arm by System Organ Class, Overall Incidence and Grade 3 and Above – Study 304

	Lenvatinib (N = 476) n (%)					Sorafenib (N = 475) n (%)				
System Organ Class	**Any Grade**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade ≥3**	**Any Grade**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade ≥3**
Gastrointestinal disorders	371 (77.9)	70 (14.7)	1 (0.2)	4 (0.8)	75 (15.8)	357 (75.2)	70 (14.7)	4 (0.8)	4 (0.8)	78 (16.4)
Investigations	304 (63.9)	127 (26.7)	23 (4.8)	0 (0.0)	150 (**31.5**)	255 (53.7)	99 (20.8)	22 (4.6)	0 (0.0)	121 (25.5)
General disorders and administration site conditions	284 (59.7)	40 (8.4)	1 (0.2)	7 (1.5)	48 (10.1)	243 (51.2)	33 (6.9)	0 (0.0)	4 (0.8)	37 (7.8)
Skin and subcutaneous tissue disorders	237 (49.8)	17 (3.6)	0 (0.0)	0 (0.0)	17 (3.6)	353 (74.3)	64 (13.5)	0 (0.0)	0 (0.0)	64 (**13.5**)
Metabolism and nutrition disorders	220 (46.2)	56 (11.8)	8 (1.7)	1 (0.2)	65 (**13.7**)	196 (41.3)	33 (6.9)	5 (1.1)	0 (0.0)	38 (8.0)
Vascular disorders	214 (45.0)	114 (23.9)	1 (0.2)	1 (0.2)	116 (**24.4**)	152 (32.0)	72 (15.2)	1 (0.2)	0 (0.0)	73 (15.4)
Respiratory, thoracic and mediastinal disorders	213 (44.7)	17 (3.6)	0 (0.0)	8 (1.7)	25 (5.3)	148 (31.2)	12 (2.5)	0 (0.0)	4 (0.8)	16 (3.4)
Musculoskeletal and connective tissue disorders	180 (37.8)	18 (3.8)	0 (0.0)	0 (0.0)	18 (3.8)	132 (27.8)	14 (2.9)	0 (0.0)	0 (0.0)	14 (2.9)
Nervous system disorders	163 (34.2)	34 (7.1)	4 (0.8)	9 (1.9)	47 (**9.9**)	106 (22.3)	14 (2.9)	5 (1.1)	1 (0.2)	20 (4.2)
Renal and urinary disorders	151 (31.7)	36 (7.6)	1 (0.2)	1 (0.2)	38 (**8.0**)	84 (17.7)	12 (2.5)	1 (0.2)	2 (0.4)	15 (3.2)
Infections and infestations	144 (30.3)	28 (5.9)	5 (1.1)	7 (1.5)	40 (8.4)	134 (28.2)	22 (4.6)	3 (0.6)	2 (0.4)	27 (5.7)
Hepatobiliary disorders	85 (17.9)	34 (7.1)	4 (0.8)	16 (3.4)	54 (11.3)	54 (11.4)	32 (6.7)	2 (0.4)	3 (0.6)	37 (7.8)
Endocrine disorders	84 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (2.5)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Blood and lymphatic system disorders	84 (17.6)	34 (7.1)	2 (0.4)	1 (0.2)	37 (7.8)	78 (16.4)	25 (5.3)	1 (0.2)	0 (0.0)	26 (5.5)
Psychiatric disorders	56 (11.8)	5 (1.1)	1 (0.2)	0 (0.0)	6 (1.3)	46 (9.7)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	51 (10.7)	12 (2.5)	3 (0.6)	13 (2.7)	28 (5.9)	57 (12.0)	16 (3.4)	0 (0.0)	16 (3.4)	32 (6.7)

Data cutoff date: 13 Nov 2016. Percentages are based on the total number of subjects within the relevant treatment group in the Safety Analysis Set. Display is in decreasing order of frequency of TEAEs in the 'Any Grade' column for the lenvatinib arm. Subjects with 2 or more TEAEs in the same System-Organ Class were counted only once.Adverse Event terms were coded using MedDRA version 19.1.Adverse events were graded using CTCAE version 4.0.
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Serious adverse event / deaths / other significant events

Serious Adverse Events

Table 68: SAEs (Fatal and Nonfatal) Occurring in ≥ 1% in any Group in the Safety Sets.

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
Preferred Term	**Lenvatinib 8 or 12 mg (N=476) n (%)**	**Sorafenib 800 mg (N=475) n (%)**	**Lenvatinib 8 or 12 mg (N=496) n (%)**	**Lenvatinib (N=1327) n (%)**
Subjects with Any SAEs	*205 (43.1)*	*144 (30.3)*	*210 (42.3)*	*713 (53.7)*
Hepatic encephalopathy	21 (4.4)	3 (0.6)	23 (**4.6**)	0
Hepatic failure	14 (2.9)	8 (1.7)	14 (**2.8**)	4 (0.3)
Ascites	12 (2.5)	11 (2.3)	12 (2.4)	2 (0.2)
Decreased appetite	11 (2.3)	2 (0.4)	11 (**2.2**)	17 (1.3)
Malignant neoplasm progression	10 (2.1)	14 (2.9)	10 (2.0)	12 (0.9)
Diarrhoea	8 (**1.7**)	2 (0.4)	8 (1.6)	18 (1.4)
Asthenia	7 (**1.5**)	1 (0.2)	7 (1.4)	18 (1.4)
Blood bilirubin increased	7 (1.5)	1 (0.2)	7 (**1.4**)	1 (0.1)
Jaundice cholestatic	7 (1.5)	3 (0.6)	7 (**1.4**)	0
Oesophageal varices haemorrhage	7 (**1.5**)	5 (1.1)	7 (1.4)	0
Sepsis	7 (**1.5**)	3 (0.6)	7 (1.4)	16 (1.2)
Abdominal pain	6 (1.3)	10 (2.1)	6 (1.2)	33 (**2.5**)
Pyrexia	6 (1.3)	5 (1.1)	6 (1.2)	13 (1.0)
Vomiting	6 (**1.3**)	0 (0.0)	6 (1.2)	30 (**2.3**)
Dyspnoea	5 (**1.1**)	2 (0.4)	5 (1.0)	29 (**2.2**)
General physical health deterioration	5 (**1.1**)	3 (0.6)	5 (1.0)	24 (**1.8**)
Pneumonia	5 (1.1)	4 (0.8)	5 (1.0)	48 (**3.6**)
Upper gastrointestinal haemorrhage	5 (1.1)	2 (0.4)	5 (**1.0**)	0
Back pain	2 (0.4)	5 (1.1)	2 (0.4)	11 (0.8)
Pathological fracture	2 (0.4)	5 (1.1)	2 (0.4)	5 (0.4)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Serious AEs include any AEs that met the criteria for seriousness, whether fatal or nonfatal. Display is in decreasing order of AE rate of preferred terms in the Lenvatinib group of the HCC Randomized Safety Set. Adverse event terms were coded using MedDRA version 19.1. Subject Incidence: Subjects with 2 or more TEAEs reported in the same PT term were counted only once. Percentages are based on the total number of subjects in the corresponding safety set within the relevant treatment group. AE Rate (episode/SY) = total occurrence of TEAE episodes (n) divided by the total exposure (SY) for the specified treatment group. AE = adverse event; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; LLT = low level term; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SAE = serious adverse event; SY = subject year; TEAE = treatment-emergent adverse event.

The SAEs reported were generally of comparable types to those in the Non-HCC Lenvatinib Monotherapy Safety Set, exception for hepatic-related SAEs.

Adjusted by treatment duration, the overall rate of SAEs was 1.26 episodes/SY for the lenvatinib arm and 0.97 episodes/SY for the sorafenib arm.

Table 69: Serious Treatment-Emergent Adverse Event Episodes Adjusted by Treatment Duration by Preferred Term and Region, Safety Analysis Set

	Asia-Pacific				Western Regions			
	Lenvatinib 8mg[a] (N = 130) Total Duration= 85.7years n (AE Rate)	Lenvatinib 12mg[a] (N = 191) Total Duration= 134.9years n (AE Rate)	Lenvatinib Total (N = 321) Total Duration= 220.5years n (AE Rate)	Sorafenib (N = 319) Total Duration= 150.2years n (AE Rate)	Lenvatinib 8mg[a] (N = 21) Total Duration= 9.5years n (AE Rate)	Lenvatinib 12mg[a] (N = 134) Total Duration= 94.2years n (AE Rate)	Lenvatinib Total (N = 155) Total Duration= 103.6years n (AE Rate)	Sorafenib (N = 156) Total Duration= 88.8years n (AE Rate)
All Serious TEAE Episodes	96 (1.12)	161 (1.19)	257 (1.17)	154 (1.03)	17 (1.80)	135 (1.43)	152 (1.47)	78 (0.88)
Hepatic encephalopathy	6 (0.07)	7 (0.05)	13 (0.06)	3 (0.02)	0 (0.0)	18 (0.19)	18 (0.17)	1 (0.01)
Ascites	1 (0.01)	10 (0.07)	11 (0.05)	11 (0.07)	0 (0.0)	3 (0.03)	3 (0.03)	2 (0.02)
Decreased appetite	4 (0.05)	6 (0.04)	10 (0.05)	2 (0.01)	1 (0.11)	1 (0.01)	2 (0.02)	0 (0.0)
Hepatic failure	5 (0.06)	4 (0.03)	9 (0.04)	4 (0.03)	0 (0.0)	5 (0.05)	5 (0.05)	4 (0.05)
Abdominal pain upper	8 (0.09)	0 (0.0)	8 (0.04)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oesophageal varices haemorrhage	1 (0.01)	6 (0.04)	7 (0.03)	5 (0.03)	0 (0.0)	1 (0.01)	1 (<0.01)	1 (0.01)
Diarrhoea	1 (0.01)	5 (0.04)	6 (0.03)	0 (0.0)	0 (0.0)	2 (0.02)	2 (0.02)	2 (0.02)
Jaundice cholestatic	4 (0.05)	2 (0.01)	6 (0.03)	3 (0.02)	0 (0.0)	1 (0.01)	1 (<0.01)	0 (0.0)
Malignant neoplasm progression	1 (0.01)	5 (0.04)	6 (0.03)	11 (0.07)	1 (0.11)	3 (0.03)	4 (0.04)	3 (0.03)
Blood bilirubin increased	2 (0.02)	3 (0.02)	5 (0.02)	1 (<0.01)	0 (0.0)	2 (0.02)	2 (0.02)	0 (0.0)
Pneumonia	3 (0.04)	2 (0.01)	5 (0.02)	3 (0.02)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.01)
Pyrexia	3 (0.04)	2 (0.01)	5 (0.02)	6 (0.04)	0 (0.0)	1 (0.01)	1 (<0.01)	0 (0.0)
Upper gastrointestinal haemorrhage	1 (0.01)	4 (0.03)	5 (0.02)	3 (0.02)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	1 (0.01)	3 (0.02)	4 (0.02)	0 (0.0)	0 (0.0)	3 (0.03)	3 (0.03)	1 (0.01)

Deaths

Table 70: Summary of All Deaths – HCC Randomized, All HCC Lenvatinib, and Non-HCC Lenvatinib Monotherapy Safety Sets

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
	Lenvatinib 8 or 12 mg (N=476) n (%)	Sorafenib 800 mg (N=475) n (%)	Lenvatinib 8 or 12 mg (N=496) n (%)	Lenvatinib (N=1327) n (%)
All Deaths	350 (73.5)	350 (73.7)	363 (73.2)	861 (64.9)
Due to progressive disease	274 (57.6)	284 (59.8)	274 (55.2)	605 (45.6)
Not due to progressive disease	32 (6.7)	17 (3.6)	32 (6.5)	56 (4.2)
Unknown[a]	44 (9.2)	49 (10.3)	57 (11.5)	200 (15.1)
Deaths on Treatment or within 30 Days of Last Dose	63 (13.2)	38 (8.0)	64 (12.9)	185 (13.9)
Due to progressive disease	44 (9.2)	30 (6.3)	44 (8.9)	93 (7.0)
Not due to progressive disease	17 (3.6)	6 (1.3)	17 (3.4)	44 (3.3)
Unknown[a]	2 (0.4)	2 (0.4)	3 (0.6)	48 (3.6)

a: If causes for deaths were not collected, the deaths were counted in the category of Unknown.

Table 71: Fatal Adverse Events Occurring in ≥ 2 Subjects in any HCC Safety Sets - all sets

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
Preferred Term	**Lenvatinib 8 or 12 mg (N=476) n (%)**	**Sorafenib 800 mg (N=475) n (%)**	**Lenvatinib 8 or 12 mg (N=496) n (%)**	**Lenvatinib (N=1327) n (%)**
Subjects with any Fatal AEs	*61 (12.8)*	*36 (7.6)*	*62 (12.5)*	*130 (9.8)*
Hepatic failure	10 (2.1)	2 (0.4)	10 (2.0)	4 (0.3)
Malignant neoplasm progression	10 (2.1)	14 (2.9)	10 (2.0)	12 (0.9)
Sepsis	5 (1.1)	1 (0.2)	5 (1.0)	6 (0.5)
Cerebral haemorrhage	3 (0.6)	0	3 (0.6)	0
Respiratory failure	3 (0.6)	3 (0.6)	3 (0.6)	4 (0.3)
Cerebrovascular accident	2 (0.4)	0	2 (0.4)	3 (0.2)
Coma hepatic	2 (0.4)	0	2 (0.4)	0
General physical health deterioration	2 (0.4)	1 (0.2)	2 (0.4)	16 (1.2)
Hepatic encephalopathy	2 (0.4)	0	2 (0.4)	0
Multiple organ dysfunction syndrome	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.2)
Pneumonia aspiration	2 (0.4)	0	2 (0.4)	0
Portal vein thrombosis	2 (0.4)	0	2 (0.4)	0
Upper gastrointestinal haemorrhage	2 (0.4)	2 (0.4)	2 (0.4)	0
Renal impairment	1 (0.2)	2 (0.4)	1 (0.2)	0
Sudden death	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.1)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Display is in decreasing order of AE rate of PTs in the lenvatinib group of the HCC Randomized Safety Set. Adverse event terms were coded using MedDRA version 19.1.
Subject Incidence: Subjects with 2 or more TEAEs reported in the same PT term were counted only once. Percentages are based on the total number of subjects in the corresponding safety set within the relevant treatment group. AE Rate (episode/SY) = total occurrence of TEAE episodes (n) divided by the total exposure (SY) for the specified treatment group. AE = adverse event; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; LLT = low level term; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SY = subject year; TEAE = treatment-emergent adverse event.

Adjusted for treatment duration, the overall rate of fatal AE episodes was 0.19 episodes/SY in the lenvatinib and 0.15 episodes/SY in the sorafenib arm. The rate of fatal AE episodes was higher in the lenvatinib arm compared with the sorafenib arm for hepatic failure sepsis and cerebral haemorrhage.

The rate of fatal AEs that were not related to PD was 0.06 and 0.03 episodes/SY in the lenvatinib and sorafenib arms, respectively.

Table 72 : Duration-adjusted Fatal Treatment-emergent Adverse Events, by CMQ for Hepatic Failure and Sepsis – Study 304 (Safety Analysis Set)

	Lenvatinib			Sorafenib
	8 mg[a] (N = 151) Total Duration= 95.1 years n (AE Rate)	12 mg[a] (N = 325) Total Duration= 229.1 years n (AE Rate)	Total (N = 476) Total Duration= 324.2 years n (AE Rate)	(N = 475) Total Duration= 239.1 years n (AE Rate)
Hepatic Failure				
Hepatic failure	4 (0.04)	6 (0.03)	10 (0.03)	2 (<0.01)
Acute hepatic failure	0 (0.0)	1 (<0.01)	1 (<0.01)	0 (0.0)
Chronic hepatic failure	0 (0.0)	1 (<0.01)	1 (<0.01)	0 (0.0)
Total	***4 (0.04)***	***8 (0.03)***	***12 (0.04)***	***2 (<0.01)***
Sepsis				
Sepsis	1 (0.01)	4 (0.02)	5 (0.02)	1 (<0.01)
Escherichia sepsis	1 (0.01)	0 (0.0)	1 (<0.01)	0 (0.0)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.01)
Total	***2 (0.02)***	***4 (0.02)***	***6 (0.02)***	***2 (<0.01)***

Table 73: Characterization of Fatal Adverse Events Not Related to Disease Progression – Safety Analysis Set

Characterization of Cause of Death	Reported Cause of Death	No. of Subjects
Lenvatinib		n=19
Hemorrhagic events	Cerebral hemorrhage (n=2) Cerebral hemorrhage, upper GI hemorrhage (n=1) Upper GI hemorrhage (n=1)	4
Arterial thromboembolic events	Cerebrovascular accident (n=2) Myocardial infarction (n=1)	3
Infectious complications	Pneumonia aspiration (n=2) Sepsis (n=1)	3
Hepatic failure (with underlying infection)	Hepatic failure and sepsis (n=1) Hepatic failure and bacterial peritonitis (n=1)	2
Hepatic failure	Hepatic failure (n=2)	2
Venous thrombotic events	Pulmonary embolism (n=1) Pulmonary infarction (n=1)	2
Other	Organ failure, unknown (n=1) Circulatory collapse (n=1) Bile duct obstruction (n=1) [a]	3
Sorafenib		n=8
Infectious complications	Sepsis (n=2)	2
Other	Sudden death, cause unknown (n=2)	2
Arterial thromboembolic events	Ischaemic stroke (n=1)	1
Hemorrhagic events	Upper GI haemorrhage (n=1)	1
Injury[b]	Traumatic haematoma and subarachnoid haemorrhage (n=1)	1
Respiratory events	Respiratory failure (n=1)	1

a: Subject experienced acute pancreatitis 2 days prior to death.
b: Subject was hit by a car.

In Study 304, 12 subjects in the lenvatinib and 6 subjects in the sorafenib arm had a Grade 5 AE that was considered treatment related by the investigator. These included:

- hepatic failure – 4 vs. 1

- respiratory failure – 2 vs. 1
- cerebral haemorrhage – 3 vs. 1

The occurrence of fatal AEs by treatment arm was analysed based on Kaplan-Meier methodology. The fatal AE-free rate was similar between the 2 treatment arms until Month 7. The sorafenib curve flattens at an earlier time point than the lenvatinib. This is attributed to the fact that ~70% sorafenib patients have discontinued treatment by Month 7 (3rd quartile for treatment duration 7.4 months vs. 11.1 months for lenvatinib). Fatal AEs are captured up to 30 days after last study drug dose. Beyond that, any death only counts as an event for the OS analysis.

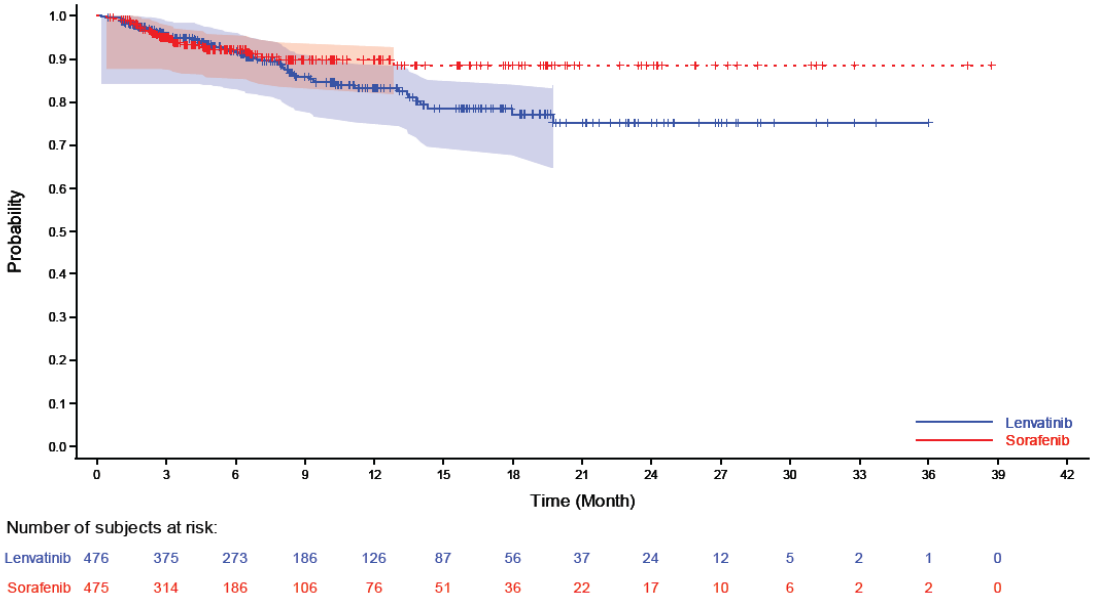


Figure 19 Kaplan-Meier Curves with 95% Hall-Wellner Confidence Bands for Time to Fatal Treatment-emergent Adverse Events – Safety Analysis Set
Subjects who did not have a fatal AE were censored at the earliest of 1) treatment end date + 30 days, 2) last date known to be alive (if subject did not die during the study), 3) date of death not caused by a fatal AE, 4) study cut-off date.
+ censored observations

Adverse Events of Special Interest

The clinically significant events include hepatotoxicity, arterial TE, cardiac dysfunction, GI perforation and fistula formation, hemorrhage, hypertension, hypocalcemia, hypothyroidism, PPE syndrome, PRES, proteinuria, QT prolongation, and renal events.

Table 74: Overall Incidence of Clinically Significant Treatment-emergent Adverse Events Identified by SMQ or CMQ Search Criteria, Overall and Severe Incidence – Safety Analysis Set

SMQ or CMQ	Lenvatinib (N = 476) n (%)					Sorafenib (N = 475) n (%)				
	Grade					Grade				
Preferred Term	Any	3	4	5	≥3	Any	3	4	5	≥3
Subjects with any Clinically Significant TEAEs	414 (87.0)	-	-	-	-	405 (85.3)	-	-	-	
Subjects with any TEAE in the CSE category of: [a]										
Hepatotoxicity	227 (47.7)	89 (18.7)	18 (3.8)	17 (3.6)	124 (26.1)	198 (41.7)	91 (19.2)	16 (3.4)	4 (0.8)	111 (23.4)
Hypertension	212 (44.5)	112 (23.5)	0 (0.0)	0 (0.0)	112 (23.5)	147 (30.9)	69 (14.5)	0 (0.0)	0 (0.0)	69 (14.5)
Palmar-Plantar erythrodysesthesia	133 (27.9)	14 (2.9)	0 (0.0)	0 (0.0)	14 (2.9)	249 (52.4)	54 (11.4)	0 (0.0)	0 (0.0)	54 (11.4)
Proteinuria	125 (26.3)	28 (5.9)	0 (0.0)	0 (0.0)	28 (5.9)	58 (12.2)	8 (1.7)	0 (0.0)	0 (0.0)	8 (1.7)
Hemorrhage	117 (24.6)	16 (3.4)	1 (0.2)	7 (1.5)	24 (5.0)	76 (16.0)	14 (2.9)	3 (0.6)	5 (1.1)	22 (4.6)
Hypothyroidism	100 (21.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal Events	34 (7.1)	7 (1.5)	1 (0.2)	1 (0.2)	9 (1.9)	19 (4.0)	3 (0.6)	1 (0.2)	2 (0.4)	6 (1.3)
QT Prolongation	33 (6.9)	5 (1.1)	0 (0.0)	0 (0.0)	5 (1.1)	24 (5.1)	5 (1.1)	0 (0.0)	0 (0.0)	5 (1.1)
Arterial TE	11 (2.3)	5 (1.1)	1 (0.2)	3 (0.6)	9 (1.9)	8 (1.7)	1 (0.2)	3 (0.6)	1 (0.2)	5 (1.1)
GI Perforation/Fistula Formation	9 (1.9)	4 (0.8)	0 (0.0)	1 (0.2)	5 (1.1)	5 (1.1)	4 (0.8)	1 (0.2)	0 (0.0)	5 (1.1)
Hypocalcemia	5 (1.1)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	8 (1.7)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac Dysfunction	3 (0.6)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Posterior Reversible Encephalopathy Syndrome	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Hepatotoxicity

The overall AE profile for hepatotoxicity is presented in the table below.

Table 75: Clinically Significant TE Hepatotoxicity AEs in ≥3 Subjects, study 304

CMQ Preferred Term	Lenvatinib 8 mg [a] (N = 151) n (%)	Lenvatinib 12 mg [a] (N = 325) n (%)	Lenvatinib Total (N = 476) n (%)	Sorafenib (N = 475) n (%)
Subjects with any Hepatotoxicity TEAEs	67 (44.4)	160 (49.2)	227 (47.7)	198 (41.7)
Blood bilirubin increased	23 (15.2)	48 (14.8)	71 (**14.9**)	63 (**13.3**)
Ascites	21 (13.9)	47 (14.5)	68 (14.3)	44 (9.3)
Aspartate aminotransferase increased	21 (13.9)	44 (13.5)	65 (13.7)	80 (16.8)
Alanine aminotransferase increased	17 (11.3)	36 (11.1)	53 (11.1)	52 (10.9)
Hypoalbuminaemia	17 (11.3)	27 (8.3)	44 (9.2)	38 (8.0)
Hepatic encephalopathy	6 (4.0)	32 (**9.8**)	38 (**8.0**)	9 (1.9)
Gamma-glutamyltransferase increased	9 (6.0)	28 (8.6)	37 (7.8)	26 (5.5)
Blood alkaline phosphatase increased	7 (4.6)	25 (7.7)	32 (6.7)	29 (6.1)
Hepatic failure	5 (3.3)	10 (3.1)	15 (3.2)	12 (2.5)
Hepatic function abnormal	2 (1.3)	10 (3.1)	12 (2.5)	13 (2.7)
Hyperbilirubinaemia	1 (0.7)	10 (3.1)	11 (2.3)	6 (1.3)
Hyperammonaemia	5 (3.3)	4 (1.2)	9 (1.9)	3 (0.6)
Jaundice cholestatic	5 (3.3)	4 (1.2)	9 (1.9)	3 (0.6)
Hepatic pain	3 (2.0)	5 (1.5)	8 (1.7)	3 (0.6)
Jaundice	0 (0.0)	6 (1.8)	6 (1.3)	7 (1.5)
Urine bilirubin increased	2 (1.3)	3 (0.9)	5 (1.1)	2 (0.4)
Hepatic cirrhosis	0 (0.0)	4 (1.2)	4 (**0.8**)	0 (0.0)
Coma hepatic	1 (0.7)	2 (0.6)	3 (0.6)	1 (0.2)
Oedema due to hepatic disease	1 (0.7)	2 (0.6)	3 (0.6)	0 (0.0)
Varices oesophageal	1 (0.7)	1 (0.3)	2 (0.4)	6 (1.3)
Portal hypertensive gastropathy	0 (0.0)	1 (0.3)	1 (0.2)	4 (0.8)

Percentages are based on the total number of subjects within the relevant treatment group in the Safety Analysis Set. Display is in decreasing order of CSE frequency in the lenvatinib total group followed by decreasing order of frequency in the sorafenib arm, then alphabetically. Subjects with 2 or more clinically significant TEAEs in the same preferred term were counted only once. Adverse event terms were coded using MedDRA version 19.1. CMQ = customized MedDRA query; CSE = clinical significant (adverse) event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
a: 8 mg and 12 mg were the lenvatinib starting doses based on the subjects' body weight (<60 kg, ≥60 kg) at Baseline.

Table 76: Overview of Hepatotoxicity – All monotherapy Safety Sets

For Hepatotoxicity per CMQ, Subjects with at least 1:	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
	Lenvatinib 8 or 12 mg (N=476) SY=324.2	Sorafenib 800 mg (N=475) SY=239.1	Lenvatinib 8 or 12 mg (N=496) SY=340.0	Lenvatinib (N=1327) SY=1544.7
TEAE, n (%)	227 (47.7)	198 (41.7)	236 (47.6)	309 (23.3)
TEAE, no. of episodes (episodes/SY)	635 (1.96)	481 (2.01)	659 (1.94)	619 (0.50)
TEAEs with maximum CTCAE Grade of,a n (%)				
1	43 (9.0)	39 (8.2)	47 (9.5)	111 (8.4)
2	60 (12.6)	48 (10.1)	62 (12.5)	122 (9.2)
≥3	124 (26.1)	111 (23.4)	127 (25.6)	76 (5.7)
3	89 (18.7)	91 (19.2)	92 (18.5)	67 (5.0)
4	18 (3.8)	16 (3.4)	18 (3.6)	4 (0.3)
5	17 (3.6)	4 (0.8)	17 (3.4)	5 (0.4)
SAE, n (%)	71 (14.9)	34 (7.2)	73 (14.7)	19 (1.4)
SAE, no. of episodes (episodes/SY)	97 (0.30)	40 (0.17)	100 (0.29)	25 (0.02)
TEAE leading to treatment discontinuation, n (%)	26 (5.5)	14 (2.9)	27 (5.4)	11 (0.8)
TEAE leading to study drug modification,b n (%)				
Dose Reduction	35 (7.4)	20 (4.2)	36 (7.3)	25 (1.9)
Dose Interruption	58 (12.2)	45 (9.5)	58 (11.7)	50 (3.8)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Serious AEs include any events that met the criteria for seriousness, whether fatal or nonfatal. For each row category, a subject with 2 or more AEs in that category was counted only once. AE Rate (episode/SY) = total occurrence of TEAE episodes (n) divided by the total exposure (SY) for the specified treatment group. AE = adverse event; CMQ = customized MedDRA query; CTCAE = Common Terminology Criteria for Adverse
Events; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SAE = serious adverse event; SY = subject year; TEAE = treatment emergent adverse event.
a: If a subject had more than 1 TEAE, the subject was only counted once at the maximum grade.
b: Study drug modification includes dose reduction or interruption. A subject could be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

Hepatic Encephalopathy

In the HCC Randomized Safety Set, 40 subjects (8.4%) in the lenvatinib and 13 subjects (2.7%) in the sorafenib arm had an event of hepatic encephalopathy per CMQ (including PTs of hepatic encephalopathy, encephalopathy, metabolic encephalopathy and coma hepatic). The event was Grade ≥3 in 26 subjects in the lenvatinib and 9 in the sorafenib arm; 4 subjects in the lenvatinib arm had a Grade 5 event. Hepatic encephalopathy was considered by the investigator as related to study drug in 18 lenvatinib and 4 sorafenib-treated subjects.

Hepatic encephalopathy was associated with PD for 13 subjects in the lenvatinib arm (12 received a starting dose of 12 mg and 1 received 8 mg) and 6 subjects in the sorafenib arm. The 13 lenvatinib-treated subjects include Subject 19011002 who had a fatal AE of hepatic coma that was not recorded as PD and a fatal AE of portal vein thrombosis that was considered PD by the investigator. An additional 5 lenvatinib-treated subjects (4 starting on 12 mg and 1 on 8 mg) had hepatic encephalopathy 7 days before or after discontinuation of study drug due to PD (radiologic or clinical).

Hepatic encephalopathy resulted in dose modification (interruption/reduction) in 21 subjects in the lenvatinib and 4 subjects in the sorafenib arm; 8 and 1 patient, respectively, discontinued treatment.

The percentage of subjects with cirrhosis at Baseline per the IIR was higher in subjects with hepatic encephalopathy than in the overall population. Lenvatinib-treated subjects who developed hepatic encephalopathy, particularly within 30 days of starting study drug, had worse baseline liver disease than subjects in the lenvatinib arm overall and sorafenib-treated subjects who developed hepatic encephalopathy. Baseline characteristics included higher mean/median ammonia concentration, greater frequency of MPVI, greater proportion of subjects with a CP score ≥6 (including 2 subjects with the score

of 7), greater liver tumour burden (measured by sums of the diameters) and cirrhosis. Most subjects had either Grade 0 or Grade 1 baseline AST, ALT and ALP levels and no correlation with the occurrence of hepatic encephalopathy was seen. No significant relationship between lenvatinib exposure and hepatic encephalopathy was detected within the exposure range of Study 304. Hepatic encephalopathy occurred more frequently in subjects aged 75 years and older.

Hepatic Failure

In the HCC Randomized Safety Set, 17 subjects (3.6%) in the lenvatinib and 12 subjects (2.5%) in the sorafenib arm had an event of hepatic failure per CMQ (including the PTs of hepatic failure, acute hepatic failure and chronic hepatic failure). Grade 5 hepatic failure per CMQ was reported in 12 lenvatinib- and 2 sorafenib-treated subjects. Hepatic failure was considered by the investigator as related to study drug in 6 lenvatinib- and 3 sorafenib-treated subjects. For 9 subjects in the lenvatinib arm (6 starting on 12 mg and 3 on 8 mg) and 6 subjects in the sorafenib arm, the hepatic failure was also associated with PD by the investigator. Hepatic failure resulted in dose modification (interruption/reduction) in 3 lenvatinib- and in 2 sorafenib-treated subjects. Review of baseline characteristics showed that lenvatinib-treated subjects with hepatic failure had worse baseline liver disease than the overall lenvatinib population and the sorafenib -treated subjects with hepatic failure. Baseline characteristics for subjects with hepatic failure included CP score of 6 or 7, greater frequency of MPVI, alpha-fetoprotein concentration ≥200 ng/mL, higher mean/median ammonia concentration and the presence of cirrhosis, per the independent imaging review. Baseline AST, ALT and ALP concentrations were either Grade 0 or 1 for most subjects who had hepatic failure and no correlation with hepatic failure was seen.

Table 77: Summary of the Presence of Cirrhosis per Independent Imaging Review at Baseline for Subjects with Hepatic Failure and Hepatic Encephalopathy per CMQ – HCC Randomized Safety Set

	Lenvatinib			Sorafenib		
	Asia-Pacific (N = 321) n (%)	Western regions (N = 155) n (%)	Total (N = 476) n (%)	Asia-Pacific (N = 319) n (%)	Western regions (N = 156) n (%)	Total (N = 475) n (%)
Subjects with any TEAE of Hepatic Failure [a]	9	8	17	4	8	12
Presence of Cirrhosis at Baseline[b]	7 (77.8)	7 (87.5)	14 (82.4)	3 (75.0)	8 (100.0)	11 (91.7)
Subjects with any TEAEs of Hepatic Encephalopathy [c]	19	21	40	8	5	13
Presence of Cirrhosis at Baseline[b]	17 (89.5)	21 (100.0)	38 (95.0)	7 (87.5)	4 (80.0)	11 (84.6)

a: The clinically significant event of “hepatic failure” per CMQ comprises the preferred terms acute hepatic failure, chronic hepatic failure, and hepatic failure.
b: Presence of cirrhosis at Baseline assessed by post-hoc independent imaging review or was present on the CRF as part of the subject’s medical or clinical history.
c: The clinically significant event of “hepatic encephalopathy” per CMQ comprises the preferred terms of hepatic encephalopathy, metabolic encephalopathy, encephalopathy, and coma hepatic.

Table 78: Summary of Baseline Characteristics for Subjects Who Had Hepatic Failure per CMQ – Safety Analysis Set

	Lenvatinib		Sorafenib	
	Subjects with HF (N=17)	All Subjects (N=476)	Subjects with HF (N=12)	All Subjects (N=475)
Baseline Child-Pugh Score, n(%)				
5	9 (52.9)	366 (76.9)	10 (83.3)	356 (74.9)
6	6 (35.3)	107 (22.5)	2 (16.7)	114 (24.0)
7	2 (11.8)	3 (0.6)	0 (0.0)	4 (0.8)
8	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Baseline MPVI, n(%)				
Yes	7 (41.2)	109 (22.9)	4 (33.3)	90 (18.9)
No	10 (58.8)	367 (77.1)	8 (66.7)	385 (81.1)
Baseline Alpha-fetoprotein Level, n(%)				
< 200 ng	7 (41.2)	254 (53.4)	4 (33.3)	285 (60.0)
>=200 ng/mL	10 (58.8)	221 (46.4)	8 (66.7)	187 (39.4)
Baseline Alpha-fetoprotein level (ng/mL)				
N	16	469	12	462
Mean (SD)	29984.9(58505.38)	17565.5(105357.7)	10632.0(30251.10)	16714.6(94889.03)
Median	5102.3	133.1	481.6	71.4
Q1, Q3	38.2, 34554.1	8.0, 3573.3	16.5, 1907.7	5.6, 1081.8
Min, Max	3.1, 227840	0.1, 1567470	2.5, 105641	0.1, 1446396
Baseline Ammonia level (µg/dL)				
N	16	454	11	452
Mean (SD)	50.0(33.76)	38.2(30.01)	41.0(14.60)	36.7(32.92)
Median	38.9	31.8	37.9	30.0
Q1, Q3	22.1, 78.5	22.0, 45.0	26.3, 48.2	21.0, 42.7
Min, Max	9.0, 124.9	4.0, 246.0	25.0, 72.0	4.0, 473.0

Deaths:

Table 79: Grade 5 Hepatic-Related Adverse Events that Occurred in the HCC Safety Sets – HCC Randomized, All HCC Lenvatinib, and Non-HCC Lenvatinib Monotherapy Safety Sets

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
Preferred Term	Lenvatinib 8 or 12 mg (N=476) n (%)	Sorafenib 800 mg (N=475) n (%)	Lenvatinib 8 or 12 mg (N=496) n (%)	Lenvatinib (N=1327) n (%)
Total	*17 (3.6)*	*4 (0.8)*	*17 (3.4)*	*4 (0.3)*
Hepatic failure	10 (2.1)	2 (0.4)	10 (2.0)	4 (0.3)
Coma hepatic	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
Hepatic encephalopathy	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
Acute hepatic failure	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Chronic hepatic failure	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Hepatic cirrhosis	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Ascites	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Hepatic function abnormal	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016.
Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies).
In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD.
Display is in decreasing order of AE rate in the lenvatinib group of the HCC Randomized Safety Set.
Subjects with 2 or more AEs in the same preferred term were counted only once.
Percentages based on total number of subjects in the corresponding safety set within the relevant treatment group.
Adverse event terms were coded using MedDRA version 19.1.

In both arms of study 304 the majority (17/21) of Grade 5 hepatic AEs were related to PD, per investigator assessment and three of the 4 remaining subjects had other relevant AEs or precipitating

factors that could have triggered the Grade 5 hepatic event. These included i) hepatic haemorrhage, ii) lung infection and sepsis, and iii) bacterial peritonitis and previous AE of gastroenteritis.

Hepatic-related deaths are not unusual in this patient population with advanced HCC, underlying cirrhosis, and hepatitis. In the Non-HCC Lenvatinib Monotherapy Safety Set, 0.3% of subjects had Grade 5 hepatic failure by PT.

Discontinuations*:* Twenty six of 227 subjects (11.5%) who had a hepatotoxicity event (any grade),in the lenvatinib arm and 14 of 198 subjects (7.1%) in the sorafenib arm discontinued treatment for the event. The median time to first onset was 6.4 weeks in the lenvatinib arm and 4.4 weeks in the sorafenib arm of study 304.

The incidence of hepatotoxicity per CMQ was evaluated by age, sex, race, ECOC PS, baseline renal function, baseline hepatic function, and region.

Comparison with the Non-HCC safety set: As expected, the incidence of hepatotoxicity events per CMQ was higher in the All HCC Lenvatinib Safety Set (47.6%; 1.94 episodes/SY) than in the Non-HCC Lenvatinib Monotherapy Safety Set (23.3%; 0.50 episodes/SY).

Pancreatitis

The evaluation of pancreatitis includes both an analysis of the CMQ of pancreatitis based on AE reports and an analysis of laboratory values for serum amylase and lipase.

Events were Grade ≥3 for 14 subjects (2.9%) in the lenvatinib arm and 12 subjects (2.5%) in the sorafenib arm. There was 1 death in the lenvatinib arm and none in the sorafenib arm: Subject 19061007 in the lenvatinib arm had an SAE of acute pancreatitis, which resulted in discontinuation of study drug, and ultimately death (however, 3 additional Grade 5 AEs were reported for this subject: bile duct obstruction, hepatic failure, and multiple organ dysfunction syndrome; all due to PD and not related to treatment, as reported by the investigator).

Grade 3 or 4 increased lipase was observed at a similar incidence in the All HCC Lenvatinib Safety Set (6.4%) and the Non-HCC Lenvatinib Monotherapy Safety Set (6.6%). Grade 3 or 4 increased amylase was observed at a lower incidence in the All HCC Lenvatinib Safety Set (1.1%) than the Non-HCC Lenvatinib Monotherapy Safety Set (3.6%).

Results were generally similar in the lenvatinib arm of the HCC Randomized Safety Set, the All HCC Lenvatinib Safety Set, and the Non-HCC Lenvatinib Monotherapy Safety Set.

There were no additional events of pancreatitis per CMQ in All HCC Lenvatinib Safety Set. The incidence of pancreatitis per CMQ was 3.8% in the All HCC Lenvatinib Safety Set and 5.0% in the Non-HCC Lenvatinib Monotherapy Safety Set.

Arterial Thromboembolic Events (Arterial TE events)

In the HCC Randomized Safety Set, the incidence of arterial TE events per CMQ was comparable in the lenvatinib and sorafenib arms: 2.3% (11/476) and 1.7% (8/475), respectively, and 0.04 episodes/SY in each arm when adjusted by treatment exposure. The most frequently reported arterial TE events were MI (lenvatinib, 4 [0.8%]; sorafenib, 1 [0.2%]) and cerebral infarction (lenvatinib, 3 [0.6%]; sorafenib, 0). Most were SAEs (10 in the lenvatinib and 6 in the sorafenib arm). There were 3 deaths due to arterial TE events in the lenvatinib arm: 2 subjects with cerebrovascular accident and 1 subject with MI. All 3 subjects had relevant medical history and comorbidities and were at increased risk. There are no changes to the previously reported safety profile of lenvatinib regarding arterial TE events.

Haemorrhage

In the HCC Randomized Safety Set, the incidence of haemorrhage events per SMQ was higher in the

lenvatinib than sorafenib arm: 24.6% (117/476) and 16.0% (76/475), respectively, 0.54 and 0.43 episodes/SY adjusted by treatment exposure. Grade 1 and 2 events contributed to the difference in incidence (93 subjects [19.5%] in the lenvatinib arm and 54 subjects [11.4%] in the sorafenib arm). The incidence of Grade ≥3 events was similar between treatment arms: 24 subjects (5.0%) in the lenvatinib arm and 22 subjects (4.6%) in the sorafenib arm.

The most frequently reported haemorrhage events in the lenvatinib and sorafenib arms, respectively, were epistaxis (34 subjects [7.1%; 0.10 episodes/SY]; 15 [3.2%; 0.07 episodes/SY]), haematuria (25 subjects [5.3%; 0.10 episodes/SY]; 10 [2.1%; 0.05 episodes/SY]) and gingival bleeding (18 subjects [3.8%; 0.06 episodes/SY]; 9 [1.9%; 0.05 episodes/SY]).

Incidence of serious haemorrhage events was similar in the lenvatinib and sorafenib arms: 25 subjects (5.3%; 0.09 episodes/SY) and 21 subjects (4.4%; 0.12 episodes/SY), respectively. The most frequently reported serious events were: oesophageal varices haemorrhage (7 subjects [1.5%; 0.02 episodes/SY]; 5 [1.1%; 0.03 episodes/SY]) and upper GI haemorrhage (5 subjects [1.1%; 0.02 episodes/SY]; 2 [0.4%; 0.01 episodes/SY]). These SAEs are consistent with complications of underlying liver disease, including coagulopathy, varices, and portal hypertension.

There were 8 (1.7%) Grade 5 haemorrhage events in the lenvatinib arm and 5 (1.1%) in the sorafenib arm. The 8 Grade 5 TEAEs comprised 3 subjects with cerebral haemorrhage and relevant risk factors (Subject 14071003 – history of hypertension; 24041001 - history of cerebrovascular malformation surgery and cerebral haemorrhage and 24111035 - AEs of BP increase and aortic dissection), 2 subjects with upper GI haemorrhage (Subjects 24041001 and 24111029), and 1 subject each with disseminated intravascular coagulation (Subject 12141007), intestinal haemorrhage (Subject 19011014) and tumour haemorrhage (Subject 44031005).

In the sorafenib arm, the 5 Grade 5 TEAEs were 2 subjects with upper GI haemorrhage (Subjects 24021011 and 24111045), and 1 subject each with traumatic hematoma (Subject 14141005), tumour haemorrhage (Subject 15041006), and oesophageal varices haemorrhage (Subject 24031002).

For subjects who had a CSE of haemorrhage per SMQ, the median time to first onset was 11.9 weeks in the lenvatinib arm and 7.2 weeks in the sorafenib arm. There are no changes to the previously reported safety profile of lenvatinib regarding haemorrhage.

Hypothyroidism (Based on Adverse Event Data)

In the HCC Randomized Safety Set, hypothyroidism events per CMQ were observed at a higher frequency in the lenvatinib compared to the sorafenib arm: 21.0% (100/476) and 2.5% (12/475), respectively and 0.32 and 0.05 episodes/SY adjusted by treatment exposure.

Hypothyroidism was the most frequently reported PT: 78 subjects (16.4%; 0.24 episodes/SY) in the lenvatinib arm and 8 subjects (1.7%; 0.03 episodes/SY) in the sorafenib arm. Blood TSH increased was reported for 23 subjects (4.8%; 0.07 episodes/SY) in the lenvatinib and 4 subjects (0.8%; 0.02 episodes/SY) in the sorafenib arm. The median time to first onset of hypothyroidism was 8.1 weeks in the lenvatinib and 13.8 weeks in the sorafenib arm.

There were no Grade ≥3 TEAEs of hypothyroidism, no SAEs, no treatment discontinuations; 1 subject in the lenvatinib arm had a TEAE leading to dose interruption and only 1 subject in the sorafenib arm had a TEAE leading to dose reduction. Overall, 66 subjects (13.9%) in the lenvatinib arm and 23 subjects (4.8%) in the sorafenib arm of the HCC Randomized Safety Set took at least 1 concomitant medication for hypothyroidism. This demonstrates that hypothyroidism could be well managed.

By subgroup, the PT of increased blood TSH occurred at a higher incidence in subjects who were male, Asian, and from the Asia-Pacific region. No other meaningful subgroup differences were observed for this CSE.

There was a higher incidence of hypothyroidism per CMQ in subjects with HCC (22.0% [0.34 episodes/SY] in the All HCC Lenvatinib Safety Set) than the Non-HCC Lenvatinib Monotherapy Safety Set (18.3%; 0.23 episodes/SY). Many subjects in the Non-HCC Lenvatinib Monotherapy Safety Set had thyroid cancer, which confounded the analysis of hypothyroidism. In subjects with an intact thyroid, the PT of hypothyroidism occurred at more than twice the rate compared to subjects with thyroid cancer due to a direct effect on the thyroid. Thyroid dysfunction is a known class effect of TKIs due to their antiangiogenic effect on the thyroid blood vessels. There is no change to the previously reported safety profile of lenvatinib regarding hypothyroidism.

Renal Events (Based on Adverse Event Data)

In the HCC Randomized Safety Set, renal events per CMQ were observed at a higher frequency in the lenvatinib compared to the sorafenib arm: 7.1% (34/476) and 4.0% (19/475), respectively; 0.14 and 0.08 episodes/SY, when adjusted by treatment exposure. Grade 1 and 2 events were the greatest contributor to the difference in the overall incidence (25 subjects [5.2%] in the lenvatinib arm and 13 subjects [2.8%] in the sorafenib arm). Events were Grade ≥3 for 9 subjects (1.9%) in the lenvatinib and 6 subjects (1.3%) in the sorafenib arm.

The most frequently reported renal events in the lenvatinib and sorafenib arms, respectively were: blood creatinine increased (10 subjects [2.1%; 0.06 episodes/SY]; 4 [0.8%; 0.02 episodes/SY]), acute kidney injury (9 subjects [1.9%; 0.03 episodes/SY]; 5 [1.1%; 0.02 episodes/SY]) and renal impairment (5 subjects [1.1%; 0.02 episodes/SY]; 6 [1.3%; 0.03 episodes/SY]). The median time to first onset was 14.3 weeks in the lenvatinib and 10.4 weeks in the sorafenib arm.

In the HCC Randomized safety Set, 7 subjects (1.5%; 0.02 episodes/SY) reported SAEs of renal event per CMQ in the lenvatinib arm and 4 subjects (0.8%; 0.02 episodes/SY) in the sorafenib arm. The most frequently reported serious renal event was acute kidney injury (lenvatinib, 3 subjects [0.6%; <0.01 episodes/SY]; sorafenib, 2 [0.4%; <0.01 episodes/SY]).

There was 1 (0.2%) Grade 5 renal event in the lenvatinib arm and 2 (0.4%) in the sorafenib arm. All 3 deaths were due to renal impairment.

There was a low incidence of discontinuations due to renal toxicity: 2 subjects (0.4%) in the lenvatinib arm and 3 subjects (0.6%) in the sorafenib arm.

Results were similar in the lenvatinib arm of the HCC Randomized Safety Set and the All HCC Lenvatinib Safety Set (1 additional Grade 3 event of blood creatinine increased that was not a SAE and did not result in treatment modification). The overall incidence of renal events per SMQ was 7.1% (0.14 episodes/SY) in the All HCC Lenvatinib Safety Set and 9.8% (0.16 episodes/SY) in the Non-HCC Lenvatinib Monotherapy Safety Set. There are no changes to the previously reported safety profile of lenvatinib, regarding renal events.

Cardiac Dysfunction (Based on Adverse Event Data)

In the HCC Randomized Safety Set, the frequency of cardiac dysfunction events per CMQ was low in both the lenvatinib and sorafenib arms: 0.6% (3/476) and 0.2% (1/475), respectively (both <0.01 episodes/SY). Events were Grade ≥3 for 2 subjects in the lenvatinib arm (1 Grade 3, 1 Grade 5cardiopulmonary failure) and none in the sorafenib arm. One subject (0.2%) in each arm had an SAE. No AEs resulted in treatment discontinuation or modification. The median time to first onset was 36.3 weeks in the lenvatinib and 26.7 weeks in the sorafenib arm.

There were no additional cardiac events per CMQ in the All HCC Lenvatinib Safety Set. The overall incidence of cardiac events per CMQ was lower in the All HCC Lenvatinib Safety Set (0.6%; <0.01 episodes/SY) than in the Non-HCC Lenvatinib Monotherapy Safety Set (4.7%; 0.06 episodes/SY). The potential to cause cardiac dysfunction is a known effect of lenvatinib and heart failure is noted in the

product information. There are no changes to the previously reported safety profile of lenvatinib regarding cardiac events.

Gastrointestinal Perforation and Fistula Formation

In the HCC Randomized Safety Set, the incidence of GI perforation and fistula formation was slightly higher in the lenvatinib than sorafenib arm: 1.9% (9/476) and 1.1% (5/475); 0.03 and 0.02 episodes/SY respectively when adjusted by treatment exposure. The most frequent event was (spontaneous) bacterial peritonitis (6 subjects [1.3%; 0.02 episodes/SY]; 1 [0.2%; <0.01 episodes/SY]).

Events were Grade ≥3 for 5 subjects (1.1%) in each arm. Three subjects (0.6%) in the lenvatinib and 2 (0.4%) in the sorafenib arm had an SAE, mainly peritonitis bacterial (lenvatinib, 2 subjects [0.4%; <0.01 episodes/SY]; sorafenib, 0). In the lenvatinib arm, 1 subject (32051003) had a Grade 5 event. One subject (0.2%) in the sorafenib arm discontinued due to an AE.

The median time to onset was 32.3 weeks in the lenvatinib arm and 7.0 weeks in the sorafenib arm of the HCC Randomized Safety Set.

By subgroup analysis, no events occurred in subjects who were ≥75 years of age or female. No other meaningful differences (difference of ≥10% or at least double) were observed in the subgroup analyses for this CSE. None of these differences were observed for the Non-HCC Lenvatinib Monotherapy Safety Set.

There were no additional events of GI perforation and fistula formation events per SMQ in the All HCC Lenvatinib Safety Set. The overall incidence of GI perforation and fistula formation events per SMQ was 1.8% (0.03 episodes/SY) in the All HCC Lenvatinib Safety Set and 2.9% (0.04 episodes/SY) in the Non-HCC Lenvatinib Monotherapy Safety Set.

There were no reports of bacterial peritonitis in the Non-HCC population; cirrhosis is a well-recognized risk factor for the development of spontaneous bacterial peritonitis SBP).

Hypertension (Based on Adverse Event Data)

For AEs, the severity definition also includes the use of antihypertensive medications (NCI CTCAE version 4.03).

In the HCC Randomized Safety Set, hypertension was present at Baseline in 49.8% of subjects in the lenvatinib and 51.4% in the sorafenib arm; 72.9% and 67.8% took concomitant antihypertensive agents. Hypertension events were more frequent in the lenvatinib than sorafenib arm: 44.5% (212/476) and 30.9% (147/475), respectively; 0.83 and 0.71 episodes/SY, when adjusted by treatment exposure.

Grade 3 hypertension events occurred in 112 subjects (23.5%) in the lenvatinib and 69 subjects (14.5%) in the sorafenib arm. No Grade 4 or Grade 5 hypertension events or SAEs were reported. The median time to first onset was 3.7 weeks in the lenvatinib and 2.1 weeks in the sorafenib arm.

One subject (0.2%) in the lenvatinib arm discontinued due to an AE. Hypertension events resulted in dose reduction for 16 subjects (3.4%) in the lenvatinib and 10 (2.1%) in the sorafenib arm, and dose interruption for 17 (3.6%) and 8 (1.7%) subjects, respectively.

By subgroup, the overall incidence and the incidence of severe (Grade ≥3) TEAEs for this CSE, was higher in the oldest age group. Incidence was also higher in females.

The overall incidence of hypertension events per SMQ was lower in subjects with HCC (46.2% [0.84 episodes/SY] in the All HCC Lenvatinib Safety Set) than in the Non-HCC Lenvatinib Monotherapy Safety Set (60.9%; 1.08 episodes/SY). Subjects with HCC received a lower lenvatinib starting dose (8 or 12 mg/day) compared with the Non-HCC Lenvatinib Monotherapy Safety Set (85% started on 24 mg QD) and hypertension is a known dose-related effect of VEGF/VEGFR-targeted therapies. There are no

changes to the previously reported safety profile of lenvatinib regarding hypertension.

Hypocalcaemia (Based on Adverse Event Data)

In the HCC Randomized Safety Set, the incidence of hypocalcaemia events per CMQ was comparable in the lenvatinib and sorafenib arms: 1.1% (5/476) and 1.7% (8/475), respectively; 0.02 episodes/SY and 0.03 episodes/SY, when adjusted by treatment exposure. Grade 3 hypocalcaemia events occurred in 2 subjects (0.4%) in the lenvatinib and 1 subject (0.2%) in the sorafenib arm. No Grade 4 or 5 hypocalcaemia events and no discontinuations due to AEs were reported in arm. One SAE of hypocalcaemia was reported in the lenvatinib arm. The median time to first onset was 31.7 weeks in the lenvatinib and 13.0 weeks in the sorafenib arm.

The overall incidence of hypocalcaemia events per CMQ was lower in the All HCC Lenvatinib Safety Set (1.4% [0.03 episodes/SY]) than in the Non- HCC Lenvatinib Monotherapy Safety Set (8.3%; 0.12 episodes/SY). There are no changes to the previously reported safety profile of lenvatinib regarding events of hypocalcaemia.

Palmar-plantar Erythrodysaesthesia Syndrome

In the HCC Randomized Safety Set, PPE events per CMQ occurred at a lower incidence in the lenvatinib than sorafenib arm: 27.9% (133/476) and 52.4% (249/475), respectively. All cases were Grades ≤3; events were Grade 3 for 14 subjects (2.9%) in the lenvatinib and 54 subjects (11.4%) in the sorafenib arm. There were no SAEs or discontinuations due to AEs in the lenvatinib arm and 3 (0.6%) subjects each with SAEs or discontinuations in the sorafenib arm. The median time to first onset was 5.3 weeks in the lenvatinib and 2.0 weeks in the sorafenib arm.

By subgroup, the overall incidence of TEAEs for this CSE tended to be lower in the oldest subjects. The incidence in Asian was higher than in White subjects.

The overall incidence of PPE was higher in the All HCC Lenvatinib Safety Set (30.0%) than the Non-HCC Lenvatinib Monotherapy Safety Set (20.9%). The proportion of Asian subjects was higher in the All HCC Lenvatinib Safety Set than in the Non-HCC Lenvatinib Monotherapy Safety Set (71.2% vs 14.2%). The incidence of PPE syndrome has also been observed to be higher with other TKIs in Asians compared with non-Asians (Ueda, et al., 2013). PPE is a known toxicity of lenvatinib and is known to occur at a higher incidence with sorafenib. There are no changes to the previously reported safety profile of lenvatinib regarding PPE.

Proteinuria (Based on Adverse Event Data)

In the HCC Randomized Safety Set, proteinuria-SMQ events were observed at a higher frequency in the lenvatinib than sorafenib arm: 26.3% (125/476) and 12.2% (58/475), respectively. Grade 3 proteinuria occurred in 28 subjects (5.9%) in the lenvatinib and 8 subjects (1.7%) in the sorafenib arm. No Grade 4 or Grade 5 proteinuria events were reported in either arm. Three subjects (0.6%) in the lenvatinib and none in the sorafenib arm reported SAEs of proteinuria. The median time to first onset was 6.1 weeks in the lenvatinib and 4.1 weeks in the sorafenib arm. There were few discontinuations due to proteinuria (0.6% [3/476] of subjects in the lenvatinib arm).

By subgroup, the incidence of TEAEs and of severe (Grade ≥3) TEAEs for this CSE tended to be higher in the 2 older age groups compared with the youngest subjects and in Asian compared with White subjects.

The overall incidence of proteinuria events per SMQ was lower in subjects with HCC (27.4% in the All HCC Lenvatinib Safety Set) than in the Non-HCC Lenvatinib Monotherapy Safety Set (35.5%), again probably due to the lower starting dose of lenvatinib in HCC. Proteinuria is a known dose-related effect of VEGF/VEGFR targeted therapies. There are no changes to the previously reported safety profile of lenvatinib regarding proteinuria.

QT Prolongation (Reported as an Adverse Event)

In the HCC Randomized Safety Set, the incidence of QT prolongation events per SMQ was comparable in the lenvatinib and sorafenib arms: 6.9% (33/476) and 5.1% (24/475); 0.14 and 0.20 episodes/SY when adjusted by treatment exposure. Grade 3 QT prolongation occurred in 5 subjects (1.1%) in each arm. No Grade 4 or 5 QT prolongation events, SAEs or treatment discontinuations were reported in either treatment arm. The median time to first onset was 31.1 weeks in the lenvatinib and 14.0 weeks in the sorafenib arm.

By subgroup, the overall incidence of TEAEs tended to be higher in females than in males; however, there were no Grade ≥3 events in females.

The overall incidence of QT prolongation events was 6.7% (0.13 episodes/SY) in the All HCC Lenvatinib and 4.3% (0.07 episodes/SY) in the Non-HCC Lenvatinib Monotherapy Safety Set. There are no changes to the previously reported safety profile of lenvatinib regarding QT prolongation.

Other Risks

These were based on the company core risk management plan and regional (including the EU) risk management plans. These comprise: GI toxicity, hypokalaemia, pancreatitis, impaired wound healing, interstitial lung disease, abnormal pregnancy and excretion of lenvatinib in milk, male and female fertility, venous TE events, and non-GI fistula. Per the applicant there were no changes to the previously reported safety profile of lenvatinib regarding these risks.

Venous Thromboembolic Events

In the HCC Randomized Safety Set, the incidence of venous TE events per CMQ was higher in the lenvatinib than sorafenib arm: 3.8% (18/476) and 1.9% (9/475); 0.06 and 0.04 episodes /SY, adjusted by treatment exposure. The most frequently reported venous TE event was portal vein thrombosis: lenvatinib, 9 subjects (1.9%; 0.03 episodes/SY); sorafenib, 3 (0.6%; 0.01 episodes/SY). Events were Grade ≥3 for 10 subjects (2.1%) in the lenvatinib and 6 subjects (1.3%) in the sorafenib arm. There were 4 (0.8%) Grade 5 events in the lenvatinib and none in the sorafenib arm. There were 10 (2.1%) SAEs in the lenvatinib and 3 (0.6%) in the sorafenib arm. The median time to first onset was 7.4 weeks in the lenvatinib and 8.1 weeks in the sorafenib arm.

By subgroup, the incidence of venous TE events was higher in White than in Asian subjects and in the Western than in the Asia-Pacific region. In the All HCC Lenvatinib Safety Set, the PT of portal vein thrombosis occurred at a higher incidence in Western than Asia- Pacific subjects; this difference was not observed for the Non-HCC Lenvatinib Monotherapy Safety Set. In addition, in the All HCC Lenvatinib Safety Set, the PT of pulmonary embolism only occurred in males and at a higher incidence in White subjects and those from the Western region; these differences were similarly observed for the Non-HCC Lenvatinib Monotherapy Safety Set.

The incidence of venous TE events per CMQ was 3.6% (0.06 episodes/SY) in the All HCC Lenvatinib Safety Set and 5.9% (0.07 episodes/SY) in the Non-HCC Lenvatinib Monotherapy Safety Set.

Laboratory findings

Haematology

Hemoglobin:

In study 304 an increase in the median haemoglobin concentration from Baseline was observed in the lenvatinib arm as early as day 15 and was generally maintained throughout treatment. In the sorafenib arm, median hemoglobin values also increased on Day 15 but then tended to return to baseline levels or slightly below thereafter. Median increases from Baseline in hemoglobin values were consistently higher

in the Non-HCC Lenvatinib Monotherapy Safety Set. See also the table below for the incidence of AEs of grade 3 and 4. TEAE anaemia (7.1% lenvatinib vs 9.1% sorafenib)

Platelets:

In the HCC Randomized Safety Set, a decrease from Baseline in median platelet values occurred in the lenvatinib arm, which was generally maintained throughout treatment (57.0% and 48.8% of lenvatinib- and sorafenib-treated subjects, respectively, experienced a worsening shift from

Baseline for platelet count decreased, likely due to the confounding effect of chronic liver disease). Median platelet values also decreased in the sorafenib arm and there were no consistent differences between the 2 treatment arms over time. Baseline platelet values were higher, and median decreases from Baseline were consistently greater, in the Non-HCC Lenvatinib Monotherapy Safety Set. Overall, the frequency of Grade 3 and 4 events of thrombocytopenia and platelet count decreased was lower than the frequency of Grade 3 and 4 platelet count decreased laboratory values but the incidence of AEs (laboratory values) grade 3 and 4 of count decreased was higher in the all HCC lenvatinib safety set than in the non-HCC safety set (see table below Table 15)

There were no SAEs of either thrombocytopenia or platelet count decreased in either lenvatinib treatment arm; SAEs of platelet count decreased were reported in 2 subjects in the sorafenib arm, one subject leading to treatment discontinuation.

White blood cells and neutrophils:

In the HCC Randomized Safety Set, decreases from Baseline in median values for neutrophils and leukocytes occurred over time in the lenvatinib arm; these changes were consistently greater than in the sorafenib arm, in which values fluctuated slightly around the median baseline value throughout treatment. In both treatment arms, neutrophil and leukocyte values recovered to Baseline levels following treatment discontinuation. From Cycle 4 onwards median decreases in neutrophil and leukocyte values were consistently greater in the All HCC Lenvatinib Safety Set than in the Non-HCC Lenvatinib Monotherapy Safety Set that was otherwise similar to the HCC safety set.

A summary of the number and percentage of subjects with least one Grade 3 or 4 postbaseline value for decreased WBC parameters is presented in the table below.

During study 304, a higher percentage (at least twice) of subjects in the lenvatinib arm had a Grade 3 or 4 postbaseline value compared with the sorafenib arm for neutrophil count decreased (7.5% vs 3.4%) and WBC decreased (5.8% vs 3.0%). There was no difference between treatment arms for lymphocyte count decreased. For WBC count decreased, and neutrophil count decreased, the incidence of Grade 3 and 4 abnormalities was higher in the All HCC Lenvatinib Safety Set than in the Non-HCC Lenvatinib Monotherapy Safety Set.

Adverse events data: In the HCC Randomized Safety Set, the following TEAEs occurred at a higher incidence (more than double) in the lenvatinib arm than the sorafenib arm, respectively: decreased WBC count (9.7% vs 4.8%), decreased neutrophil count (8.4% vs 2.3%), and neutropenia (3.8% vs 1.5%). The incidence and rate of decreased lymphocyte count, leukopenia, and lymphopenia did not differ between treatment arms. The decreases in WBC and neutrophil counts occurred at comparable incidences through the entire treatment period. There were no SAEs of decreased WBC count or neutropenia and no discontinuations due to these AEs. There was only 1 SAE of decreased neutrophil count and 1 discontinuation due to this event (lenvatinib arm of HCC Randomized Safety Set). There were no infections associated with Grade 3 or 4 events of decreased neutrophil count and thus no clinical consequences linked to this observation of a higher incidence of decreased WBC and neutrophil counts, and neutropenia in the lenvatinib arm.

For platelet count decreased, WBC count decreased, and neutrophil count decreased, the incidence of

Grade 3 and 4 abnormalities was higher in the All HCC Lenvatinib Safety Set than in the Non-HCC Lenvatinib Monotherapy Safety Set.

Table 80: Treatment-emergent Laboratory grade 3 or 4 AE for haematology - all safety sets

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
Hematology Parameter Worst Postbaseline Grade	**Sorafenib 8 or 12 mg (N=476) n (%)**	**Lenvatinib 800 mg (N=475) n (%)**	**Lenvatinib 8 or 12 mg (N=496) n (%)**	**Lenvatinib (N=1327) n (%)**
Hemoglobin decreased				
Study Overall, n[a]	469	471	489	1243
Grade 3, n (%)	20 (4.3)	24 (5.1)	21 (4.3)	22 (1.8)
Grade 4, n (%)	0	0	0	0
Hemoglobin increased				
Study Overall, n[a]	469	471	489	1243
Grade 3, n (%)	1 (0.2)	0	1 (0.2)	4 (0.3)
Grade 4, n (%)	0	0	0	0
Platelet count decreased				
Study Overall, n[a]	467	471	487	1238
Grade 3, n (%)	40 (8.6)	31 (6.6)	48 (**9.9**)	22 (1.8)
Grade 4, n (%)	6 (1.3)	6 (1.3)	6 (1.2)	5 (0.4)
White blood cells increased				
Study Overall, n[a]	469	471	489	1242
Grade 3, n (%)	0	0	0	0
Grade 4, n (%)	0	0	0	0
White blood cells decreased				
Study Overall, n[a]	469	471	489	1242
Grade 3, n (%)	25 (5.3)	12 (2.5)	25 (**5.1**)	9 (0.7)
Grade 4, n (%)	2 (0.4)	2 (0.4)	2 (0.4)	1 (0.1)
Neutrophil count decreased				
Study Overall, n[a]	467	467	487	1217
Grade 3, n (%)	28 (6.0)	9 (1.9)	28 (**5.7**)	16 (1.3)
Grade 4, n (%)	7 (1.5)	7 (1.5)	7 (1.4)	5 (0.4)
Lymphocyte count decreased				
Study Overall, n[a]	467	466	487	1149
Grade 3, n (%)	39 (8.4)	46 (9.9)	39 (8.0)	134 (11.7)
Grade 4, n (%)	4 (0.9)	5 (1.1)	4 (0.8)	10 (0.9)
Lymphocyte count increased				
Study Overall, n[a]	467	466	487	1149
Grade 3, n (%)	0	0	0	3 (0.3)
Grade 4, n (%)	0	0	0	0

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Subjects are counted only once for each row. Laboratory results were graded using CTCAE version 4.03. CTCAE = Common Terminology Criteria for Adverse Events, HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; QD = once daily.
a: Indicates the number of subjects with nonmissing baseline and postbaseline data; this number is used to calculate percentages within each laboratory test.

ALT, AST, ALP, bilirubin, and GGT

Shifts in CTCAE grade from Baseline to the worst postbaseline grade for liver parameters were presented and treatment-emergent laboratory results with CTCAE Grade 3 or 4 were summarized. Most changes were Grade 3. In the HCC Randomized Safety Set, there were Grade 3 or 4 increases in blood bilirubin (13.2% with lenvatinib vs 9.5% with sorafenib), ALT (7.9% vs 9.3%), AST (12.1% vs 17.9%), GGT (31.4% vs 37.7%), and ALP (6.6% vs 5.3%).

Application of the Hy's Law criteria to the HCC population was considered problematic due to the combination of underlying cirrhosis, other aetiologies, hepatitis and HCC; therefore, evaluation of hepatotoxicity was performed through evaluation of reported AEs rather than laboratory criteria.

The incidence of Grade ≥3 postbaseline values was higher in the All HCC Lenvatinib Safety Set than in the Non-HCC Lenvatinib Monotherapy Safety Set for AST, ALT, ALP, GGT and bilirubin, consistent with a diagnosis of HCC.

Application of Hy's Law criteria to the HCC population is problematic due to the combination of underlying cirrhosis, hepatitis, HCC, and other underlying aetiologies; therefore, the evaluation of hepatotoxicity is performed through evaluation of reported AEs rather than laboratory criteria.

ALT and AST: Sorafenib induced a higher increase of AST values than sorafenib. Several subjects in both treatment arms has grade 3 ALT/AST values at Baseline.

ALP: An increase is observed in both the lenvatinib and the sorafenib arms and results are similar in the Non-HCC safety set.

GGT: Lenvatinib induced a decrease of GGT, sorafenib a slight increase while little changes were observed in the Non-HCC safety set. Grade 3 and 4 AEs occurred in respectively 19.6% and 0.4% for lenvatinib and 20.8% and 0.8% for sorafenib.

Bilirubin: Median bilirubin values increased slightly in both arms and results are comparable with those observed in the Non-HCC safety set. A slightly higher incidence of Grade 3 or 4 bilirubin increased occurred with lenvatinib (13.2% vs 9.5%).

Renal Events

In the HCC Randomized Safety Set, 10 subjects (2.1%) in each treatment arm had Grade 3 increases in creatinine, and 1 subject (0.2%) in the sorafenib arm had a Grade 4 increase. More subjects in the lenvatinib (n=83 [17.6%]) than the sorafenib arm (n=33 [7.0%]) had shifts from Grade 0 or 1 to Grade 2 increases in creatinine.

In the sorafenib arm median creatinine values decreased while no change of the median values from baseline were observed for the lenvatinib safety sets that were comparable to those of the Non-HCC.

Increases in creatinine in the All HCC Lenvatinib Safety Set were consistent with those in the lenvatinib arm of the HCC Randomized Safety Set and the Non-HCC Lenvatinib Monotherapy Safety Set, although there were more Grade 2 increases in the HCC than the non-HCC set (17.4 vs. 13.8%).

Hypocalcaemia

In the HCC Randomized Safety Set, 2 subjects (0.8%) in the lenvatinib and no subjects in the sorafenib arm had a shift from Grade 0 or Grade 1 at Baseline to Grade 3 during treatment. Consistent with the AE data, fewer subjects had decreases in calcium from Grade 0 or 1 to Grade 3 or 4 in the All HCC Lenvatinib Safety Set (0.8%) than in the Non-HCC Lenvatinib Monotherapy Safety Set (2.6%).

Proteinuria (Based on Urinalysis)

In the HCC Randomized safety Set, a total of 10.9% (51/468) of subjects in the lenvatinib and 3.6% (17/470) of subjects in the sorafenib arm had a shift in urine dipstick protein from a score of negative, absent, or trace at Baseline to +3 during treatment. An additional 3.2% (15/468) of subjects in the lenvatinib and 0.9% (4/470) of subjects in the sorafenib arm had a shirt to +4.

Consistent with the AE data, more subjects in the Non-HCC Lenvatinib Monotherapy Safety Set had shifts to +3 or +4 during treatment (13.5% and 5.6%, respectively) compared to the All HCC lenvatinib Safety Set (11.1% and 3.7%, respectively).

Thyroid Stimulating Hormone

In the HCC Randomized Safety Set, baseline TSH was ≤ the upper limit of normal (ULN) in 89.6% of subjects in the lenvatinib arm and 90.1% in the sorafenib arm. The worst postbaseline value was >ULN in 69.6% of subjects in the lenvatinib arm and 32.2% in the sorafenib arm.

Thyroid-stimulating Hormone at Baseline and Worst Postbaseline Value – HCC Randomized, All HCC Lenvatinib, and Non-HCC Lenvatinib Monotherapy Safety Sets

Echocardiogram Data

In the HCC Randomized Safety Set, most subjects had a normal LVEF value at Baseline, with no postbaseline shift (lenvatinib, 98.8% [242/245]; sorafenib, 97.8% [268/274]). One subject (0.4%) in the lenvatinib arm had a shift from normal at Baseline to moderate dysfunction postbaseline. In the sorafenib arm, 2 subjects (0.7%) shifted from normal to mild and 1 subject (0.4%) to moderate dysfunction postbaseline. The maximum decrease from Baseline in mean LVEF was -0.2% in the lenvatinib arm and -0.5% in the sorafenib arm. No TEAEs of "ejection fraction decreased" were reported in either treatment arm.

Echocardiogram data were consistent in the lenvatinib arm of the HCC Randomized Safety Set and the All HCC Lenvatinib Safety Set. In the Non-HCC Lenvatinib Monotherapy Safety Set, there were greater changes in LVEF.

Blood Pressure Data

In the HCC Randomized Safety Set, 15.4% of subjects (72/468) in the lenvatinib and 11.0% of subjects (52/471) in the sorafenib arm had a shift from Grade 0 or Grade 1 at Baseline to Grade 3 during treatment. Consistent with the higher incidence of hypertension reported as an AE, more subjects in the Non-HCC Lenvatinib Monotherapy Safety Set (30.8%) had changes from Grade 0 or 1 to Grade 3 hypertension based on vital sign data compared with subjects with HCC (16.0% in the All HCC Lenvatinib Safety Set).

In the HCC Randomized Safety Set, increases in SBP and DBP were observed in both the lenvatinib and sorafenib treatment arms starting on Cycle 1 Day 15. For both arms, the largest change from Baseline occurred on Cycle 2 Day 1. Both DBP and SBP appeared to stabilize by Cycle 3 or Cycle 4, probably due to the introduction of antihypertensive medication(s), dose reduction of study drug, or both. The maximum increase in median SBP and DBP did not exceed +6.0 mmHg in either arm.*QT Prolongation Based on Electrocardiogram Data*

In the HCC Randomized Safety Set, 37 subjects (8.1%) in the lenvatinib arm and 20 subjects (4.3%) in the sorafenib arm had >60 msec increases in QTcF from baseline. Eleven subjects (2.4%) in each treatment arm had at least 1 postbaseline value of >500 msec in QTcF. Fewer subjects in the All Lenvatinib HCC Safety Set compared to the Non-HCC Lenvatinib Monotherapy Safety Set had at least 1 postbaseline QTcF value of >500 msec in (2.3% vs 5.7%).

Body Weight

In the HCC Randomized Safety Set, decreases in BW were observed in both the lenvatinib and sorafenib arms starting on Cycle 1 Day 15. The maximum decrease from Baseline in median BW was 5.1 kg with lenvatinib (on Cycle 21 Day 1) and 3.5 kg with sorafenib (on Cycle 11 Day 1). Decreases in BW in the lenvatinib arm were consistent with those observed in the Non-HCC Lenvatinib Monotherapy Safety Set.

Safety in special populations

Subgroup analyses were conducted in special populations as described and key observations were as follows:

- The incidence of Grade ≥3 TEAEs and SAEs increased with increasing age
- Females had a higher incidence of Grade ≥3 related TEAEs and of TEAEs leading to study drug dose reduction or interruption than did males.
- Asian and White lenvatinib-treated subjects had a similar safety profile.
- Lenvatinib-treated subjects from the Asia-Pacific and Western regions had a similar safety profile
- In Study 304, the overall AE profile for lenvatinib-treated subjects with baseline renal impairment (creatinine clearance <60 mL/min) was similar to those without renal impairment (creatinine clearance ≥60 mL/min) except for a higher incidence of TEAEs leading to study drug dose reduction in subjects with renal impairment.
- In Study 304, the incidence of Grade ≥3 TEAEs, SAEs, and TEAEs leading to study drug discontinuation was higher in subjects with a baseline CP score of 6 than of 5 in both the lenvatinib and sorafenib arms (HCC ISS Table 10.1.3). Lenvatinib-treated subjects with a baseline CP score of 6 also had a higher incidence of TEAEs leading to dose modifications (interruption, reduction).

Analyses of TAES based on intrinsic and extrinsic factors (subgroups) was performed. These included:

- Baseline demographic characteristics (drug-demographic interactions): age; sex; geographic region (Asia-Pacific; Western regions) and race.
- Baseline disease characteristics (drug-disease interactions): Baseline ECOG PS (score 0, ≥1); hepatic function (CP score 5, 6); and renal function (CrCl <60, ≥60 mL/min). Analyses of baseline hepatic and renal function were performed for the HCC Randomized Safety Set only.
- Region (Western, Asia-Pacific)
- Starting dose (8, 12 mg) for the HCC Randomized Safety Set and region (Western, Asia-Pacific)

If the incidence in one subgroup was ⩾10% higher or, for incidences less than 10%, if the incidence in one subgroup was at least twice that in another subgroup, that was considered an increase. Where similar between subgroup trends were <u>not</u> observed for the Non-HCC Lenvatinib Safety Set, these TEAEs are in italics.

<u>Age (<65, 65- <75, and ≥75 years)</u>

Most subjects were <65 years, 30% were 65- <75 years and ~ 13% were ≥75 years. The incidence of Grade ≥3 TEAEs and SAEs was highest in the oldest age group. TEAEs leading to withdrawal of study drug or dose modification also increased with increasing age. The incidence of the following common TEAEs was highest in the oldest age group: *decreased appetite, dehydration, arthralgia*, asthenia, *dizziness*, *dysphonia*, *hypertension*, *hypoalbuminemia*, *malaise*, peripheral oedema, proteinuria and pruritus. Hepatic encephalopathy, occurred at more than twice the incidence in the oldest age group (17.2%) than in the other 2 age groups (7.1% in each); a similar pattern was observed for the exposure-adjusted rate, SAEs and fatal AEs.

Serious AEs for which the incidence was higher in the oldest age group than in 1 or both the other age groups in the All HCC Lenvatinib Safety Set were (italics if a similar trend was <u>not</u> observed for the Non-HCC Lenvatinib Monotherapy Safety Set): *asthenia*, *hepatic encephalopathy*, *MI* and *pneumonia*; similar results were observed for the exposure-adjusted rates except for hypoalbuminemia and malaise, which were also highest in the oldest age group in the Non-HCC Lenvatinib Monotherapy Safety Set.

<u>Sex</u>

Across Studies 304 and 202, most subjects were male (>5:1 ratio). There was a higher incidence of Grade ≥3 related TEAEs (67.1% vs. 54.8%) and of TEAEs leading to dose reduction or interruption (71.2% vs. 60.0%) in females than in males. No between-sex differences were observed in the exposure-adjusted rates of episodes.

Table 81: Overview of Exposure-adjusted Treatment-emergent Adverse Events by Sex – HCC Randomized, All HCC Lenvatinib, and Non-HCC Monotherapy Safety Sets

	HCC Randomized Safety Set				All HCC Lenvatinib Safety Set		Non-HCC Lenvatinib Monotherapy Safety Set	
	Lenvatinib 8 or 12 mg		Sorafenib 800 mg		Lenvatinib 8 or 12 mg			
Episodes	Male (N=403) SY=281.6 n (AE Rate)	Female (N=73) SY=42.6 n (AE Rate)	Male (N=400) SY=197.0 n (AE Rate)	Female (N=75) SY=42.1 n (AE Rate)	Male (N=423) SY=297.4 n (AE Rate)	Female (N=73) SY=42.6 n (AE Rate)	Male (N=666) SY=628.7 n (AE Rate)	Female (N=661) SY=616 n (AE Rate)
All TEAEs	5133 (18.23)	991 (23.25)	3837 (19.48)	881 (20.91)	5500 (18.49)	991 (23.25)	14342 (22.81)	15083 (24.49)
Grade ≥3 TEAEs	847 (3.01)	176 (4.13)	646 (3.28)	149 (3.54)	896 (3.01)	176 (4.13)	1454 (2.31)	1750 (2.84)
Fatal AEs	54 (0.19)	7 (0.16)	32 (0.16)	4 (0.09)	55 (0.18)	7 (0.16)	68 (0.11)	62 (0.10)
Nonfatal SAEs	330 (1.17)	49 (1.15)	172 (0.87)	35 (0.83)	335 (1.13)	49 (1.15)	704 (1.12)	720 (1.17)

For the All HCC Lenvatinib Safety Set, the following common events occurred at a higher incidence in males than in females: *dysphonia, increased ALT, insomnia* and *musculoskeletal pain*. The following occurred at a higher incidence in females than in males: alopecia, *anaemia*, *prolonged QT*, *fatigue* and *hypertension.* Similar findings were observed for the exposure-adjusted episodes of events, except that the difference for hypertension was also observed for the Non-HCC Lenvatinib Monotherapy Safety Set.

The incidence of SAEs of hepatic encephalopathy did not differ between males and females but the SAE of hepatic failure (including fatal events) only occurred in males. The SAEs of cholestatic jaundice and upper GI haemorrhage occurred more frequently in females than in males in the All HCC Lenvatinib Safety Set.

Race

All subjects in Study 202 and most subjects in Study 304 were Asian (>2:1 ratio). There were 7 Black or African American subjects in the All HCC Lenvatinib Safety Set. The primary comparison is between the White and Asian subjects.

There was a higher incidence of severe (Grade ≥3) TEAEs, severe (Grade ≥3) related TEAEs and of TEAEs leading to study drug dose reduction in White than in Asian subjects. The incidence of fatal AEs was higher in White (17.2%) than in Asian subjects (11.0%) in the All HCC Lenvatinib Safety Set, although, this did not meet the 10% difference criterion. A similar numerical difference was not observed in the Non-HCC Lenvatinib Monotherapy Safety Set (10.1% vs 9.0%, respectively). The exposure-adjusted rates of episodes were numerically higher in White subjects than in Asian subjects for all categories of TEAEs.

For the All HCC Lenvatinib Safety Set, the following common events occurred at a higher incidence in White than in Asian subjects: acute kidney injury, asthenia, *fatigue*, flatulence, *hepatic encephalopathy*, *increased blood ALP*, *nausea*, *somnolence, thrombocytopenia* and *vomiting*. The following occurred at a higher incidence in Asian than in White subjects: *abdominal distension*, *alopecia*, decreased neutrophil count, decreased platelet count, decreased WBC count, maculo-papular rash, malaise, PPE syndrome and proteinuria. Similar findings were observed for the exposure-adjusted episodes of events except that an increased AE rate of nausea and of vomiting in White subjects was observed in the Non-HCC Lenvatinib Monotherapy Safety Set.

For the All HCC Lenvatinib Safety Set, the following SAEs occurred at a higher incidence in White than in Asian subjects: abdominal pain, accidental overdose, *hepatic encephalopathy*, multi organ dysfunction, MI, *pneumonia aspiration*, *portal vein thrombosis*, *seizure*, *umbilical hernia* and *urinary tract infection*. The following occurred at a higher incidence in Asian than in White subjects: cancer pain, *cholestatic jaundice*, *oesophageal varices haemorrhage*, pneumonia, *pyrexia*, and *upper GI haemorrhage*.

For the All HCC Lenvatinib Safety Set, the following fatal AEs (that occurred in at least 2 subjects in a racial group) occurred at a higher incidence in White subjects than in Asian subjects: general physical health deterioration, *hepatic encephalopathy*, multi organ dysfunction syndrome, *pneumonia aspiration*, and *portal vein thrombosis*. The following occurred at a higher incidence in Asian subjects than in White subjects: respiratory failure and *upper GI haemorrhage.*

Baseline ECOG PS score (0 vs. ≥1)

The incidence of TEAEs in the 2 ECOG PS groups in the All HCC Lenvatinib Safety Set was consistent with the known safety profile for lenvatinib, including a higher incidence of fatal AEs (19.2% vs. 9.2%; 0.29 vs. 0.13 episodes/SY) and a lower incidence of TEAEs leading to study drug dose reduction (30.2% vs. 43.4%) in subjects with an ECOG PS score ⩾1 than in those with a score of 0. No common TEAEs or SAEs occurred at a higher incidence in subjects with an ECOG PS score ⩾1 than those with a score of 0. The incidence of SAEs of hepatic encephalopathy was higher in subjects with an ECOG PS score of 0 than in those with a score ≥1, whilst the fatal AE of sepsis occurred at a higher incidence in subjects with an ECOG PS score ≥1.

Baseline renal function (CrCl <60 mL/min vs. ≥60 mL/min)

In general, the incidence of overall TEAEs was similar for subjects split by baseline CrCl. There was a higher incidence of TEAEs leading to study drug dose reduction (48.4% vs. 37.2%) in subjects with renal impairment (CrCl <60 mL/min).

The following common events occurred at a higher incidence in those with lower baseline in both treatment groups: dehydration, dysphonia, hepatic encephalopathy, hypothyroidism, peripheral oedema, and proteinuria; and in the lenvatinib-treated subjects for constipation, decreased appetite, diarrhoea, fatigue and vomiting.

The incidence of Grade ≥3 TEAEs was higher in the subjects with baseline CrCl <60 mL/min compared with CrCl ≥60 mL/min in both treatment groups for the following events: anaemia, decreased lymphocyte count, pneumonia and respiratory failure; and in the lenvatinib-treated subjects for cachexia, dehydration, dyspnoea, hyponatremia, MI, portal vein thrombosis, syncope and upper GI haemorrhage.

The incidence of SAEs was higher in the subjects with lower baseline CrCl in both treatment groups for pneumonia; and in the lenvatinib-treated subjects for hyponatremia, muscular weakness, MI and peripheral oedema.

Baseline hepatic function

Most subjects (>75%) had a baseline CP score of 5 (N=722), 221 subjects had a score of 6, 7 subjects had a score of 7 and 1 subject had a score of 8. The analysis was limited to subjects with a baseline CP score of 5 or 6.

The incidence of Grade ≥3 TEAEs (86% vs. 71.6%), SAEs (56.1% vs. 38.8%) and TEAEs leading to study drug discontinuation (27.1% vs. 16.9%) was higher in subjects with a baseline CP score of 6 than of 5 in both the lenvatinib and sorafenib arms (% provided for lenvatinib arm). Lenvatinib-treated subjects with a baseline CP score of 6 also had a higher incidence of TEAEs leading to dose modifications (70.1% vs. 59.6%).

The incidence of Grade ≥3 TEAEs was higher in the subjects with baseline CP score of 6 compared with 5 in both treatment groups for: abdominal pain, oesophageal varices haemorrhage, fatigue, general physical health deterioration and hyperkalaemia; and in lenvatinib-treated subjects for anaemia, decreased blood sodium, prolonged QT, headache, hepatic cirrhosis, hepatic encephalopathy, hyperbilirubinemia, hypoalbuminemia, hypokalaemia, increased blood bilirubin, increased blood sodium,

increased lipase, liver abscess, peripheral oedema, pneumonia aspiration, portal vein thrombosis and upper GI haemorrhage.

The incidence of SAEs was higher in subjects with baseline CP score of 6 compared with 5 in both treatment groups for oesophageal varices haemorrhage and general physical health deterioration; and in the lenvatinib-treated subjects for bile duct obstruction, dyspnoea, headache, hepatic cirrhosis, hepatic encephalopathy, hepatic failure, liver abscess, pneumonia aspiration, portal vein thrombosis, proteinuria, pyrexia, umbilical hernia and upper GI haemorrhage.

Geographic Region (Asia-Pacific vs. Western)

There were approximately twice as many subjects from the Asia-Pacific compared to the Western region in both HCC safety sets. There was a higher incidence of Grade ≥3 TEAEs (83.2% vs. 71.0%), Grade ≥3 related TEAEs (65.8% vs. 52.3%) and TEAEs leading to dose reduction (46.5% vs. 34.9%) in subjects from the Western region than in those from Asia-Pacific; this trend was in the opposite direction for the Non-HCC Lenvatinib Monotherapy Safety Set.

Table 82: Overview of Treatment-Emergent Adverse Event Episodes Adjusted for Treatment Exposure by Starting dose and Region - Safety Analysis Set

	HCC Randomized Safety Set							
	Lenvatinib Starting Dose 8 mg[a]		Lenvatinib Starting Dose 12 mg[a]		Lenvatinib Total		Sorafenib 800 mg	
Episodes	Asia-Pacific (N=130) SY=85.7 n (AE Rate)	Western Region (N=21) SY=9.5 n (AE Rate)	Asia-Pacific (N=191) SY=134.9 n (AE Rate)	Western Region (N=134) SY=94.2 n (AE Rate)	Asia-Pacific (N=321) SY=220.5 n (AE Rate)	Western Region (N=155) SY=103.6 n (AE Rate)	Asia-Pacific (N=319) SY=150.2 n (AE Rate)	Western Region (N=156) SY=88.8 n (AE Rate)
All TEAEs	1531 (17.87)	206 (21.79)	2454 (18.19)	1933 (20.52)	3985 (18.07)	2139 (20.64)	2939 (19.56)	1779 (20.02)
Related TEAEs	868 (10.13)	106 (11.21)	1486 (11.02)	1086 (11.53)	2354 (10.67)	1192 (11.50)	1778 (11.83)	1087 (12.23)
Grade ≥3 TEAEs	244 (2.85)	34 (3.60)	409 (3.03)	336 (3.57)	653 (2.96)	370 (3.57)	509 (3.39)	286 (3.22)
Related Grade ≥3 TEAEs	109 (1.27)	17 (1.80)	223 (1.65)	168 (1.78)	332 (1.51)	185 (1.79)	266 (1.77)	164 (1.85)
All SAEs	96 (1.12)	17 (1.80)	161 (1.19)	135 (1.43)	257 (1.17)	152 (1.47)	154 (1.03)	78 (0.88)
Fatal AEs [a]	12 (0.14)	2 (0.21)	25 (0.19)	22 (0.23)	37 (0.17)	24 (0.23)	25 (0.17)	11 (0.12)
Nonfatal SAEs	92 (1.07)	16 (1.69)	149 (1.10)	122 (1.30)	241 (1.09)	138 (1.33)	134 (0.89)	73 (0.82)

The incidence of fatal AEs was numerically higher in subjects from the West (15.5%) than from Asia-Pacific (11.1%) in the All HCC Lenvatinib Safety Set; a difference was observed in the Non-HCC Lenvatinib Monotherapy Safety Set (10.3% vs 7.6%, respectively). For the exposure-adjusted rates, there was an increase in TEAEs leading to dose reduction interruption in subjects from the Western region compared with those from Asia-Pacific for the All HCC Lenvatinib Safety Set.

More subjects in the Western than in the Asia-Pacific region had cirrhosis at Baseline as assessed by independent imaging review (81.9% vs 71.0%, respectively).

For the All HCC Lenvatinib Safety Set, the following TEAEs occurred at a higher incidence in subjects from Asia-Pacific than from the West: *abdominal distension*, alopecia, decreased neutrophil count, decreased platelet count, decreased WBC count, PPE syndrome and proteinuria. The following TEAEs occurred at a higher incidence in subjects from the West: *arthralgia*, asthenia, *hepatic encephalopathy*, *nausea*, *thrombocytopenia* and *vomiting*. Similar findings were observed for the exposure-adjusted episodes.

The following SAEs occurred at a higher incidence in subjects from Asia-Pacific than from the West: *ascites*, cancer pain, *cholestatic jaundice*, decreased appetite, *dyspnoea*, *oesophageal varices haemorrhage*, pneumonia, *pyrexia*, and *upper GI haemorrhage*. The following SAEs occurred at a higher incidence in subjects from the West: *abdominal pain*, general physical health deterioration, *hepatic encephalopathy*, *hyponatremia*, multi organ dysfunction syndrome, MI, *nausea*, *pneumonia aspiration*, *portal vein thrombosis*, pulmonary embolism, seizure, *umbilical hernia*, *urinary tract infection* and vomiting.

The following fatal AEs occurred at a higher incidence in subjects from Asia-Pacific: *respiratory failure*, *sepsis* and *upper GI haemorrhage*. The following fatal AEs occurred at a higher incidence in subjects from the West: general physical health deterioration, *hepatic encephalopathy*, multi organ dysfunction syndrome, *pneumonia aspiration* and *portal vein thrombosis.*

Lenvatinib starting dose

Starting dose was based on body weight rather than randomised; therefore, there were different numbers of subjects (325 for the 12-mg vs 151 for the 8-mg) and differences in demographic and baseline disease characteristics between the starting dose groups. A lower proportion of subjects from the Asia Pacific region (58.4% vs. 86.1%) and a higher proportion of males (91.4% vs. 70.2%) received the 12mg compared with the 8mg starting dose. Median duration of treatment was slightly longer in the 12-mg (6.3 months) compared with the 8-mg (5.6 months) starting dose group in Study 304.

The incidence of Grade ≥3 and of related Grade ≥3 TEAEs was higher in the 12mg than the 8mg starting dose group. There were no notable differences in the AE profile when adjusted by treatment duration.

The rates (episodes/ SY) of TEAEs were assessed by starting dose and by region (Asia-Pacific and Western). For the Western region, the episodes of Grade ≥3 TEAEs that only occurred in the 12-mg starting dose group were small (≤10), except for hepatic encephalopathy (20 episodes; AE rate 0.21 episodes/SY) and increased blood bilirubin (13 episodes; AE rate 0.14 episodes/SY). These differences were not observed within the Asia-Pacific region. There was a higher AE rate for hepatic encephalopathy in the 12-mg starting dose compared with the 8-mg starting dose (AE rates, 0.19 episodes/SY vs 0) in the Western region. However, there were 134 subjects in the ≥60 kg group (12 mg) compared with only 21 subjects in the <60 kg group (8-mg) in Western region, making comparison difficult.

Safety related to drug-drug interactions and other interactions

See section on clinical pharmacology.

Discontinuation due to adverse events

Adverse Events Leading to Treatment Discontinuation

Table 83: Subject Disposition and Reasons for Discontinuation from Treatment – All Safety Sets

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
	Lenvatinib 8 or 12 mg (N=476) n (%)	Sorafenib 800 mg (N=475) n (%)	Lenvatinib 8 or 12 mg (N=496) n (%)	Lenvatinib (N=1327) n (%)
Treated	476	475	496	1327[a]
Treatment ongoing at data cutoff date	27 (5.7)	25 (5.3)	27 (5.4)	61 (4.6)
Discontinued Treatment	449 (94.3)	450 (94.7)	469 (94.6)	1236 (93.1)
Primary reason(s) for discontinuation from treatment[b]				
Disease Progression	311 (65.3)[c]	347 (**73.1**)[c]	324 (65.3)	735 (55.4)
Clinical Progression	32 (6.7)[d]	33 (6.9)[d]	na	Na
Adverse event	63 (**13.2**)	43 (9.1)	67 (13.5)	277 (20.9)
Subject choice	28 (**5.9**)	14 (2.9)	28 (5.6)	46 (3.5)
Lost to follow-up	3 (0.6)	1 (0.2)	3 (0.6)	4 (0.3)
Administrative	44 (9.2)	45 (9.5)	47 (9.5)	174 (13.1)
Withdrawal of consent from study	9 (1.9)	5 (1.1)	9 (1.8)	31 (2.3)
Other	3 (0.6)[e]	7 (1.5)f	38 (7.7)[g]	143 (10.8)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Percentages are based on total number of subjects in the corresponding safety set within the relevant treatment group.

CRF = case report form; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; na = not available; QD = once daily.

a: 30 subjects (6 from Study 104, 23 from Study 208, and 1 from Study 209) completed treatment before the data cutoff date and are not included in either the “Treatment ongoing at data cutoff date” and “Discontinued treatment” subcategories.

b: Primary reasons for discontinuation from treatment are based on CRF disposition page.

c: Radiological progression per modified Response Evaluation Criteria for Solid Tumours.

d: Clinical progression was collected under the "Other" category in the CRF.

e: Other reasons for discontinuation in the lenvatinib arm: subject required surgery (n=2) and investigator choice (n=1).

f: Other reasons for discontinuation in the sorafenib arm: investigator choice (n=5); need for a prohibited medication (warfarin; 1 subject); and discontinuation to undergo liver transplantation (n=1).

g: Includes subjects from Study 304 with clinical progression.

TEAEs leading to discontinuation in ⩾2 subjects in any group in the HCC Safety Sets are summarized by preferred term in the table below.

Table 84: TEAEs leading to Treatment discontinuation in 2 or more patients, all safety sets.

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
Preferred Term	**Lenvatinib 8 or 12 mg (N=476) n (%)**	**Sorafenib 800 mg (N=475) n (%)**	**Lenvatinib 8 or 12 mg (N=496) n (%)**	**Lenvatinib (N=1327) n (%)**
Subjects with any TEAEs Leading to Treatment Discontinuation	94 (19.7)	69 (14.5)	100 (20.2)	336 (25.3)
Fatigue	7 (1.5)	5 (1.1)	7 (1.4)	23 (1.7)
Hepatic encephalopathy	7 (1.5)	0	**8 (1.6)**	0
Blood bilirubin increased	6 (1.3)	1 (0.2)	**6 (1.2)**	1 (0.1)
Hepatic failure	5 (1.1)	3 (0.6)	**5 (1.0)**	1 (0.1)
Cerebral haemorrhage	3 (0.6)	0	**3 (0.6)**	0
Jaundice cholestatic	3 (0.6)	1 (0.2)	**3 (0.6)**	0
Myocardial infarction	3 (0.6)	0	3 (0.6)	4 (0.3)
Proteinuria	3 (0.6)	1 (0.2)	6 (1.2)	22 (1.7)
Sepsis	3 (0.6)	0	3 (0.6)	8 (0.6)
Abdominal pain	2 (0.4)	5 (1.1)	2 (0.4)	4 (0.3)
Abdominal pain upper	2 (0.4)	0	2 (0.4)	2 (0.2)
Bile duct obstruction	2 (0.4)	0	2 (0.4)	0
Cerebrovascular accident	2 (0.4)	0	2 (0.4)	7 (0.5)
ECOG PS worsened	2 (0.4)	1 (0.2)	2 (0.4)	0
General physical health deterioration	2 (0.4)	4 (0.8)	2 (0.4)	10 (0.8)
Malignant neoplasm progression	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.2)
Multiple organ dysfunction syndrome	2 (0.4)	1 (0.2)	2 (0.4)	0
Portal vein thrombosis	2 (0.4)	0	2 (0.4)	0
Upper gastrointestinal haemorrhage	2 (0.4)	1 (0.2)	2 (0.4)	0
Ascites	1 (0.2)	4 (0.8)	1 (0.2)	1 (0.1)
Renal impairment	1 (0.2)	2 (0.4)	1 (0.2)	0
Respiratory failure	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.1)
Sudden death	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.1)
Tumour rupture	1 (0.2)	0	2 (0.4)	0
Jaundice	0	3 (0.6)	0	1 (0.1)
PPE	0	3 (0.6)	0	3 (0.2)
Diarrhoea	0	2 (0.4)	0	8 (0.6)
Drug eruption	0	2 (0.4)	0	0
Gastrointestinal haemorrhage	0	2 (0.4)	0	0
Rash maculo-papular	0	2 (0.4)	0	0
Tumour pain	0	2 (0.4)	0	0

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD.
Display is in decreasing order of AE rate in the Lenvatinib group of the HCC Randomized Safety Set. Subjects with 2 or more AEs in the same preferred term were counted only once. Percentages are based on the total number of subjects in the corresponding safety set within the relevant treatment group. Adverse event terms were coded using MedDRA version 19.1.
AE = adverse event; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; TEAE = treatment-emergent adverse event; PPE = Palmar-plantar erythrodysaesthesia syndrome; ECOG PS = Eastern Cooperative Oncology Group Performance Status

Adverse Events Leading to Treatment Modification

TEAEs leading to treatment modification (interruption or reduction) in ≥2% of subjects in any group in the HCC Safety Sets are summarized by PT in the table below.

Table 85: TEAEs Leading to Treatment Modification (Interruption or Reduction) in ≥2% in any Safety Sets

	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
Preferred Term	**Lenvatinib 8 or 12 mg (N=476) n (%)**	**Sorafenib 800 mg (N=475) n (%)**	**Lenvatinib 8 or 12 mg (N=496) n (%)**	**Lenvatinib (N=1327) n (%)**
Subjects with any TEAEs Leading to Treatment Modification	*294 (61.8)*	*264 (55.6)*	*309 (62.3)*	*958 (72.2)*
Decreased appetite	36 (**7.6**)	15 (3.2)	38 (7.7)	117 (8.8)
Diarrhoea	36 (7.6)	35 (7.4)	36 (7.3)	198 (14.9)
Proteinuria	33 (**6.9**)	7 (1.5)	37 (7.5)	209 (15.7)
Hypertension	29 (6.1)	18 (3.8)	29 (5.8)	217 (16.4)
Fatigue	27 (5.7)	17 (3.6)	29 (5.8)	164 (12.4)
Palmar-plantar erythrodysaesthesia syndrome	25 (5.3)	88 (18.5)	27 (5.4)	94 (7.1)
Platelet count decreased	22 (4.6)	12 (2.5)	25 (**5.0**)	16 (1.2)
Blood bilirubin increased	20 (4.2)	14 (2.9)	20 (**4.0**)	6 (0.5)
Hepatic encephalopathy	20 (**4.2**)	3 (0.6)	21 (**4.2**)	0 (0.0)
Weight decreased	20 (**4.2**)	4 (0.8)	21 (4.2)	112 (8.4)
Asthenia	16 (3.4)	9 (1.9)	16 (3.2)	80 (6.0)
Nausea	16 (3.4)	9 (1.9)	17 (3.4)	113 (8.5)
Pyrexia	12 (**2.5**)	5 (1.1)	12 (**2.4**)	15 (1.1)
Vomiting	12 (**2.5**)	6 (1.3)	13 (2.6)	92 (6.9)
Neutrophil count decreased	11 (**2.3**)	5 (1.1)	11 (**2.2**)	5 (0.4)
Ascites	10 (2.1)	5 (1.1)	10 (**2.0**)	0 (0.0)
Aspartate aminotransferase increased	9 (1.9)	18 (3.8)	9 (1.8)	18 (1.4)
Rash	2 (0.4)	10 (2.1)	2 (0.4)	13 (1.0)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Display is in decreasing order of AE rate in the Lenvatinib group of the HCC Randomized Safety Set. Subjects with 2 or more adverse events in the same preferred term were counted only once. Percentages are based on the total number of subjects in the corresponding safety set within the relevant treatment group. Adverse event terms were coded using MedDRA version 19.1. AE = adverse event; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; TEAE = treatment-emergent adverse event.

Post marketing experience

Lenvatinib was first approved on 13 Feb 2015 (International Birth Date [IBD]) in the USA for the "treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC." Subsequently, lenvatinib has been approved for radiotherapy refractory-DTC in over 50 countries worldwide, including the EU on 28 May 2015. The RCC indication has been approved in over 30 countries worldwide. Approximately 6,400 new patients have been exposed to lenvatinib from the IBD until the data lock date of the most recent PSUR (12 Feb 2017). The most frequently reported adverse reactions post-marketing are hypertension, proteinuria, diarrhoea, PPE syndrome and decreased appetite. Cumulatively, 2435 patients have been exposed to lenvatinib in clinical trials. Marketing exposure (new patients) is estimated at 2208 patients and 6367 patients cumulatively. The most frequently reported adverse reactions postmarketing are hypertension, proteinuria, diarrhoea, PPE syndrome and decreased appetite. Signals for pancreatitis and cholecystitis were evaluated in the PSUR reporting period and the CCDS was updated to include cholecystitis, pancreatitis, lipase increase and amylase increase in Section 4.8, Undesirable effects. Evaluation of a signal of interstitial lung disease is ongoing.

2.5.1. Discussion on clinical safety

Clinical safety data in support of the sought new indication for hepatocellular carcinoma (HCC) patients are based primarily on results of one pivotal randomised study (study 304). The starting dose of

lenvatinib was based on baseline body weight (BW): 12 mg QD for subjects with a BW of ≥60 kg (325 pts) and 8 mg QD for subjects with a BW of <60 kg (151 pts).

The main issues identified are SAEs associated with decreased liver function due to the underlying disease and AEs in special populations.

Safety findings in study 304

The safety findings in the lenvatinib arm of study 304 were generally consistent with the known safety profile of lenvatinib monotherapy previously observed in DTC and described in the SmPC.

The majority of patients exposed to lenvatinib reported adverse events (AEs). The toxicity of lenvatinib was overall manageable, by dose interruptions and dose reductions.

The increased rate of hepatotoxicity (hepatic failure/ hepatic encephalopathy) with lenvatinib can to some extent be attributed to imbalances in baseline risk factors. However the proportions of patients with elevated ALT/ AST was similar in the 2 treatment arms, including at the end of therapy.

The difference between treatment duration and time to progression in the lenvatinib arm was remarkable while medians for the duration of treatment and time to progression were the same in the sorafenib arm. This could be explained by differences in baseline characteristics and treatment discontinuation. The information regarding duration of treatment is provided in the SmPC.

Section 4.8 of the SmPC has been updated to describe the safety profile of lenvatinib based on data from 496 HCC patients in addition to 452 DTC patients thus allowing characterisation of common adverse drug reactions in DTC and HCC patients. The incidences of the following ADRs “leukopenia”, “neutropenia”, “hypothyroidism”, “blood bilirubin increased”, “hypoalbuminaemia”, “alanine transferase increased” and “aspartate aminotransferase increased” were found to be increased from “common” in the DTC patients to “very common” in the HCC patients.

The most frequently reported adverse reactions (occurring in ≥30% of patients) are hypertension (44.0%), diarrhoea (38.1%), decreased appetite (34.9%), fatigue (30.6%), and weight decreased (30.4%).

The most important serious adverse reactions were hepatic failure (2.8%), hepatic encephalopathy (4.6%), oesophageal varices haemorrhage (1.4%), cerebral haemorrhage (0.6%), arterial thromboembolic events (2.0%) including myocardial infarction (0.8%), cerebral infarction (0.4%) and cerebrovascular accident (0.4%) and renal failure/impairment events (1.4%). There was a higher incidence of decreased neutrophil count in patients with HCC (8.7% on lenvatinib than in other non- HCC tumour types (1.4%)), which was not associated with infection, sepsis or bacterial peritonitis. No new ADR was observed in study 304

When reviewed by region and adjusted for treatment duration, the highest rate of TEAEs, Grade ≥3 TEAEs, non-fatal SAEs and fatal AEs appeared to occur in the Western region in lenvatinib treated patients, although most fatal AEs were attributed to PD. There were more TEAEs leading to dose reduction in the West compared to Asia Pacific. More subjects in the Western than in the Asia-Pacific region had cirrhosis at Baseline as assessed by independent imaging review (81.9% vs 71.0%, respectively) but not per CRF.

In the Phase 3 HCC trial, hypertension (including hypertension, blood pressure increased, blood pressure diastolic increased and orthostatic hypertension) was reported in 44.5% of lenvatinib-treated patients and Grade 3 hypertension occurred in 23.5%. The median time to onset was 26 days. The majority of cases recovered following dose interruption or reduction, which occurred in 3.6% and 3.4% of patients respectively. One subject (0.2%) discontinued lenvatinib due to hypertension.

Proteinuria was reported in 26.3% of lenvatinib-treated patients and Grade 3 reactions occurred in 5.9%. The median time to onset was 6.1 weeks. The majority of cases recovered following dose interruption or reduction, which occurred in 6.9% and 2.5% of patients respectively. Proteinuria led to permanent treatment discontinuation in 0.6% of patients.

Renal failure/impairment event developed in 7.1% of lenvatinib-treated patients. Grade 3 or greater reactions occurred in 1.9% of lenvatinib-treated patients.

Cardiac dysfunction (including congestive cardiac failure, cardiogenic shock, and cardiopulmonary failure) was reported in 0.6% of patients (0.4% were Grade ≥ 3) in the lenvatinib-treated group.

There was 1 event of PRES (Grade 2) in the lenvatinib-treated group.

In the Phase 3 REFLECT trial, the most commonly reported hepatotoxicity adverse reactions were increased blood bilirubin (14.9%), increased aspartate aminotransferase (13.7%), increased alanine aminotransferase (11.1%), hypoalbuminaemia (9.2%), hepatic encephalopathy (8.0%), increased gamma-glutamyltransferase (7.8%) and increased blood alkaline phosphatase (6.7%). The median time to onset of hepatotoxocity adverse reactions was 6.4 weeks. Hepatotoxicity reactions of ≥ Grade 3 occurred in 26.1% of lenvatinib-treated patients. Hepatic failure (including fatal events in 12 patients) occurred in 3.6% of patients (all were ≥ Grade 3). Hepatic encephalopathy (including fatal events in 4 patients) occurred in 8.4% of patients (5.5% were ≥ Grade 3). There were 17 (3.6%) deaths due to hepatotoxicity events in the lenvatinib arm and 4 (0.8%) deaths in the sorafenib arm. Hepatotoxicity adverse reactions led to dose interruptions and reductions in 12.2% and 7.4% of lenvatinib-treated patients respectively, and to permanent discontinuation in 5.5%.

Across clinical studies in which 1327 patients received lenvatinib monotherapy in indications other than HCC, hepatic failure (including fatal events) was reported in 4 patients (0.3%), liver injury in 2 patients (0.2%), acute hepatitis in 2 patients (0.2%), and hepatocellular injury in 1 patient (0.1%).

Patients with worse hepatic impairment and/or greater liver tumour burden at baseline had a higher risk of developing hepatic encephalopathy and hepatic failure. Hepatic encephalopathy also occurred more frequently in patients aged 75 years and older. Approximately half of the events of hepatic failure and one third of the events of the hepatic encephalopathy were reported in patients with disease progression.

Data in HCC patients with moderate hepatic impairment (Child-Pugh B) are very limited and there are currently no data available in HCC patients with severe hepatic impairment (Child-Pugh C). Since lenvatinib is mainly eliminated by hepatic metabolism, an increase in exposure in patients with moderate to severe hepatic impairment is expected.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. Patients with HCC should be monitored for worsening liver function including hepatic encephalopathy (see section 4.4 of the SmPC).

In the Phase 3 REFLECT trial, arterial thromboembolic events were reported in 2.3% of patients treated with lenvatinib.

In the Phase 3 REFLECT trial, haemorrhage was reported in 24.6% of patients and 5.0% were Grade ≥ 3. Grade 3 reactions occurred in 3.4%, Grade 4 reactions in 0.2% and 7 patients (1.5%) had a grade 5 reaction including cerebral haemorrhage, upper gastrointestinal haemorrhage, intestinal haemorrhage and tumour haemorrhage. The median time to first onset was 11.9 weeks. A haemorrhage event led to dose interruption or reduction in 3.2% and 0.8% patients respectively and to treatment discontinuation in 1.7% of patients.

Screening for and subsequent treatment of oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with lenvatinib.

Hypocalcaemia was reported in 1.1% of patients, with grade 3 reactions occurring in 0.4%. Lenvatinib dose interruption due to hypocalcaemia occurred in one subject (0.2%) and there were no dose reductions or discontinuations.

Events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients.

QT/QTc interval prolongation was reported in 6.9% of lenvatinib-treated patients. The incidence of QTcF interval prolongation of greater than 500ms was 2.4%.

In the Phase 3 HCC trial, 89.6% of patients had a baseline TSH level of less than the upper limit of normal. Elevation of TSH above the upper limit of normal was observed post baseline in 69.6% of lenvatinib-treated patients.

Diarrhoea was reported in 38.7% of patients treated with lenvatinib (4.2% were Grade ≥ 3).

Special populations

Patients of age ≥75 years were more likely to experience hypertension, proteinuria, decreased appetite, asthenia, dehydration, dizziness and hepatic encephalopathy. Hepatic encephalopathy occurred at more than twice the incidence in patients aged ≥75 years (17.2%) than in those <75 years (7.1%). Hepatic encephalopathy tended to be associated with adverse disease characteristics at baseline or with the use of concomitant medications. Arterial thromboembolic events also occurred at an increased incidence in this age group.

Females had a higher incidence of hypertension, fatigue and ECG QT prolongation. Hepatic failure events were observed in male patients only.

Asian patients had a higher incidence than Caucasian patients of proteinuria, decreased neutrophil count, decreased platelet count, decreased white blood count and PPE syndrome, while Caucasian patients had a higher incidence of fatigue, hepatic encephalopathy, acute kidney injury, anxiety, asthenia, nausea, thrombocytopenia and vomiting.

Patients with a baseline Child Pugh (CP) score of 6 compare to a baseline CP score of 5 had a higher incidence of decreased appetite, fatigue, proteinuria, hepatic encephalopathy and hepatic failure. Hepatotoxicity events and haemorrhage events also occurred at a higher incidence in CP score 6 patients compared to CP score 5 patients.

Patients with baseline renal impairment had a higher incidence of fatigue, hypothyroidism, dehydration, diarrhoea, decreased appetite, proteinuria and hepatic encephalopathy. These patients also had a higher incidence of renal reactions and arterial thromboembolic events.

In 496 patients with HCC, dose modification (interruption or reduction) and discontinuation were the actions taken for an adverse reaction in 62.3% and 20.2% of patients, respectively. Adverse reactions that most commonly led to dose modifications (in ⩾5% of patients) were decreased appetite, diarrhoea, proteinuria, hypertension, fatigue, PPE and platelet count decreased. Adverse reactions that most commonly led to discontinuation of lenvatinib were hepatic encephalopathy, fatigue, blood bilirubin increased, proteinuria and hepatic failure (see section 4.8 of the SmPC).

A post-marketing Phase IV safety study will be performed to gather further data in the EU population (or relevant Western population) and to better characterise safety concern of hepatotoxicity (including hepatic encephalopathy) in real-life conditions and to accurately collect baseline demographic and disease-related characteristics for potential determination of risk factors contributing to incidence and severity of hepatic-related events and mortality. It is recommended that both Child-Pugh A and B

patients are included to mirror expected clinical use. The MAH will ensure that a sufficient number of patients with Child-Pugh B is studied (see RMP).

Baseline information of importance includes: Child-Pugh score, ECOG, BCLC, Stage, previous treatments, extrahepatic spread/ vascular invasion, bilirubin, albumin, INR, ascites, encephalopathy, aetiology (HBV, HCV, ETOH, NASH, other), cirrhosis, weight. Child-Pugh score and performance status changes should be collected during the study, as well as dose modifications/discontinuations, weight, concomitant medications.

The MAH should also discuss relevant comparisons (preferably within the study) of the lenvatinib data to allow an assessment of hepatic safety in an EU-population treated with lenvatinib.

The study protocol should be submitted within 3 months *of* the approval of the new indication.

PRO analyses

Assessments of HRQoL scores were performed using the generic cancer HRQoL instrument (EORTC QLQ-C30), the HCC-specific module (EORTC QLQ-HCC18), and the generic HRQoL instrument, EQ-5D. Patients were asked to complete each of the 3 questionnaires at Baseline, on Day 1 of each subsequent cycle, and at the OTV. Due to the open-label nature of the study, results should be interpreted with caution.

2.5.2. Conclusions on clinical safety

The incidence and the severity of AEs in lenvatinib group are somewhat higher than the one observed with sorafenib. In particular, incidence of hepatic-related serious AEs and hepatic-related deaths, including lethal hepatic failure) was higher in the lenvatinib arm (n=21) than in sorafenib arm (n=2). Hepatic encephalopathy was 4 times more frequent in lenvatinib arm and remained higher after adjustment by duration of exposure (0.17 rate in lenvatinib arm, n=55; 0.04 rate in sorafenib arm, n=10), mostly due to cases occurred with the lenvatinib dose of 12mg (0.20 rate, n = 45). Given that patient with better prognosis has been enrolled in the Study 304 comparing with historical trials and that more vulnerable patient population would be exposed to lenvatinib in real life conditions, further characterisation of safety profile is needed in EU population (Western group represented 1/3 of the trial population). All the episodes of hepatic encephalopathy with the dose of 12 mg occurred in Western population.

Patients with well-preserved liver function (Child-Pugh A) have been included in the study and uncertainty remains as to the safety profile of lenvatinib in patients with liver impairment, who represent a significant proportion of patients in real life conditions.

The CHMP considers the following measures necessary to address issues related to safety:

A non-interventional post-marketing Phase IV safety study will be performed in the EU (or Western population) to better characterise safety, primarily hepatotoxicity, in real-life conditions and to inform further on contributing factors. The study protocol will be submitted within 3 months of the approval of the new indication (see RMP).

2.5.3. PSUR cycle

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

2.6. Risk management plan

Safety concerns

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 • Hypothyroidism • Gastrointestinal perforation and fistula formation • Non-Gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine)
Important potential risks	• Venous thromboembolic events (VTEs) • Abnormal pregnancy outcome, excretion of lenvatinib in milk • Male and female fertility • Bone and teeth abnormalities in the paediatric population • Impaired wound healing • Interstitial Lung Disease (ILD)-like conditions • Potential of lenvatinib for induction/inhibition of CYP-3A4 Mediated Drug Metabolism • Overdose (concomitant everolimus) (RCC)
Missing information	• Use in severe hepatic impairment • Use in severe renal impairment • Use in patients from ethnic origins other than Caucasian or Asian • Long-term use

Pharmacovigilance plan

Table 86 On-going and planned additional PhV studies/activities in the pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
Study 109 (Interventional Clinical Study: Category 3)	A drug-drug interaction (DDI) study to investigate the potential of lenvatinib for CYP3A4 inhibition/induction	To investigate correctly the potential of lenvatinib for CYP3A4 inhibition/induction, an in vivo study with midazolam as a probe substrate for CYP3A4.	Planned	Mar 2018
Study E7080-A001-010 (Interventional Clinical Study: Category 3)	A Multicenter Phase 0 Study In Healthy Subjects As Well As Subjects With Either Hepatic Or Renal Impairment To Obtain Plasma To Assess In Vitro Lenvatinib Protein Binding	In order to define correctly the dose-adjustment in patients with severe hepatic and renal impairment and determine unbound drug concentration	Planned	June 2019
DTC				
Study 201 (Interventional Clinical Study: Category 3)	To evaluate the long-term safety of lenvatinib in Medullary and Iodine-131 Refractory, Unresectable DTC, Stratified by Histology	Continue to characterize/ confirm current safety profile of lenvatinib in DTC	Completed *	Feb 2014
Study 303 (Interventional Clinical Study: Category 3)	To evaluate long-term safety of lenvatinib in patients with RR-DTC in a randomized, double-blind, placebo-controlled Phase 3 study.	Continue to characterize/ confirm current safety profile of lenvatinib in DTC	Completed *	Ongoing

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
Study 211 (Interventional Clinical Study: Category 3)	Primary Objective • To determine whether a starting dose of lenvatinib 20 mg or 14 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 6 months [ORR6M]) with an improved safety profile compared to 24 mg QD (based on treatment-emergent adverse events [TEAEs] of Grade 3 or higher in the first 6 months after randomization). Secondary Objectives: • To evaluate PFS • To evaluate PFS2 • To evaluate safety and tolerability • To evaluate PK-PD relationship between exposure and biomarkers /efficacy/safety • To evaluate impact on HR QOL Exploratory Objectives: • To explore OS •To explore TSH, and other serum biomarkers as potential biomarkers for tumour response • To explore DNA sequence variants in genes that may influence PK, safety, or pharmacodynamics data	Characterize/ confirm safety profile of lenvatinib in DTC at lower doses, to determine whether a lower dose starting dose of lenvatinib will provide comparable efficacy with an improved safety profile.	First patient in (ICF signed): 12 Mar 2016	31 Aug 2020

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
RCC				
Study 205 (Interventional Clinical Study: Category 3)*	An Open-Label, Multicenter Phase 1b/2 Study of E7080 Alone, and in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF Targeted Treatment	To continue to characterize/confirm the current safety profile of lenvatinib either as monotherapy or in combination with everolimus in advanced RCC	Completed *	Final report: Dec 2018
Study 218 (Interventional Clinical Study: Category 3)	Primary objective: •To assess whether a starting dose of lenvatinib 14 mg in combination with everolimus 5 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 24 weeks [ORR24W]) with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg (based on treatment-emergent intolerable Grade 2 or any ≥Grade 3 adverse events in the first 24 weeks after randomization). Secondary objectives: •To assess PFS •To assess ORR •To determine the tolerability and safety profile of lenvatinib in combination with	To continue to characterize/confirm the current safety profile of lenvatinib either as monotherapy or in combination with everolimus in advanced RCC	Planned	Final protocol and data analysis plan submission: Nov 2016 Study completion: Nov 2020 Periodic interim analyses by independent Data Monitoring Committee Final report submission: Jul 2021

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
	everolimus •To assess proportion of subjects who discontinued treatment due to toxicity •To assess time to treatment failure •To assess PK profiles of lenvatinib and everolimus during combination therapy and to assess PK and PD drug-drug interactions •To evaluate OS •To evaluate impact on HR QOL •To evaluate PFS2 Exploratory objectives: •To explore blood biomarkers which correlate with efficacy-related endpoints of this study. •To develop exposure/biomarker/ clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data that will allow exploration of alternative dosing regimens with a better efficacy/safety profile than the 18mg/5mg dose.			
Study 221 (Interventional Clinical Study:	Primary Objective: •To evaluate objective response rate (ORR) of	To characterize the safety profile of lenvatinib +	Final protocol 13 May	Final report submission: Q4 2019

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
Category 3)	lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease Secondary Objectives: •To assess safety and tolerability of lenvatinib in combination with everolimus •To evaluate progression-free survival (PFS) •To evaluate overall survival (OS) •To assess the pharmacokinetic (PK) profiles of lenvatinib and everolimus during combination therapy in subjects with nccRCC. Exploratory Objectives: • To explore clinical benefit rate (CBR) • To explore disease control rate (DCR) • To explore duration of response (DOR) •To identify and explore tumour and blood biomarkers that correlate with clinical outcomes, including efficacy •To explore the relationship of population	everolimus in subjects with nccRCC who have not received any chemotherapy for advanced disease	2016	

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
	PK derived exposure parameters to biomarker, safety, and efficacy data using a model-based approach			
Study 307 (Interventional Clinical Study: Category 3)	Primary Objective: • To demonstrate that lenvatinib in combination with everolimus (Arm A) or pembrolizumab (Arm B) is superior compared to sunitinib alone (Arm C) in improving progression-free survival (PFS) (by independent imaging review [IIR] using Response Evaluation Criteria In Solid Tumours [RECIST 1.1]) as first-line treatment in subjects with advanced renal cell carcinoma (RCC). Secondary Objectives: To compare objective response rate (ORR) and overall survival (OS) of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib. To compare safety and tolerability of treatment with lenvatinib in combination with everolimus or pembrolizumab versus	To continue to characterize/confirm the current safety profile of lenvatinib in combination with everolimus in advanced RCC	Planned	The protocol and the data analysis plan for PK/PD should be submitted by: Nov 2016 Periodic interim analyses by independent Data Monitoring Committee Final report submission 15 Jun 2020

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
	sunitinib, including the assessment of the proportion of subjects who discontinued treatment due to toxicity and time to treatment failure due to toxicity. To compare the impact of treatment on Health-Related Quality of Life (HRQoL) for subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib. To assess progression-free survival (PFS) based on investigator assessment per RECIST 1.1, and to assess PFS on next-line therapy (PFS2). To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with everolimus or pembrolizumab, and of everolimus and pembrolizumab when co-adminstered with lenvatinib. To asses the PK/pharmacodynamic relationship between exposure and efficacy/biomarkers/safety, if possible using a holistic			

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual
	approach.			
HCC				
Observational Clinical Study: Category 3)	To characterise hepatic-related toxicity and overall safety profile (SAEs, Grade 3-5 AEs, dose modifications and discontinuations due to AEs) in real-life conditions in the EU (Western population) in HCC patients, including patients with Child-Pugh B. Overall survival data and detailed baseline charateristics will also be collected.	Hepatotoxicity in HCC patients	Pending protocol and feasibility assessment	Protocol to be submitted by 28 Sep 2018

Risk minimisation measures

Table 87. Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Identified Risks		
Hypertension	Sections 4.2, 4.4, 4.8 of the SmPC. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Proteinuria	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Renal failure or impairment	Sections 4.2, 4.4, 4.8 of the SmPC. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hypokalaemia	Hypokalaemia is listed in Section 4.8 of the SmPC as a very common (≥1/10) adverse reaction	None planned
Cardiac failure	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Posterior reversible encephalopathy syndrome (PRES)	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Hepatotoxicity	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Haemorrhagic events	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Arterial thromboembolic events (ATEs)	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
QTc prolongation	Sections 4.4, 4.8 of the SmPC	None planned
Hypocalcaemia	Sections 4.4, 4.8 of the SmPC	None planned.
Hypothyroidism	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Gastrointestinal perforation and fistula formation	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned.
Non-Gastrointestinal fistula formation	Sections 4.4, 4.8 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	
Potential Risks		
Venous thromboembolic events (VTEs)	Pulmonary embolism is listed in Section 4.8. of the SmPC	None planned.
Abnormal pregnancy outcome, excretion in breast milk	Sections 4.6 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Male and female fertility	Section 4.6 and 5.3. of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Bone and teeth abnormalities in the paediatric population	Sections 4.2, 5.3 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Impaired Wound Healing	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data.	None planned
Interstitial Lung Disease (ILD)¬like conditions	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine.	None planned
Potential of lenvatinib for induction/inhibition of CYP-3A4 mediated drug metabolism	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine.	None planned

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Overdose (concomitant everolimus)	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine.	None planned
Missing Information		
Use in severe hepatic impairment	Sections 4.2 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in severe renal impairment	Sections 4.2 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Use in patients from ethnic origins other than Caucasian or Asian	Sections 4.2 of the SmPC Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies.	None planned
Long-term use	AEs such as cardiovascular events may emerge during long-term treatment, and continuous collection of long-term safety data is relevant for all indications. In RCC, no risk minimization measures are recommended at present as the duration of exposure to the combination covers the lifespan of the treated patient population: 72% of total subject-years of exposure were contributed by patients treated for at least 12 months, whilst median survival for mRCC patients treated with the combination is 25.5 months. Prescription only medicine. Use restricted to health care professionals experienced in the use of anticancer therapies	None planned

The CHMP endorsed the Risk Management Plan version 10.6.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, section 4.2 of the SmPC is being updated to add that the product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include the unique identifier.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

In accordance with the EU “Guidance concerning consultations with target patient groups for the package leaflet; Article 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC” and “Guideline on the readability of the labelling and package leaflet of medicinal products for human use, Revision 1, 12 Jan 2009”, the changes made as part of this application are not significant in nature and hence do not require a user consultation. There is no change in layout, and no major change in the patient target group profile, nor any critical changes in terms of the safety information presented.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HCC is a cancer that usually occurs in the setting of liver cirrhosis, because of chronic infections with hepatitis B virus or hepatitis C virus, alcohol consumption, non-alcoholic steatohepatitis, or diabetes (EASL&EORTC 2012). It is the third-leading cause of cancer-related death, and the global incidence is rising, with approximately 700,000 cases diagnosed worldwide in 2012 alone (Lozano et al. 2010, Torre et al. 2015).

3.1.2. Available therapies and unmet medical need

For patients with unresectable HCC eligible for systemic therapy, the oral multikinase inhibitor sorafenib was until recently the only treatment option. The approval was based on the results of a large Phase-3 clinical trial (Study 100554 SHARP) conducted in 602 HCC patients (Llovet et al. 2008). The study demonstrated significantly increased survival under sorafenib (plus BSC) compared to placebo (plus BSC) (HR 0.69; p=0.0005), with a median survival rate for the sorafenib arm of 10.6 months, compared with 7.9 months for the placebo arm. Currently, another oral multikinase inhibitor regorafenib (Stivarga) is indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

3.1.3. Main clinical studies

The pivotal study supporting this application is Study 304 (REFLECT), a multi-centre, multi-national, randomized, open-label phase III trial comparing lenvatinib versus sorafenib in patients with unresectable HCC naïve to systemic therapy. A total of 954 subjects (63.9% of screened patients) were randomly assigned in a 1:1 ratio to receive either lenvatinib 12 mg (baseline body weight [BW] $\geqslant$60 kg) or 8 mg (baseline BW <60 kg) given once daily (QD) orally or sorafenib 400 mg given twice daily (BID) orally. The proposed dosing regimen in patients with HCC is different from that in patients with DTC (24 mg QD) and RCC (18mg QD in combination with everolimus 5mg QD).

3.2. Favourable effects

Lenvatinib demonstrated non-inferiority for overall survival compared to sorafenib in the treatment of patients with advanced/ unresectable HCC. The final OS analysis based on 701 events (73.4% in the lenvatinib arm, 73.5% in the sorafenib arm) (cut-off date 13 Nov 2016) shows results within the non-inferiority margin for hazard ratio (Lenvatinib vs. Sorafenib) of 1.08 (HR 0.92, 95% CI 0.79-1.06, p=0.00002), with similar median OS of 13.6 months (12.1, 14.9) for lenvatinib vs 12.3 months (10.4, 13.9) for sorafenib. The NI margin was adequately defined and the benefit with sorafenib was at least as good as the historical studies. The median OS results for both arms were consistent in the FAS and PPS,

by stratification factors in the IxRS and the CRF and across most subgroups. The HR for OS was consistent across most subgroups analysed.

3.3. Uncertainties and limitations about favourable effects

In contrast with the population included in the pivotal study, the HCC patient population treated in clinical practice is very heterogeneous in terms of disease burden/presence of comorbidity and includes also patients with ECOG PS >1, Child Pugh B and C, with significant renal impairment, with cardiovascular co-morbidities. The MAH will conduct a post authorisation observational study to collect efficacy and safety data in patients in real life conditions (see RMP).

3.4. Unfavourable effects

The overall safety profile of lenvatinib was consistent with other VEGFR targeted therapies, with its known safety profile and its toxicity was usually predictable and in general manageable. The most frequently reported TEAEs with lenvatinib were as expected for a VEGF TKI i.e. hypertension, diarrhoea, PPE, decreased appetite and proteinuria. These events could generally be managed with dose interruption or reduction, which occurred in about 60% of patients. The rate of discontinuations due to AEs was reported as 20.2% in the All HCC safety set and as 14.5% in the sorafenib arm. Adverse events leading to dose reductions, interruptions and modifications (reduction and/or interruptions) were reported respectively in 38.7%, 52.1% and 61.8% of patients in lenvatinib arm and in 38.9%, 40.6% and 55.6% of patients in the sorafenib arm.

Grade ≥3 TEAEs, SAEs and fatal AEs occurred at higher frequency in the lenvatinib (56.7%) than sorafenib (48.6%) arm. The incidence of Grade 5 adverse events was higher for lenvatinib, particularly hepatic encephalopathy, hepatic failure, sepsis and cerebral haemorrhage.

The incidence of AEs in the all HCC lenvatinib monotherapy safety set was usually lower than in the non-HCC safety set, except for ascites (14.3%), platelet count decreased (18.1%), ALT (11.1%), ASP (13.7%) and bilirubin (14.3%) increased and Palmar-Plantar Erythrodysesthesia syndrome (PPE) (29%). Hepatic related AEs including hepatic encephalopathy and hepatic failure (both with lethal cases) were also observed at a higher rate in this population of subjects with advanced HCC.

3.5. Uncertainties and limitations about unfavourable effects

Patients with well-preserved liver function (Child-Pugh A) have been included in the study and uncertainty remains as to the safety profile of lenvatinib in patients with liver impairment, who represent a significant proportion of patients in real life conditions. A post authorisation observational study will be conducted to address this uncertainty (see RMP).

3.6. Effects Table

Table88: Effects Table for Lenvatinib in HCC patients (data cut-off: 13 November 2016)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
OS (median)	Gain in	Mo	13.6	12.3	Non-inferiority of	See clinical

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	survival		HR=0.92 95% CI: 0.79-1.06		lenvatinib to sorafenib established. Upper limit of two-sided 95% CI of HR was less than non-inferiority margin of 1.08 Results obtained in selected patient population as defined by strict enrolment criteria	efficacy section of this AR

Effect	Short Description	Unit	Study 304 Treatment lenvatinib 8 or 12 mg 476 pts	Control sorafenib 475 pts	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
At least 1 AE	all grades	% Pts	98.7%	99.4%	Randomised data from open-label trial	
Related AEs	grade 3 -5		56.7%	48.6%		
Serious AE	Serious		43.1%	30.3%		
Fatal AE	Fatal		12.8%	7.6%		
AE leading to dose discontinuation	Discontinuation		19.7%	14.5%		
hypertension	all grades	% Pts	42.2%	30.3%		
Weight decreased	all grades		30.9%	22.3%		
Diarrhoea	all grades		38.7%	46.3%		
Fatigue	all grades		29.6%	25.1%		
PPE syndrome	all grades		26.9%	52.4%		
proteinuria	all grades		24.6%	11.4%		
Hepatic encephalopathy and coma hepatic	Serious	% Pts	4.4% (21/476)	0.6% (3/475)	Low numbers and patients' underlying condition result in uncertainties	
	death		0.8% (4/476)	0% (0/475)		
Hepatic failure	Serious		2.9% (14/476)	1.7% (8/475)		
	death		2.1% (10/476)	0.4% (2/475)		

Abbreviations:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Advanced hepatocellular carcinoma (HCC) not amenable for surgery, is a highly invalidating and life threatening condition with an overall poor prognosis. Currently there are two systematic therapy options

registered in Europe for this patient population, namely sorafenib approved initially for palliative systemic treatment regardless of the line of therapy and regorafenib, recently approved as second-line therapy after prior sorafenib.

Lenvatinib demonstrated efficacy in the treatment of HCC and was non-inferior to sorafenib in terms of overall survival. On subgroup analysis, the OS trend favoured sorafenib in the Western region. This may be due to different aetiologies for HCC in the West, with more alcohol and less hepatitis C induced cirrhosis, leading to an increased propensity to develop hepatic encephalopathy.

In some patients, underlying liver function maybe too poor to tolerate treatment with lenvatinib and, despite observed efficacy, subsequent liver damage negatively affects prognosis. The risk of hepatic failure/ encephalopathy should be further analysed in real-life setting given that lenvatinib will be also used in more vulnerable non-selected population. Due to inclusion criteria used in the pivotal study, more homogenous patient population with better prognosis has been enrolled. Therefore, uncertainties remain as to efficacy and safety in more heterogeneous and less fit patient population in real life conditions.

Data in EU population (or relevant Western population) were obtained in one third of patients enrolled in the study. Only patients with well-preserved liver function have been included and more data needs to be collected in a real-life setting. An observational clinical trial (PASS category 3 study in the RMP) aims to further characterise safety (mainly hepatic-related events) and to collect OS data. Accurate reporting of baseline disease-related, other baseline characteristics and AEs in this study would allow further correlative analysis of risk factor for hepatic-related toxicity.

3.7.2. Balance of benefits and risks

Although patients with advanced-stage HCC and intermediate-stage who progress after locoregional therapy are currently treated with sorafenib, lenvatinib is considered as a possible treatment option based on the results of the Study 304. Non-inferiority in terms of OS is supported by results of surrogate endpoints (PFS, TTP, ORR).

3.8. Conclusions

The overall B/R of Lenvima as monotherapy is positive for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy (see Section 5.1)'.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of adult patients with advanced or unresectable

hepatocellular carcinoma (HCC) who have received no prior systemic therapy; consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are being updated and the package leaflet is updated accordingly. In addition, section 4.2 of the SmPC is being updated to add that the product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include the unique identifier. The RMP was updated (version 10.6). The Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The group of variations leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).