1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-M001-222
Study Protocol Title:	A Single-Arm, Multicenter, Phase 2 Trial to Evaluate Safety and Efficacy of Treatment of Physician Choice (TPC) Following First-Line Treatment of Lenvatinib in Subjects With Unresectable Hepatocellular Carcinoma (uHCC)
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US
Investigational Product Name:	LENVIMA® (E7080/Lenvatinib)
Indication:	Hepatocellular Carcinoma (HCC)
Phase:	2
Approval Date(s):	20 Dec 2017 Original Protocol 26 Jan 2018 Amendment 01 15 Mar 2018 Amendment 02 24 Sep 2018 Amendment 03
IND Number:	115650
GCP Statement:	This study is to be performed in full compliance with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

REVISION HISTORY

Revisions per Amendment 03

Date: 24 Sep 2018

Change	Rationale	Affected Protocol Sections
The term "systemic" was added to Treatment of Physician's choice (TPC) to specify and add clarity that only systemic treatment following lenvatinib treatment will be considered as subsequent TPC.	The update was made to highlight that only "systemic" treatment will be considered as subsequent TPC for the study and that locoregional procedures will not be considered as subsequent TPC.	Synopsis: Objectives, Study Design, Study Treatments, Subsequent Treatment of Physician Choice (TPC), Endpoints Section 7.1 Section 8.1 Section 8.2 Section 9.1 Section 9.1.2.2 Section 9.1.2.3 Section 9.2 Section 9.4.1.2 Section 9.7.1.1.1 Section 9.7.1.1.2
It was clarified that any locoregional therapies (ie, chemoembolization / radioembolization, etc.) will not be considered as second line treatment following lenvatinib.	The update was made to highlight that locoregional procedures will not be considered as subsequent TPC for the study.	Synopsis: Study Design Section 9.1.2.2 Section 9.4.1.2
Remove ambiguous wording in the protocol to make clear that the TPC period is not optional. The continuation to second line treatment is expected as long as commercially available systemic second line treatment is deemed by the physician to be clinically appropriate. The choice of which second line treatment is used is at the discretion of the physician.	The change was made to highlight that the subsequent TPC period following lenvatinib is not optional, and that if eligible, subjects should receive systemic TPC as second line treatment.	Synopsis: Subsequent Treatment of Physician Choice (TPC) Section 9.1 Section 9.4.1.2
Study rationale was updated to further clarify the purpose of the study with focus on addressing the unmet medical need for data for safety and efficacy on the subsequent sequential therapies after 1st line therapy with lenvatinib in uHCC patients,	The study rationale was updated to provide additional clarity for the purpose of the study.	Section 7.1

US package insert was replaced with the lenvatinib Global Investigator's Brochure (GIB) as a reference for the dose adjustments and drug-drug interactions for lenvatinib.	The US package insert was replaced with the GIB as the source of reference for the drug-drug interaction section since the GIB is provided to all investigators for reference and includes all information presented in the section on drug-drug interactions in the protocol. Also, the GIB would be an appropriate reference for sites in Canada.	Section 9.4.7.1
Updated information for lenvatinib interactions with other co- administered drugs which are CYP3A4/Pgp substrates: "In a formal drug-drug interaction study, lenvatinib did not alter plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate). Thus, lenvatinib is not expected to alter the metabolism of other co administered drugs which are CYP3A4/Pgp substrates".	The information was updated to present the latest information on lenvatinib drug-drug interactions.	Section 9.4.7.1
Clarified that echocardiograms (ECHO) should be performed locally in accordance with the institution's standard practice. The requirement to submit ECHO and MUGA scans to the central laboratory for analysis and archiving was deleted.	Reference to central laboratory in previous protocol versions was an error, and was removed to reflect that the study does not require a central laboratory for these assessments (ECHO and MUGA scans).	Section 9.5.1.5.7
Clarified that a gastroenterological endoscopy at screening is necessary only if more than 3 months have passed since the previous assessment. Gastroenterological endoscopy must have been performed within 3 months prior to receiving first dose of the study treatment.	Added to emphasize the requirement of a gastroenterological endoscopy within 3 months prior to receiving the first dose of the study treatment.	Section 9.5.2.1 (Table 3 – Footnote e)

Revisions per Amendment 02
Date: 15 Mar 2018

Change	Rationale	Affected Protocol Sections
Secondary objective was updated as follows: • Evaluation of objective response rate (ORR) and clinical benefit rate (CBR) in both the first-line lenvatinib treatment period and the subsequent TPC period was deleted. • Progression-free survival (PFS) and time to progression (TTP) will be evaluated for the subsequent treatment of physician choice (TPC) starting from the first dose of first-line lenvatinib treatment.	The changes to the secondary objective were made because there is no meaningful way to summarize the ORR for the duration of the study. Clarify that PFS and TTP will be evaluated for the subsequent treatment of physician choice (TPC) starting from the first dose of first-line lenvatinib treatment	Synopsis: Secondary Objectives Section 7.1 Section 8.2
Secondary endpoints were updated in line with changes in the secondary objective as follows: • Progression-free survival (PFS), defined as the time from the date of first dose of first-line lenvatinib treatment to the date of first documentation of disease progression, or date of death during the subsequent TPC, whichever occurs first. • Time to progression (TTP), defined as the time from the date of first dose of first-line lenvatinib treatment to the date of first documentation of disease progression during subsequent TPC. • Evaluation of ORR and CBR was deleted.	Secondary endpoints were updated to align with the changes in the secondary objective.	Synopsis: Secondary Endpoints Section 9.7.1.1.2
Efficacy analysis: • Evaluation of PFS and TTP for both treatment periods was deleted since PFS and TTP will be evaluated for the subsequent TPC period following first-line lenvatinib treatment. • Evaluation of ORR was deleted.	Efficacy analyses were updated based on changes in secondary objectives and secondary endpoints.	Synopsis: Efficacy Analyses Section 9.7.1.6

Change	Rationale	Affected Protocol Sections
Sample size rationale was updated.	The rationale was updated to be consistent with the primary objective.	Synopsis: Sample Size Rationale Section 9.7.2
Study rationale was updated for further clarity. Data presented formerly in Introduction section regarding survival follow-up period in Study E7080-G000-304 was moved to Study Rationale section to provide additional clarity for rationale of the study.	To provide more clarity for the rationale of the study.	Section 7 Section 7.1
Study design text was updated to clarify that the study will evaluate safety and efficacy of subsequent TPC (commercially available) following first-line lenvatinib treatment.	Text was updated to align with the primary objective.	Synopsis: Study Design Section 7.1 Section 9.1 Section 9.2
Criterion for non-hepatic target lesion in the inclusion criteria was updated to delete specifications for porta hepatis lymph node.	To avoid confusion for the inclusion criteria for non-hepatic lesions.	Synopsis: Inclusion criteria Section 9.3.1 Appendix 2
Information on treatment included in TPC was added in the section for study treatments.	To provide TPC information in synopsis.	Synopsis: Study Treatments
For the TPC, the following sentence was deleted 'Once the dose has been reduced, it cannot be increased at a later date'.	To emphasize that decisions on dosing reduction/interruptions will be based on the prescribing information for the TPCs.	Synopsis: Subsequent Treatment of Physician Choice (TPC) - Dose Reduction and Interruption Section 9.4.1.2
Definition of concomitant medications was updated to include medications up to 28 days after last dose of TPC if subject does not stay in the TPC period for the 8 weeks of safety monitoring.	To align data collection.	Section 9.4.7 Section 9.5.2.1 (Table 3) Section 9.7.1.5
Appendix 2 for mRECIST was updated to include additional examples for non-target lesions.	To provide additional examples for selection of non-target lesions.	Appendix 2
Table in Appendix 8 for CYP3A4 substrates, inhibitors, and inducers was deleted and it was clarified that the http://medicine.iupui.edu/clinpharm/ddis/ website should be referred to for most updated information on CYP3A4 substrates, inhibitors, and inducers.	To refer to most updated information on CYP3A4 substrates, inhibitors, and inducers.	Appendix 8

Revisions per Amendment 01

Date: 26 Jan 2018

Change	Rationale	Affected Protocol Sections
Title of the protocol was reworded to "A Single-Arm, Multicenter, Phase 2 Trial to Evaluate Safety and Efficacy of Treatment of Physician Choice (TPC) Following First-Line Treatment of Lenvatinib in Subjects With Unresectable Hepatocellular Carcinoma (uHCC).	The title of the protocol was reworded to add clarity and to align with the updated text for the primary objective and the primary endpoint.	Title page Synopsis: Study Protocol Title
Primary objective and primary endpoint were reworded as assessment of safety and tolerability of subsequent TPC following the first-line lenvatinib treatment in uHCC subjects.	Updated to add clarity.	• Synopsis: Primary Objective, Primary Endpoint • Section 8.1 • Section 9.7.1.1.1
The schedule for safety data collection during TPC (ie, Treatment Period 2 [TP2]) was specified with updates made in Table 3. It was also specified that AEs will be reported until 28 days after the last dose of lenvatinib treatment if subjects do not enter TPC period, or for 8 weeks after the start of TPC period. SAE information should be collected for 8 weeks after the start of the TPC, or for at least 28 days after the last dose of lenvatinib/TPC if subjects do not continue into the TPC period or do not stay in the TPC period for the 8 weeks of safety monitoring (Table 3, footnote "z", Section 9.5.1.5.1, and Section 9.5.4.1). The following footnote (footnote "aa") was added in Table 3 to clarify assessments after week 16: After week 16, only tumor assessment and TPC dose information will be collected until the end of TPC (disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor).	The schedule for data collection during TPC was specified to allow systematic collection of safety data during TPC period following 1st line lenvatinib treatment of uHCC.	• Synopsis: Study Design, Safety Assessments • Section 9.1.2.2 • Section 9.5.1.5 • Section 9.5.2.1 (Table 3)

For TP2, it was clarified that subjects starting subsequent TPC ≥8 weeks after lenvatinib off-treatment visit may be considered after discussion with sponsor.	To add clarity about the TPC period duration.	• Synopsis: Study Design • Section 9.1.2.2
For subsequent TPC definition, it was clarified that the first treatment of a single agent or combination of multiple drugs after lenvatinib treatment will be considered as the subsequent TPC. Chemoembolization procedures will not be considered as a second line treatment following lenvatinib. If commercially available TPC is not used as the subsequent treatment following lenvatinib treatment, subjects will be followed in the survival follow up period.	To provide clarity of definition of TPC. Added in 1 to provide clarity on chemoembolization procedures.	• Section 9.4.1.2 • Section 9.1.2.2
For the duration of TPC, it was clarified that subjects will continue to receive TPC treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor.		• Synopsis: Duration of Treatment • Section 9.4.1.2
For concomitant medications, it was clarified that concomitant medications will be recorded until 28 days after last dose of lenvatinib treatment if subjects do not enter TPC period, or for 8 weeks after the start of TPC period. All anticancer therapy will be recorded until time of death or termination of survival follow-up.	Updated to adjust the assessment schedule.	• Section 9.4.7 • Section 9.7.1.5 • Section 9.5.2.1 (Table 3)
Assessment of special chemistries was added at Baseline and C1D15. Pregnancy test at the Treatment Period 1 off -treatment visit was deleted. Also, it was clarified that NYHA cardiac disease classification should only be performed at Screening if needed.	Updated to adjust the assessment schedule.	• Section 9.5.2.1 (Table 3)

For the pharmacodynamic blood (serum/plasma) biomarkers and pharmacogenetic biomarkers assessments, it was clarified that samples will be collected at week 8 and week 16 (±1 week), and that subjects entering the subsequent TPC period should have TPC baseline sample collected unless the lenvatinib Off-Treatment visit in the lenvatinib treatment period is ≤28 days before the subsequent treatment starts, in which case those samples may be used as the TPC period baseline.	This was added for clarity on biomarker data collection during TPC period.	• Synopsis: Pharmacodynamic Blood Biomarkers, Pharmacogenetic Biomarker Assessments. • Section 9.5.1.4.2 • Section 9.5.2.1 (Table 3)
Blood (whole blood) sample collection for potential genetic analysis from all enrolled subjects was added to evaluate whether genetic variation within a clinical study population correlates with response to the study treatment. The following was additionally added: Biomarker correlative analyses may be performed to explore blood or tumor biomarkers that may be useful to predict subject's response in a retrospective manner. The results of these studies are to gain further insight into the clinical mechanism of action for study drug but not foreseen to result in commercially valuable products. This study will collect biomarker samples in all enrolled subjects who have consented for participation of the biomarker assessments. Participation of any future exploratory research of left over material will be optional.	This was added to allow potential genetic analysis from all enrolled subjects, to evaluate whether genetic variation within a clinical study population correlates with response to the study treatment.	• Synopsis: Pharmacogenetic Biomarker Assessments • Section 9.5.1.4.2 • Section 9.5.2.1 (Table 3)
It was specified that in TPC period, PRO-CTCAE questionnaires will be collected 2 weeks for the first 4 weeks, and then at week 8, and week 16 (±1 week). A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed within 7 days prior to the first TPC treatment.	Updated to adjust the assessment schedule.	• Synopsis: Other assessments • Section 9.5.1.6 • Section 9.5.2.1 (Table 3)

The analysis of extent of exposure was updated to include summarization of percentage of subjects that receive TPC, average dose intensity and relative dose intensity of lenvatinib treatment and TPC, and feasibility rate.	To obtain comprehensive information about the extent of exposure.	• Section 9.7.1.8.1

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title

A Single-Arm, Multicenter, Phase 2 Trial to Evaluate Safety and Efficacy of Treatment of Physician Choice (TPC) Following First-Line Treatment of Lenvatinib in Subjects With Unresectable Hepatocellular Carcinoma (uHCC)

Investigators

United States (US), Canada

Sites

Approximately 20 to 25 sites

Study Period and Phase of Development

Approximately 30 months from first subject enrolled to end of last subject in TPC.

Phase 2

Objectives

Primary Objective

- To assess the safety and tolerability of subsequent systemic TPC following first-line lenvatinib treatment in uHCC subjects.

Secondary Objectives

- To evaluate overall survival (OS) in uHCC subjects treated with lenvatinib as the first-line treatment followed by systemic TPC.
- To evaluate progression-free survival (PFS) and time to progression (TTP) of subsequent systemic TPC starting from the first dose of first-line lenvatinib treatment using modified Response Evaluation Criteria in Solid Tumors (mRECIST).
- To evaluate OS by subgroups of systemic TPC.

Exploratory Objectives

- To measure the patient perceived burden by Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in the subsequent TPC period.
- To explore biomarkers based on availability of serum and tissue samples.

Study Design

This study is a single-arm, open-label, multicenter, phase 2 trial to evaluate safety and efficacy of subsequent systemic TPC (commercially available) following first-line lenvatinib treatment in subjects with uHCC.

The study will consist of a Pretreatment Phase and a Treatment Phase. The pretreatment phase will last up to 21 days and will include the Screening Period to obtain informed consent and establish protocol eligibility, and the Baseline Period to confirm protocol eligibility and disease characteristics.

The Treatment Phase consists of 2 treatment periods (Lenvatinib Treatment Period [Treatment Period 1] and the Subsequent TPC Treatment Period [Treatment Period 2]) and a Follow-Up Period. The Lenvatinib Treatment Period (Treatment Period 1) for each subject will begin at the time of the first dose of lenvatinib study treatment and will consist of lenvatinib treatment on 28-day cycles until

completion of the lenvatinib Off-Treatment Visit that will occur within 30 days after the final administration of lenvatinib.

Lenvatinib treatment cycles will be counted continuously regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments. Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor.

Subjects will be permitted to continue lenvatinib treatment beyond mRECIST defined disease progression as long as the treating investigator considers that there is clinical benefit and, the subject is tolerating study treatment. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Eisai Medical Monitor. Subjects will discontinue study treatment upon evidence of further progression and/or loss of clinical benefit, as judged by the investigator.

The Subsequent Treatment Period (TPC period, Treatment Period 2) will begin upon the completion of lenvatinib Off-Treatment Visit in first-line treatment of lenvatinib. Subjects will be treated by commercially available systemic TPC for uHCC. Locoregional therapies (ie, chemoembolization/radioembolization, etc.) will not be considered as a second line treatment following lenvatinib. If the investigator deems a subject inappropriate for commercially available systemic TPC as the subsequent treatment following lenvatinib, subjects will be followed in the survival Follow-Up period. All treatment following lenvatinib will be captured in the case report form. Data will be collected from the start of TPC, then at intervals as indicated in Schedule of Procedures/Assessments (Table 3).

Subjects starting subsequent systemic TPC ≥8 weeks after lenvatinib off-treatment visit may be considered after discussion with sponsor.

The Follow-Up Period will begin immediately after the final visit in the subsequent treatment period (Treatment Period 2). Subjects will be followed every 12 weeks for survival and will continue as long as the study subject is alive, unless the subject withdraws consent. If the investigator deems a subject inappropriate for commercially available subsequent systemic TPC, the subject will be followed for survival every 12 weeks after the lenvatinib Off-Treatment Visit in the lenvatinib treatment period (Treatment Period 1). Subjects' survival status and all additional anticancer treatments received will be recorded.

The sponsor may decide to terminate survival follow-up of subjects after the completion of the primary analysis or when all subjects have discontinued study treatment.

Number of Subjects

Approximately 100 subjects with uHCC will be enrolled to the first-line treatment of lenvatinib.

Inclusion Criteria

1. Subjects must have confirmed diagnosis of uHCC with any of the following criteria:
   a. Histologically or cytologically confirmed diagnosis of uHCC
   b. Clinically confirmed diagnosis of uHCC according to American Association for the Study of Liver Diseases (AASLD) criteria, including cirrhosis of any etiology or with chronic hepatitis B or C infection criteria
2. At least one measurable target lesion regardless if hepatic or non-hepatic according to mRECIST meeting the following criteria:
   a. Hepatic lesion
      - The lesion can be accurately measured in at least one dimension as ≥1.0 cm (viable tumor

for typical; and longest diameter for atypical), and
- The lesion is suitable for repeat measurement,

b. Nonhepatic lesion
- Lymph node lesion that measures at least one dimension as ≥1.5 cm in the short axis
- Non-nodal lesion that measures ≥1.0 cm in the longest diameter

Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion.

3. Subjects categorized on the Barcelona Clinic Liver Cancer (BCLC) staging system to Stage B (not applicable for transarterial chemoembolization [TACE]) or Stage C
4. Adequate bone marrow function, defined as:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   - Hemoglobin ≥8.5 g/dL
   - Platelet count $\geq 75 \times 10^9$/L
5. Adequate liver function, defined as:
   - Albumin ≥2.8 g/dL
   - Bilirubin ≤3.0 mg/dL
   - Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) ≤5 × the upper limit of normal (ULN)
6. Adequate blood coagulation function, defined as international normalized ratio (INR) ≤2.3
7. Adequate renal function defined as creatinine clearance >30 mL/min calculated per the Cockcroft and Gault formula
8. Adequate pancreatic function, defined as lipase ≤1.5 × ULN
9. Adequately controlled blood pressure (BP) with up to 3 antihypertensive agents, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive therapy within 1 week prior to Cycle 1/Day 1
10. Child-Pugh A
11. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
12. Survival expectation of 12 weeks or longer before starting study drug
13. Males or females aged at least 18 years at the time of informed consent
14. Provide written informed consent
15. Willing and able to comply with all aspects of the protocol

Exclusion Criteria

1. Imaging findings for HCC corresponding to any of the following:
   a. HCC with ≥50% liver occupation
   b. Clear invasion into the bile duct
   c. Portal vein invasion at the main portal branch (Vp4)
2. Subjects who have received any systemic chemotherapy, including sorafenib, regorafenib or other anti-vascular endothelial growth factor (VEGF) therapy, nivolumab, or any systemic investigational anticancer agents, including lenvatinib, for advanced/uHCC. Note: Subjects who have received local hepatic injection chemotherapy (if not within 28 days prior to the first dose of lenvatinib study treatment) are eligible
3. Subjects who have received any anticancer therapy (including surgery, percutaneous ethanol injection, radio frequency ablation, transarterial [chemo] embolization, hepatic intra-arterial

chemotherapy, biological, immunotherapy, hormonal, or radiotherapy) or any blood enhancing treatment (including blood transfusion, blood products, or agents that stimulate blood cell production, eg, granulocyte colony-stimulating factor [G-CSF]) within 28 days prior to the first dose of lenvatinib study treatment

4. Subjects who have not recovered from toxicities as a result of prior anticancer therapy such as the local hepatic injection chemotherapy or any prior therapy for other cancer types. Recovery is defined as <Grade 2 severity per Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03), except alopecia and infertility
5. Significant cardiovascular impairment within 6 months of the first dose of study drug: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke, cardiac arrhythmia associated with hemodynamic instability, or a left ventricular ejection fraction (LVEF) below the institutional normal range as determined by multigated acquisition (MUGA) scan or echocardiogram
6. Prolongation of QTcF (QT interval corrected for heart rate using Fridericia's correction) interval to >480 ms
7. Gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib in the opinion of the investigator
8. Bleeding or thrombotic disorders or use of anticoagulants such as, warfarin or similar agents requiring therapeutic INR monitoring. (Treatment with low molecular weight heparin is allowed.)
9. Gastrointestinal bleeding event or active hemoptysis (bright red blood of at least half teaspoon) within 28 days prior to the first dose of lenvatinib study treatment
10. Gastric or esophageal varices that require treatment
11. Active malignancy (except for HCC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 36 months
12. Any history of, or current brain or subdural metastases
13. Subjects having >1+ proteinuria on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible.
14. Arterial-portal venous shunt or arterial-venous shunt preventing proper diagnosis of tumor
15. Any medical or other condition that in the opinion of the investigator would preclude the subject's participation in a clinical study
16. Known intolerance to lenvatinib or any of the excipients
17. Human immunodeficiency virus (HIV) positive or active infection requiring treatment (except for hepatitis virus)
18. Any history of drug or alcohol dependency or abuse within the prior 2 years
19. Any subject who cannot be evaluated by either triphasic liver computed tomography (CT) or triphasic liver magnetic resonance imaging (MRI) because of allergy or other contraindication to both CT and MRI contrast agents
20. Major surgery within 3 weeks prior to the first dose of lenvatinib study treatment or scheduled for surgery during the study
21. Subject has had a liver transplant
22. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate

baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug

23. Females of childbearing potential who:

- Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
  - total abstinence (if it is their preferred and usual lifestyle)
  - an intrauterine device or intrauterine hormone-releasing system (IUS)
  - a contraceptive implant
  - an oral contraceptive (with additional barrier method) (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation).
  - have a vasectomized partner with confirmed azoospermia.
- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

  For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as latex or synthetic condom plus diaphragm or cervical/vault cap with spermicide.

  All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

24. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 96 days after study drug discontinuation). No sperm donation is allowed during the study period and for 96 days after study drug discontinuation.

Study Treatments

Test Drug: Lenvatinib is provided as 4 mg capsules.

Starting dose of lenvatinib will be based on baseline body weight (BW) as follows:

- BW ≥60 kg — Lenvatinib 12 mg (three 4 mg capsules) once daily (QD) will be taken orally.
- BW <60 kg — Lenvatinib 8 mg (two 4 mg capsules) QD will be taken orally.

Study medication should be taken at approximately the same time each day.

If a dose is missed and cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Study medication may be taken in a fasting state or following a meal.

Treatment of Physician Choice (TPC): TPC is limited to commercially available systemic products for uHCC.

Dose adjustments for management of toxicities will be made according to the guidelines provided in the table below.

Study Treatment Dose Reduction and Interruption Instructions

Dose reductions occur in succession based on the previous dose level (eg, 12, 8, and 4 mg/day, and 4 mg every other day for the subjects with initial BW ≥60 kg). Any dose reduction below 4 mg every other day must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date.

Non-Hematologic Toxicities		
Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d] or Grade 3[e,d]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	One-level reduction
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	One-level reduction
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	One-level reduction
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[g]: Discontinue Study Treatment		
Hematologic Toxicities and Proteinuria		
Treatment-Related Toxicity[a]	**Management**	**Dose Adjustment**
Grade 1 or Grade 2		
	Continue treatment	No change
Grade 3		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Fourth occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Fifth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor
Grade 4		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor

Note: Grading according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.
AEs = adverse events, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal
a: An interruption of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment at least every 7 days (until restarting administration).
b: Initiate optimal medical management for nausea, vomiting, diarrhea and/or hypothyroidism prior to any study treatment, interruption, or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and physician to be intolerable.
d; For proteinuria, interrupt until Grade 0-2.
e: Not applicable to abnormal clinical laboratory values that require no treatment (eg, sodium). Manage ALT, AST, and gamma-glutamyltransferase values 10 × ULN or higher as Grade 3.
f: Please ignore this step for subjects who start at 8 mg once daily.

g: Excluding laboratory abnormalities judged to be non-life-threatening, which should be managed as Grade 3.

Management of Hypertension and Proteinuria

Management of Hypertension

Hypertension is a recognized side-effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP ≤150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/Assessments. Hypertension will be graded using CTCAE v4.03, based on BP measurements only (and not on the number of antihypertensive medications).

Only one BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of these 2 measurements done at least 5 minutes apart is defined as one BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory BP assessment should be obtained at least 30 minutes later by performing 2 measurements at least 5 minutes apart (to yield a mean value).

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) is confirmed on 2 assessments at least 30 minutes apart. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is first observed on 2 assessments at least 30 minutes apart. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred.

Study drug should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the subject has been on same hypertensive medications for at least 48 hours and the BP is controlled, study drug should be resumed as described below.

Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles. If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles.

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat measurements after 30 minutes:

- Continue study drug and institute antihypertensive therapy for subjects not already receiving antihypertensive medication.
- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be

added.

- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then study drug administration should be interrupted and restarted at a dose of 8 mg QD (one dose level reduction as specified in table above) only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
  - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the 8 mg QD dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a dose of 4 mg QD (one dose level reduction as specified in the table above) only when systolic BP ≤150 mmHg and diastolic BP ≤95mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
  - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the 4 mg QD dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and a restart of study medication should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue study drug

Management of Proteinuria

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments. Guidelines for assessment and management of proteinuria are summarized as follows:

Grading of Proteinuria

- Grading of proteinuria according to CTCAE v4.03 will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to the Dose Modification Guidelines.

Detection and Confirmation

1. Perform urine dipstick testing per the Schedule of Assessments
2. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot urine protein-to-creatinine ratio (UPCR) test is required in the following situations:
   a. The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
   b. A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
   c. When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Monitoring

- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

Subsequent Treatment of Physician Choice (TPC)

The Subsequent Treatment Period (TPC period, Treatment Period 2) will begin upon the completion of lenvatinib Off-Treatment Visit in first-line treatment with lenvatinib. Subjects will be treated by commercially available, systemic TPC for uHCC. .

Dose Reduction and Interruption

For subjects who experience TPC-related toxicity, dose reduction and/or interruption will be in accordance with the prescribing information for each medication.

Duration of Treatment

Lenvatinib treatment (Treatment Period 1)

Lenvatinib treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or sponsor termination of the study. The duration of lenvatinib treatment for each subject is estimated to be 6 to 8 months.

Once disease progression occurs, lenvatinib treatment may not be restarted and subject should be considered for subsequent TPC.

Subsequent treatment of physician choice (Treatment Period 2)

Subjects will continue to receive TPC treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor.

Concomitant Drug/Therapy

The following concomitant therapies will be prohibited from the time of informed consent for this study until discontinuation from lenvatinib study treatment. Additional antihypertensive treatment is allowed as appropriate if the BP increases once the subject has been enrolled.

1. Surgery or radiotherapy for the treatment of HCC; Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted without being considered progressive disease (PD).
2. Systemic therapy, hepatic intra-arterial chemotherapy, immunological therapy (eg, interferon, interferon-type drugs, etc), hormonal therapy, or local therapy of any kind (eg, percutaneous ethanol inject [PEI], radiofrequency ablation [RFA], TACE, etc) for the treatment of HCC. Subjects who are receiving antiviral therapy for hepatitis B virus (HBV) may continue to receive this therapy at the discretion of the investigator.
3. Other investigational drugs.
4. Antiplatelet agents and anticoagulants that require INR monitoring, such as warfarin (treatments that do not require INR monitoring, such as low molecular weight heparin and certain factor X inhibitors are permitted).

Assessments

Efficacy Assessments

All efficacy endpoints, other than OS, will be based on the tumor response evaluation as determined by investigator assessment according to mRECIST (and including the RECIST 1.1 conventions for non-hepatic lesions). Tumor assessments will be performed at the site by appropriately qualified personnel. Treatment decisions will be based on tumor response assessments determined by the investigator.

Tumor Assessments

Tumor assessments will be performed during the Screening/Baseline phase (standard of care scans performed up to 28 days before the first dose of study treatment are acceptable) and then every 8 weeks (±1 week), or sooner if clinically indicated, during lenvatinib treatment phase until disease

progression.

Subjects who discontinue lenvatinib treatment without disease progression should have tumor assessments performed (within 1 week of the lenvatinib Off-Treatment Visit) if more than 4 weeks have passed since the previous assessment and if the subject will not continue with follow-up scans.

Subjects entering subsequent treatment period (Treatment Period 2) should have TPC baseline tumor assessments performed unless the last tumor assessment performed in lenvatinib treatment period is less than 28 days before the subsequent treatment starts, in which case those scans may be used as the TPC period baseline. A new tumor assessment baseline (selection of target and non-target lesions and calculation of a new baseline sum of diameters (SOD) must be established before beginning TPC. Subjects will continue tumor assessments during subsequent treatment period every 8 weeks (±1 week), or until disease progression, subject death, withdrawal or loss to follow-up.

Tumor assessments will be performed per mRECIST. Copies of all tumor imaging scans will be sent to an imaging core laboratory designated by the sponsor for potential future review. All subjects are required to undergo chest, abdomen, and pelvis imaging at Baseline and all follow-up time points. Contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis, and any other areas of disease, as clinically indicated, will be acquired at Screening and at all imaging time points. Liver CT or MRI must be performed using triphasic scanning technique optimized to capture precontrast, arterial and portal venous phase.

The tumor assessment schedule should not be affected by interruptions in therapy, or any other events that might lead to imbalance between the treatment groups with regard to the timing of disease assessments.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Pharmacodynamic Blood Biomarkers

Blood serum samples for pharmacodynamic and exploratory biomarkers analysis will be collected at the following time points:

- Treatment Period 1: Before dosing (predose) lenvatinib on Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of all subsequent cycles, and at the off-treatment assessment.
- Treatment Period 2: Subjects entering the subsequent TPC period should have TPC baseline sample collected unless the lenvatinib Off-Treatment visit in the lenvatinib treatment period is ≤28 days before the subsequent treatment starts, in which case those samples may be used as the TPC period baseline. Samples will then be collected at week 8 and week 16 (±1 week).

A detailed biomarker analysis plan will be prepared separately.

Pharmacogenetic Biomarker Assessments

Archived, fixed tumor tissue from the most recent surgery or biopsy will be collected (if available) from all enrolled subjects for potential assessment of mutations and other genetic alterations or genes and/or proteins that may be important in the development and progression of cancer as well as in response to study drug treatment for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available. Note that in order to understand tumor-specific mutations, it may be necessary to compare the tumor genome with the germline genome.

A blood plasma sample to isolate circulating cell-free nucleic acids will be collected at the following time points:

- Treatment Period 1: Before dosing (predose) lenvatinib on Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of all subsequent cycles, and at the off-treatment assessment.
- Treatment Period 2: Subjects entering the subsequent TPC period should have TPC baseline sample collected unless the lenvatinib Off-Treatment visit in the lenvatinib treatment period is

≤28 days before the subsequent treatment starts, in which case those samples may be used as the TPC period baseline. Samples will then be collected at week 8 and week 16 (±1 week).

A blood sample will be collected for potential genetic analysis from all enrolled subjects to evaluate whether genetic variation within a clinical study population correlates with response to the study treatment. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

A detailed biomarker analysis plan will be prepared separately.

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to study treatment, cancer and/or for potential diagnostic development.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Biomarker correlative analyses may be performed to explore blood or tumor biomarkers that may be useful to predict subject's response in a retrospective manner. The results of these studies are to gain further insight into the clinical mechanism of action for study drug but not foreseen to result in commercially valuable products.

This study will collect biomarker samples in all enrolled subjects who have consented for participation of the biomarker assessments. Participation of any future exploratory research of leftover material will be optional.

Safety Assessments

During lenvatinib treatment period, safety assessments will consist of monitoring and recording all adverse events (AEs), including all CTCAE v4.03 grades (for increasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, electrocardiograms (ECGs), and echocardiograms or MUGA scans including LVEF; and the performance of physical examinations.

Safety assessments will be performed at intervals as indicated in Schedule of Procedures/Assessments (Table 3) in both treatment periods.

Other Assessments

Subjects perceived burden post lenvatinib treatment in Treatment Period 2 will be measured by completed PRO-CTCAE questionnaires. PRO-CTCAE data will be collected only at the lenvatinib Off-Treatment Visit during Treatment Period 1, and every 2 weeks for the first 4 weeks, and then at week 8, and week 16 ± (1 week) in Treatment Period 2. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed within 7 days prior to the first TPC treatment.

Bioanalytical Methods

Not Applicable

Statistical Methods

Study Endpoints

Primary Endpoint

The primary endpoint is the safety and tolerability of subsequent systemic TPC following the first-line lenvatinib treatment in uHCC subjects, and will be analyzed by summarizing the incidence of treatment-emergent adverse events (TEAEs) and SAEs.

Secondary Endpoints

- Overall survival (OS), measured from the date of first dose of study treatment until date of death from any cause. Subjects who are lost to follow-up will be censored at the last date the subject was known to be alive, and subjects who remain alive will be censored at the time of data cutoff.
- Progression-free survival (PFS), defined as the time from the date of first dose of first-line lenvatinib treatment to the date of first documentation of disease progression, or date of death, during the subsequent systemic TPC, whichever occurs first.
- Time to progression (TTP), defined as the time from the date of first dose of first-line lenvatinib treatment to the date of first documentation of disease progression during the subsequent systemic TPC.

Exploratory Endpoint

- Patient-reported outcome (PRO) results from a well-defined PRO instrument will be determined by scores in the subsequent TPC period

Analysis Sets

Safety Analysis Set (Full Analysis Set) is the group of subjects who received at least 1 dose of the lenvatinib treatment. This will be the analysis set for all safety and efficacy evaluations.

The Pharmacodynamic Analysis Set is all the subjects who have received at least 1 dose of lenvatinib and had sufficient pharmacodynamic data to derive at least 1 pharmacodynamic measurement and with documented dosing history.

Efficacy Analyses

Efficacy analyses will be performed based on Safety Analysis Set (Full Analysis Set

OS

The median OS and the cumulative probability of OS at selected time points will be calculated and presented with 2-sided 95% confidence intervals (CIs). The selected time points will depend on the OS times that are observed during the study and will be specified in the SAP. Kaplan-Meier (KM) estimates of OS will be plotted over time.

PFS

Median PFS time and the cumulative probability of PFS at selected time points will be calculated, and presented with corresponding 2-sided 95% CIs. The selected time points will depend on the PFS times that are observed during the study and will be specified in the SAP. KM estimates of PFS will be plotted over time.

TTP

TTP (based on the tumor response evaluation as determined by investigator assessment according to mRECIST) will be evaluated using same procedure as used for PFS.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The effect of study treatment on soluble, tissue, genetic and/or other relevant biomarkers will be summarized using descriptive statistics using the Pharmacodynamic Analysis Set and correlated with clinical outcomes-related endpoints for safety and/or efficacy as appropriate. Details will be included in a separate analysis plan.

Safety Analyses

All safety analyses based on Safety Analysis Set will be performed for each treatment period. Safety data will be summarized on an "as treated" basis. The incidence of TEAEs and SAEs will be summarized. Laboratory test results, vital signs and their changes from baseline, and 12-lead ECG and echocardiogram results including LVEF, will be summarized using descriptive statistics. Abnormal values will be flagged.

Other Analyses To assess subjects' perceived burden following lenvatinib treatment, PRO-CTCAE questionnaire results will be summarized descriptively.
Interim Analyses No interim analysis is planned in this study.
Sample Size Rationale With the sample size of 100 subjects, assuming that more than 50% of subjects will go on to receive TPC, and that the rate of TEAE with CTCAE Grade ≥3 is 75%, the half width of the 95% CI for the rate of TEAE with CTCAE Grade ≥3 will be no more than 12%.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ß-hCG	beta-human chorionic gonadotropin
BCLC	Barcelona Clinic Liver Cancer
BOR	best overall response
BP	blood pressure
BW	body weight
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT/DLTs	dose-limiting toxicity/dose-limiting toxicities
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ELISA	enzyme-linked immunosorbent assay
FGF	fibroblast growth factor
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	informed consent form

Abbreviation	Term
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
KM	Kaplan Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PEI	percutaneous ethanol inject
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principal investigator
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
QTcF	corrected QT interval using Fridericia's correction
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SOC	system organ class
SOD	sum of diameters
TACE	transarterial chemoembolization

Abbreviation	Term
TEAEs	treatment emergent adverse events
TKI	tyrosine kinase inhibitor
TPC	treatment of physician choice
TTP	time to progression
uHCC	unresectable hepatocellular carcinoma
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
VEGF	vascular endothelial growth factor

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) E6 Good Clinical Practice (GCP), Section 3, and any local regulations (eg, Code of Federal Regulations, Title 21 CFR Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate(s) [CRA(s)], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The definition for end of the study is the date of data cutoff for the final analysis or last subject/last visit including discontinuation from the study for any reason, whichever occurs later. Subjects who remain on treatment at the cutoff for the final analysis will continue receiving the same treatment in consecutive cycles as long as they do not meet any of the study discontinuation criteria as detailed in the protocol.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki, 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 20 to 25 investigational sites in the US and Canada.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organizations (CROs) are listed in Investigator Study File provided to each site.

7 INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and the second leading cause of cancer-related deaths globally. Patients with advanced HCC that is not amenable to surgical resection or local treatment have few effective treatment options. At present, sorafenib (Nexavar®, Bayer), a small-molecule multikinase inhibitor, is the only FDA approved first-line treatment option for patients with advanced HCC (Gosalia, et al., 2017). In previously untreated patients with advanced disease, the median overall survival (OS) was 10.7 months in those treated with sorafenib and 7.9 months in those who received placebo (P<0.001) (Llovet, et al., 2008).

A recent prospective, observational registry study (GIDEON study) evaluated the safety of sorafenib and treatment practices in HCC patients. This large global database allowed for assessment of the use and tolerability of sorafenib in patients with liver dysfunction. Within the overall safety population enrolled to this study, 2,708 patients had known Child-Pugh status at the start of sorafenib therapy; of these, 73% (n=1968) had Child-Pugh A, 25% (n=666) had Child-Pugh B, and 3% (n=74) had Child-Pugh C. In the intent-to-treat population (n=3213), median OS (months [95% confidence interval (CI)]) was longer in Child-Pugh A patients (13.6 [12.8-14.7]) compared with Child-Pugh B patients (5.2 [4.6-6.3]) (Marrero, et al., 2016).

Recent approval of regorafenib (Stivarga®, Bayer) and nivolumab (Opdivo®, BMS) for the treatment of patients with HCC who have been previously treated with sorafenib has provided clinicians with two standard of care treatment options as the second-line therapy of HCC.

In selected HCC subjects who tolerated sorafenib but progressed while on therapy, regorafenib has been reported to provide an OS benefit compared with placebo (10.6 months vs 7.8 months; P<0.001). Although structurally similar, regorafenib is more potent than sorafenib, with a similar side-effect profile. In the Phase 3 clinical RESORCE (Regorafenib After Sorafenib in Patients With HCC) study, subjects with Child-Pugh Class A cirrhosis and advanced HCC who progressed on sorafenib had a significantly longer overall median survival of 10.6 months in the regorafenib arm vs 7.8 months in the placebo arm (P<0.001). Progression-free survival (PFS) and response to therapy were also significantly higher in subjects treated with regorafenib (Bruix, et al., 2017).

Immunotherapies that inhibit the immune checkpoint interaction between programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) have shown substantial survival benefit in some patients with metastatic carcinomas of multiple tissue origins. Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that disrupts PD-1 immune checkpoint signaling and thereby restores the antitumor activity of otherwise suppressed effector T cells. CheckMate 040 (NCT 01658878) is a global, open-label, Phase 1b/2 study of nivolumab in subjects with advanced HCC with or without chronic viral hepatitis who were previously treated or untreated with sorafenib (El-Khoueiry, et al., 2017). In September of 2017, FDA approved nivolumab (Opdivo) as the second-line treatment of patients with HCC who have been previously treated with sorafenib. The approval was based on a 154-patient subgroup of CheckMate 040, conducted in subjects with HCC and Child-Pugh A chronic liver disease who progressed on or were intolerant to sorafenib. The confirmed objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), as assessed by blinded independent central imaging review, was 14.3%, with 3 complete responses (CRs) and 19 partial responses (PRs). Response duration ranged from 3.2 to 38.2+ months; 91% of responders had responses lasting 6 months or longer and 55% had responses lasting 12 months or longer (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577166.htm). A Phase 3 randomized study of nivolumab monotherapy compared with sorafenib in the first-line setting is ongoing.

Lenvatinib (LENVIMA®) is a kinase inhibitor that was approved by FDA for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer as well as for the treatment of advanced renal cell carcinoma in combination with everolimus following one prior anti-angiogenic therapy.

The recently concluded Study E7080-G000-304 (REFLECT) [Study 304] investigated the effect of lenvatinib vs sorafenib in subjects with HCC. Sorafenib is the standard of care for first-line treatment of advanced HCC. Study 304 was a multicenter, randomized, open-label, noninferiority Phase 3 study comparing the efficacy and safety of lenvatinib versus sorafenib as a first-line systemic treatment in subjects with unresectable HCC (uHCC). Study 304 is a positive study with an adequately defined non-inferiority margin and valid assay sensitivity that met its primary endpoint showing that OS with lenvatinib was noninferior to sorafenib. Lenvatinib also demonstrated statistically significant and clinically meaningful improvement for all secondary efficacy endpoints (PFS, time to progression [TTP] and ORR) (Cheng, et al., 2017).

Post-progression therapy may have affected survival in both arms and especially in the sorafenib group as more subjects received post-treatment anticancer therapy in the sorafenib arm than in the lenvatinib arm, particularly in the Western region. After study treatment, subjects on the sorafenib arm were eligible for second-line studies targeting enrollment of sorafenib failures and/or sorafenib-intolerant subjects, while subjects on the lenvatinib arm were not.

Initial clinical experience with lenvatinib in advanced HCC was obtained in a Phase 1/2 clinical study (E7080-J081-202). The recommended Phase 2 dose was determined to be

12 mg for HCC subjects with Child-Pugh Class A. In subjects with Child-Pugh scores of 7-8, the maximum tolerated dose (MTD) was 8 mg once daily (QD). In Study 304, lenvatinib had an acceptable safety profile in HCC subjects when treatment was initiated at 8 mg or 12 mg QD (based on body weight [BW]) and adjusted by a dose-reduction algorithm to manage toxicity (Study E7080-G000-304 Clinical Study Report, 2017). Results from Study 304 provide evidence for lenvatinib as a potential effective and safe first-line treatment for patients with HCC.

Additionally, all subjects included in Study 304 and the Phase 2 study (Study 202) had preserved liver function (Child-Pugh A) (Study E7080-G000-304 Clinical Study Report, 2017) (Ikeda, et al., 2017), and our knowledge regarding the efficacy of lenvatinib in subjects with worse hepatic impairment is limited to very small subgroups of subjects (Ikeda, et al., 2016).

7.1 Study Rationale

Since 2007 there has been only 1 approved systemic medication (sorafenib) for patients with uHCC. Because of this fact in the treatment landscape, studies that evaluated second line treatment of HCC required prior sorafenib as first line therapy. Therefore, the currently approved second line medications (regorafenib and nivolumab) were studied as subsequent sequential therapies to sorafenib. Results from the phase 3 REFLECT study (Study 304) demonstrated the treatment effect of lenvatinib on OS, which was statistically confirmed by non-inferiority to sorafenib for first-line treatment for patients with uHCC. Therefore, it is important to address unmet medical need for data for safety and efficacy on the subsequent sequential therapies after 1st line therapy with lenvatinib in uHCC patients.

The safety and efficacy of lenvatinib in first line uHCC has been established in the large Phase 3 international REFLECT study. This has led to the approval of lenvatinib as first line treatment in uHCC in Japan, EU and in the US. In the REFLECT study, upon progression with first line lenvatinib, 32.6% of patients received subsequent anticancer medications. The information on safety of the subsequent medications after lenvatinib was not captured in the REFLECT study, since patients on lenvatinib were followed post-progression only for OS. Therefore, the objective of study E7080-M001-222 is to capture the safety and tolerability of the subsequent sequential therapy after first-line lenvatinib in patients with uHCC.

The survival follow-up from Study 304 has shown some preliminary information of subsequent treatment following the first-line lenvatinib treatment in HCC subjects during the study period (01 Mar 2013 to 13 Nov 2016). During survival follow-up in Study 304, the percentage of subjects receiving post-treatment anticancer medications (not given for a procedure) in the lenvatinib arm compared with sorafenib arm was 32.6% vs 38.7%, respectively. Sorafenib was the most common anticancer agent given to lenvatinib-treated subjects during survival follow-up, taken by 25.3% of subjects; 11.8% of sorafenib-treated subjects restarted or continued sorafenib during survival follow-up. The percentage of subjects who took investigational anticancer drugs during survival follow-up in the lenvatinib arm compared with the sorafenib arm was 3.1% vs 9.5%, respectively. These investigational agents were mostly administered within clinical trials (eg, regorafenib, cabozantinib), which

required failure of sorafenib therapy as an entry criteria, thus precluding enrollment of lenvatinib-treated subjects in these studies (Study E7080-G000-304 Clinical Study Report, 2017).

This is a single-arm, open-label, multicenter, Phase 2 study to evaluate the safety and efficacy of subsequent systemic treatment of physician choice (TPC) (commercially available) following first-line lenvatinib treatment for uHCC.

The primary objective of the study is to evaluate the safety and tolerability of subsequent systemic TPC following first-line lenvatinib treatment in uHCC subjects. The secondary objectives include evaluation of OS in uHCC subjects treated with lenvatinib as first-line treatment followed by TPC, and evaluation of PFS and TTP of subsequent systemic TPC starting from the first dose of first-line lenvatinib treatment.

Approximately 100 subjects will be enrolled to first-line treatment with lenvatinib. Subjects with Child-Pugh A will be included in this study. Starting dose of lenvatinib will be based on baseline BW: 12 mg QD or 8 mg QD will be orally administered for subjects' BW ≥60 kg or <60 kg, respectively.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To assess the safety and tolerability of subsequent systemic TPC following the first-line lenvatinib treatment in uHCC subjects.

8.2 Secondary Objectives

- To evaluate OS in uHCC subjects treated with lenvatinib as the first-line treatment followed by systemic TPC
- To evaluate PFS and TTP of subsequent systemic TPC starting from the first dose of first-line lenvatinib treatment using modified RECIST (mRECIST)
- To evaluate OS by subgroups of systemic TPC

8.3 Exploratory Objectives

- To measure the patient perceived burden by Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in the subsequent TPC period
- To explore biomarkers based on availability of serum and tissue samples

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a single-arm, open-label, multicenter, phase 2 study to evaluate the safety and efficacy of subsequent systemic TPC (commercially available) following first-line lenvatinib treatment for uHCC.

Approximately 100 subjects with uHCC will be enrolled to receive first-line treatment with lenvatinib in 28-day treatment cycles. Subjects with Child-Pugh A are eligible for this study.

Subjects will continue to receive lenvatinib treatment in continuous 28-day cycles until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor. Upon subject's completion of lenvatinib Off-Treatment Visit in first-line treatment of lenvatinib, subjects will be treated by commercially available, systemic TPC for uHCC in the subsequent TPC period.

The study will consist of Pretreatment Phase, Treatment Phase, and Post-Treatment Phase.

9.1.1 Pretreatment Phase

The pretreatment phase will last up to 21 days and will include Screening Period and a Baseline Visit/Period.

9.1.1.1 Screening Period

The Screening Period will last no longer than 21 days and will occur between Day –21 and Day –2. The purpose of the Screening Period is to obtain informed consent and establish protocol eligibility and disease characteristics. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Informed consent may be taken up to 4 weeks prior to Cycle 1 Day 1.

The Screening Disposition case report form (CRF) must be completed to indicate whether the subject is eligible to enroll in the study and to provide reasons for screen failure, if applicable.

Subjects must be screened within 21 days prior to the first dose of study treatment. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit.

9.1.1.2 Baseline Period/Visit

Baseline assessments can be performed on Day –1 or prior to the start of study treatment on Cycle 1 Day 1. The purpose of the Baseline Visit is to confirm protocol eligibility and

disease characteristics, as specified in the inclusion/exclusion criteria (as detailed in Section 9.3.1 and Section 9.3.2).

The screening assessment can serve as the baseline assessment, if performed within 72 hours before the first dose of study treatment. If the screening physical examination is performed >7 days prior Cycle 1 Day 1, it must be repeated at the Baseline Visit. Laboratory tests and a pregnancy test (for female subjects of childbearing potential) may be performed up to 72 hours before the first dose of study treatment.

Subjects who complete the baseline assessment and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the treatment phase. Results of baseline assessments must be obtained prior to the first dose of study treatment (Cycle 1 Day 1).

9.1.2 Treatment Phase

There will be 2 treatment periods in this study: Lenvatinib Treatment Period (Treatment Period 1) and the Subsequent TPC Treatment Period (Treatment Period 2).

9.1.2.1 Lenvatinib Treatment Period (Treatment Period 1)

Lenvatinib Treatment Period for each subject will begin with the administration of first dose of lenvatinib on Cycle 1 Day 1 and will consist of administration of lenvatinib in 28-day treatment cycles. Treatment Period 1 will continue until completion of the lenvatinib Off-Treatment Visit that will occur within 30 days after the final administration of lenvatinib.

Lenvatinib treatment cycles will be counted continuously regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 3). Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor.

Subjects will be permitted to continue lenvatinib treatment beyond mRECIST defined disease progression as long as the treating investigator considers that there is clinical benefit and, the subject is tolerating study treatment. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Eisai Medical Monitor. Subjects will discontinue study treatment upon evidence of further progression and/or loss of clinical benefit, as judged by the investigator.

9.1.2.2 Subsequent Treatment Period (TPC Period, Treatment Period 2)

The subsequent TPC period will begin upon the completion of the lenvatinib Off-Treatment Visit in first-line treatment of lenvatinib. Subjects will be treated with commercially available systemic TPC for uHCC. The first treatment of a single agent or combination of multiple drugs after lenvatinib treatment will be considered as the subsequent TPC. Locoregional therapies (ie, chemoembolization/radioembolization, etc) procedures will not

be considered as a second line treatment following lenvatinib. If the investigator deems a subject inappropriate for commercially available systemic TPC as the subsequent treatment following lenvatinib, subjects will be followed in the survival Follow-Up period. All treatment following lenvatinib will be captured in the case report form. Data will be collected from the start of TPC, then at intervals as indicated in Schedule of Procedures/Assessments (Table 3).

Subjects starting subsequent TPC ≥8 weeks after lenvatinib off-treatment visit may be considered after discussion with sponsor.

9.1.2.3 Follow-Up Period (Survival Follow-Up)

The Follow-Up Period will begin immediately after the final visit of the subsequent TPC period (Treatment Period 2). Subjects will be followed every 12 weeks for survival and will continue as long as the study subject is alive or the subject withdraws consent. If the investigator deems a subject inappropriate for commercially available subsequent systemic TPC, the subject will be followed for survival every 12 weeks after the lenvatinib Off-Treatment Visit of the Lenvatinib Treatment Period (Treatment Period 1). Subjects' survival status and all additional anticancer treatments received will be recorded.

The sponsor may decide to terminate survival follow-up of subjects after the completion of the primary analysis or when all subjects have discontinued study treatment.

9.2 Discussion of Study Design, Including Choice of Control Groups

This open-label, multicenter, phase 2 study will employ a single-arm design to evaluate the safety and efficacy of subsequent systemic TPC (commercially available) following first-line lenvatinib treatment of uHCC, and to gain more understanding of the safety and efficacy of other systemic anti-HCC therapy following lenvatinib treatment.

9.3 Selection of Study Population

Approximately 100 subjects with uHCC are planned to be enrolled at approximately 20 to 25 sites in the US and Canada. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Subjects must have confirmed diagnosis of uHCC with any of the following criteria:
   a. Histologically or cytologically confirmed diagnosis of HCC
   b. Clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria, including cirrhosis of any etiology or with chronic hepatitis B or C infection criteria
2. At least one measurable target lesion regardless if hepatic or non-hepatic according to

mRECIST meeting the following criteria:

a. Hepatic lesion
   - The lesion can be accurately measured in at least one dimension as ≥1.0 cm (viable tumor for typical; and longest diameter for atypical), and
   - The lesion is suitable for repeat measurement,

b. Nonhepatic lesion
   - Lymph node lesion that measures at least one dimension as ≥1.5 cm in the short axis
   - Non-nodal lesion that measures ≥1.0 cm in the longest diameter

Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion.

3. Subjects categorized on the Barcelona Clinic Liver Cancer (BCLC) staging system to Stage B (not applicable for transarterial chemoembolization [TACE]) or Stage C
4. Adequate bone marrow function, defined as:
   - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
   - Hemoglobin ≥8.5 g/dL
   - Platelet count ≥75 × 10^9/L
5. Adequate liver function, defined as:
   - Albumin ≥2.8 g/dL
   - Bilirubin ≤3.0 mg/dL
   - Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) ≤5 × the upper limit of normal (ULN)
6. Adequate blood coagulation function, defined as international normalized ratio (INR) ≤2.3
7. Adequate renal function defined as creatinine clearance >30 mL/min calculated per the Cockcroft and Gault formula
8. Adequate pancreatic function, defined as lipase ≤1.5 × ULN
9. Adequately controlled blood pressure (BP) with up to 3 antihypertensive agents, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive therapy within 1 week prior to Cycle 1/Day 1
10. Child-Pugh A
11. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
12. Survival expectation of 12 weeks or longer before starting study drug
13. Males or females aged at least 18 years at the time of informed consent
14. Provide written informed consent
15. Willing and able to comply with all aspects of the protocol

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Imaging findings for HCC corresponding to any of the following:
   a. HCC with ≥50% liver occupation
   b. Clear invasion into the bile duct
   c. Portal vein invasion at the main portal branch (Vp4)
2. Subjects who have received any systemic chemotherapy, including sorafenib, regorafenib or other anti-vascular endothelial growth factor (VEGF) therapy, nivolumab, or any systemic investigational anticancer agents, including lenvatinib, for advanced/uHCC. Note: Subjects who have received local hepatic injection chemotherapy (if not within 28 days prior to the first dose of lenvatinib study treatment) are eligible
3. Subjects who have received any anticancer therapy (including surgery, percutaneous ethanol injection, radio frequency ablation, transarterial [chemo] embolization, hepatic intra-arterial chemotherapy, biological, immunotherapy, hormonal, or radiotherapy) or any blood enhancing treatment (including blood transfusion, blood products, or agents that stimulate blood cell production, eg, granulocyte colony-stimulating factor [G-CSF]) within 28 days prior to the first dose of lenvatinib study treatment.
4. Subjects who have not recovered from toxicities as a result of prior anticancer therapy such as the local hepatic injection chemotherapy or any prior therapy for other cancer types. Recovery is defined as <Grade 2 severity per Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03), except alopecia and infertility
5. Significant cardiovascular impairment within 6 months of the first dose of study drug: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke, cardiac arrhythmia associated with hemodynamic instability, or a left ventricular ejection fraction (LVEF) below the institutional normal range as determined by multigated acquisition (MUGA) scan or echocardiogram
6. Prolongation of QTcF (QT interval corrected for heart rate using Fridericia's correction) interval to >480 ms
7. Gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib in the opinion of the investigator
8. Bleeding or thrombotic disorders or use of anticoagulants such as, warfarin or similar agents requiring therapeutic INR monitoring (Treatment with low molecular weight heparin is allowed)
9. Gastrointestinal bleeding event or active hemoptysis (bright red blood of at least half teaspoon) within 28 days prior to the first dose of lenvatinib study treatment
10. Gastric or esophageal varices that require treatment
11. Active malignancy (except for HCC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 36 months
12. Any history of, or current brain or subdural metastases
13. Subjects having >1+ proteinuria on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible.

14. Arterial-portal venous shunt or arterial-venous shunt preventing proper diagnosis of tumor
15. Any medical or other condition that in the opinion of the investigator would preclude the subject's participation in a clinical study
16. Known intolerance to lenvatinib or any of the excipients
17. Human immunodeficiency virus (HIV) positive or active infection requiring treatment (except for hepatitis virus)
18. Any history of drug or alcohol dependency or abuse within the prior 2 years
19. Any subject who cannot be evaluated by either triphasic liver computed tomography (CT) or triphasic liver magnetic resonance imaging (MRI) because of allergy or other contraindication to both CT and MRI contrast agents
20. Major surgery within 3 weeks prior to the first dose of lenvatinib study treatment or scheduled for surgery during the study
21. Subject has had a liver transplant
22. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
23. Females of childbearing potential who:

- Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
  - total abstinence (if it is their preferred and usual lifestyle)
  - an intrauterine device or intrauterine hormone-releasing system (IUS)
  - a contraceptive implant
  - an oral contraceptive (with additional barrier method) (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
  - have a vasectomized partner with confirmed azoospermia.
- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as latex or synthetic condom plus diaphragm or cervical/vault cap with spermicide.

All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

24. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 96 days after study drug discontinuation). No sperm donation is allowed during the study period and for 96 days after study drug discontinuation.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents.

Follow-Up Period will begin immediately after the final visit in subsequent TPC period. Subjects will be followed every 12 weeks for survival and will continue as long as the study subject is alive unless the subject withdraws consent. Subjects who do not take subsequent TPC will be followed for survival every 12 weeks after the lenvatinib Off-Treatment Visit of Lenvatinib Treatment Period.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

9.4 Treatments

9.4.1 Treatments Administered

9.4.1.1 Test Drug: Lenvatinib

Lenvatinib capsules will be administered orally, QD in continuous 28-day cycles. The starting dose of lenvatinib will be based on the subject's baseline BW as follows:

- BW ≥60 kg — Lenvatinib 12 mg (taken as three 4-mg capsules) QD.
- BW <60 kg — Lenvatinib 8 mg (taken as two 4-mg capsules) QD.

Study medication should be taken at approximately the same time each day in a fasting state or following a meal.

If a dose is missed and cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Lenvatinib treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or termination of the study

by the sponsor. The duration of lenvatinib treatment for each subject is estimated to be 6 to 8 months.

If holidays or personal schedules make administration impossible on the scheduled days, then administration should be resumed as soon as possible.

9.4.1.1.1 DOSE REDUCTION AND INTERRUPTION OF LENVATINIB

Dose adjustments for management of intolerable toxicities will be made according to the guidelines provided in Table 1.

Table 1 Dose Modification and Treatment Discontinuation Guidelines for Management of Lenvatinib-Related Toxicity

Study Treatment Dose Reduction and Interruption Instructions		
Dose reductions occur in succession based on the previous dose level (eg, 12, 8, and 4 mg/day, and 4 mg every other day for the subjects with initial BW ≥60 kg). Any dose reduction below 4 mg every other day must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date.		
Non-Hematologic Toxicities		
Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d] or Grade 3[e,d]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	One-level reduction
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	One-level reduction
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	One-level reduction
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[g]: Discontinue Study Treatment		
Hematologic Toxicities and Proteinuria		
Treatment-Related Toxicity[a]	**Management**	**Dose Adjustment**
Grade 1 or Grade 2		
	Continue treatment	No change
Grade 3		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Fourth occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Fifth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor
Grade 4		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction

Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	One-level reduction
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor

Note: Grading according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.
AEs = adverse events, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

a: An interruption of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment at least every 7 days (until restarting administration).
b: Initiate optimal medical management for nausea, vomiting, diarrhea and/or hypothyroidism prior to any study treatment, interruption, or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and physician to be intolerable.
d: For proteinuria, interrupt until Grade 0-2.
e: Not applicable to abnormal clinical laboratory values that require no treatment (eg, sodium). Manage ALT, AST, and gamma-glutamyltransferase values 10 × ULN or higher as Grade 3.
f: Please ignore this step for subjects who start at 8 mg once daily.
g: Excluding laboratory abnormalities judged to be non-life-threatening, which should be managed as Grade 3.

9.4.1.1.2 MANAGEMENT OF HYPERTENSION

Hypertension is a recognized side-effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP ≤150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/Assessments. Hypertension will be graded using CTCAE v4.03, based on BP measurements only (and not on the number of antihypertensive medications).

Only one BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of these 2 measurements done at least 5 minutes apart is defined as one BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory BP assessment should be obtained at least 30 minutes later by performing 2 measurements at least 5 minutes apart (to yield a mean value).

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) is confirmed on 2 assessments at least 30 minutes apart. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is first observed on 2 assessments at least 30 minutes apart. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of

antihypertensive should be added. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred.

Study drug should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the subject has been on same hypertensive medications for at least 48 hours and the BP is controlled, study drug should be resumed as described below.

Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles. If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles.

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat measurements after 30 minutes:

- Continue study drug and institute antihypertensive therapy for subjects not already receiving antihypertensive medication.
- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.
- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then study drug administration should be interrupted and restarted at a dose of 8 mg QD (one dose level reduction as specified in table above) only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the 8 mg QD dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a dose of 4 mg QD (one dose level reduction as specified in the table above) only when systolic BP ≤150 mmHg and diastolic BP ≤95mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the 4 mg QD dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and a restart of study medication should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue study drug.

9.4.1.1.3 MANAGEMENT OF PROTEINURIA

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments. Guidelines for assessment and management of proteinuria are summarized as follows:

Grading of Proteinuria

- Grading of proteinuria according to CTCAE v4.03 will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to the Dose Modification Guidelines (Table 1).

Detection and Confirmation

1. Perform urine dipstick testing per the Schedule of Assessments
2. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot urine protein-to-creatinine ratio (UPCR) test is required in the following situations:
   a. The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
   b. A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
   c. When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Monitoring

- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

9.4.1.1.4 MANAGEMENT OF HEPATOTOXICITY

Regular monitoring of liver function tests (eg, ALT, AST, bilirubin levels) should be conducted as detailed in the Schedule of Assessments/Procedures (Table 3) and as clinically indicated. Worsening liver function including hepatic encephalopathy should be closely monitored. If signs occur indicating a decrease in liver function by 1 grade or more from baseline, the instructions contained in Table 1 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, lenvatinib must be discontinued.

9.4.1.1.5 MANAGEMENT OF THROMBOEMBOLIC EVENTS

Subjects should be advised to pay attention to the symptoms suggestive of venous thromboembolic events, which include acute onset of dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower-extremity swelling, redness and warmth to touch or tenderness. In case any of these signs or symptoms appear, subjects should be instructed to report such signs and symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 1 should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, lenvatinib must be discontinued.

9.4.1.1.6 MANAGEMENT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES, dose interruptions, reductions, or discontinuation may be required per instructions included in Table 1. Please refer to Section 7 of the Investigator's Brochure for further information on lenvatinib, including the full set of special warnings and precautions for use (Section 7.4.4).

9.4.1.2 Subsequent Treatment of Physician Choice (TPC)

The Subsequent Treatment Period (TPC period, Treatment Period 2) will begin upon the completion of lenvatinib Off-Treatment Visit in first-line treatment of lenvatinib. Subjects will be treated by commercially available, systemic TPC for uHCC. The first treatment of a single agent or combination of multiple drugs after lenvatinib treatment will be considered as the subsequent TPC. Locoregional therapies (ie, chemoembolization/radioembolization, etc.) will not be considered as a second line treatment following lenvatinib. If the investigator deems a subject inappropriate for commercially available systemic TPC as the subsequent treatment following lenvatinib, subjects will be followed in the survival Follow-Up Period.

All treatment following lenvatinib will be captured in the case report form. Data will be collected from the start of TPC, then at intervals as indicated in Schedule of Procedures/Assessments (Table 3).

Subjects starting subsequent systemic TPC ≥8 weeks after lenvatinib off-treatment visit may be considered after discussion with sponsor.

For subjects who experience TPC-related toxicity, dose reduction and/or interruption will be in accordance with the prescribing information for each medication.

Subjects will continue to receive TPC treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor.

9.4.2 Identity of Investigational Product

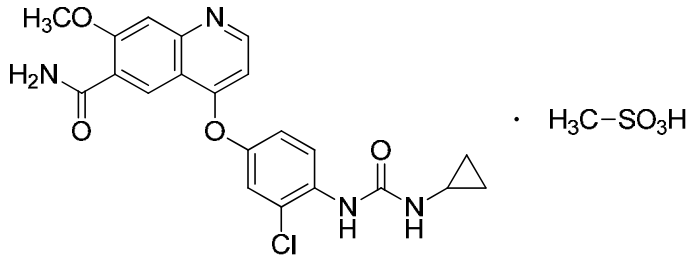
The test drug (lenvatinib) in Treatment Period 1 will be supplied to the study sites by the sponsor packaged as open-label #4-size hydroxypropyl methylcellulose 4-mg capsules (yellowish-red cap and body, containing 4 mg lenvatinib [anhydrous free base]) in labeled containers.

Commercially available treatment chosen by investigator (TPC) for subsequent treatment of uHCC will be supplied by the local pharmacy.

Labelling, packaging and storage of the commercially available TPC must be in accordance with local regulations and manufacturer's instructions.

9.4.2.1 Chemical Name, Structural Formula of E7080 (Lenvatinib)

- Test drug code: E7080
- Generic name: Lenvatinib
- Chemical name: 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate
- Molecular formula: $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$
- Molecular weight: 522.96
- Structural formula:



9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Lenvatinib will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language for each of those countries.

Medications chosen by investigator for subsequent treatment will not be provided by the sponsor.

9.4.2.4 Storage Conditions

The sponsor will prepare the "Procedures for Handling Investigational Drug'' which will be provided to the investigator, head of medical institution (as required by regional authority), or designated study drug manager before the investigational drug is delivered. The investigational drug will be stored in accordance with the "Procedures for Handling Investigational Drug."

Lenvatinib will be stored in accordance with the labeled storage conditions. The expiry date for lenvatinib will be established based on the date that manufacturing/packing is completed or will be based on formulation testing, and will therefore be described in the "Procedures for Handling Investigational Drug."

Study drug to be used in Period 2 will be stored as described in the locally approved product label or in the applicable Summary of Product Characteristics.

Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained. The temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive lenvatinib treatment in Treatment Period 1 followed by the TPC in Treatment Period 2. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

In Study 304, lenvatinib had an acceptable safety profile in HCC subjects when treatment was initiated at 8 mg or 12 mg QD (based on BW) and adjusted by a dose-reduction algorithm to manage toxicity (Study E7080-G000-304 Clinical Study Report, 2017). Based

on these data, the starting dose of lenvatinib in this study will be based on baseline BW of the subjects: 12 mg QD for BW ≥60 kg and 8 mg QD for <60 kg.

9.4.5 Selection and Timing of Dose for Each Subject

Lenvatinib capsules are to be taken orally, QD in continuous 28-day cycles at approximately the same time each day in a fasting state or after a meal.

Administration of TPC should be in accordance with the approved prescribing information for the chosen treatment.

9.4.6 Blinding

The study will be open label.

9.4.7 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 28 days after last dose of lenvatinib treatment if subjects do not enter TPC period, or for 8 weeks after the start of TPC period, or up to 28 days after last dose of TPC if subject does not stay in the TPC period for the 8 weeks of safety monitoring. All anticancer therapy will be recorded until time of death or termination of survival follow-up. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with the study medication may be continued during the study.

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

Aspirin, nonsteroidal anti-inflammatory drugs, and low-molecular-weight heparin are permissible but should be used with caution. g-CSF or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

9.4.7.1 Drug-Drug Interactions

The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (lenvatinib – Global Investigator's Brochure).

No dose adjustment of lenvatinib is recommended when coadministered with CYP3A, PgP, and breast cancer resistance protein (BCRP) inhibitors, and with CYP3A and PgP inducers

(lenvatinib – Global Investigator's Brochure). In a formal drug-drug interaction study, lenvatinib did not alter plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate). Thus, lenvatinib is not expected to alter the metabolism of other co-administered drugs which are CYP3A4/Pgp substrates (lenvatinib – Global Investigator's Brochure).

A population PK analysis also indicated that agents that raise gastric pH (eg, H2-blockers, proton pump inhibitors, antacids) do not have a significant effect on the absorption and bioavailability of lenvatinib (CPMS-E7080-007R-v1).

Please refer to Flockhart DA, 2007 for the most current information regarding inhibitors and inducers of CYP3A4.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

The following concomitant therapies will be prohibited from the time of informed consent for this study until discontinuation from lenvatinib treatment:

- Surgery or radiotherapy for the treatment of HCC. Palliative radiotherapy of up to 2 painful pre-existing nontarget bone metastases will be permitted without being considered progressive disease (PD).
- Systemic therapy, hepatic intra-arterial chemotherapy, immunological therapy (eg, interferon, interferon-type drugs, etc), hormonal therapy, or local therapy of any kind (eg, percutaneous ethanol inject [PEI], radiofrequency ablation [RFA], TACE, etc) for the treatment of HCC. Subjects who are receiving antiviral therapy for hepatitis B virus will be allowed to continue to receive this therapy at the discretion of the investigator.
- Other investigational drugs
- Antiplatelet agents and anticoagulants that required INR monitoring, such as warfarin. (Treatments that do not require INR monitoring, such as low molecular weight heparin and certain factor X inhibitors are permitted.)

If subjects receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These subjects should complete all off-treatment assessments and continue to be followed for survival in the Follow-Up Period.

Drugs that are not prohibited for concomitant use include drugs used to treat complications or AEs, or drugs used to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, steroids, antidiarrheal drugs, and tranquilizers, etc). These drugs and treatments can be concomitantly used, based on the judgment of the investigator or subinvestigator.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study other than the parent, guardian, or authorized legal representative of a study subject.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to:
(a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, MHRA). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected during Screening. Demography information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

Baseline assessments will be performed at Day -1 or at Cycle 1 Day 1 prior to treatment. The screening assessment can serve as the baseline assessment, if performed within 72 hours of the first dose of study treatment. Assessments will include confirmation of subject eligibility with the inclusion and exclusion criteria, medical and surgical history, prior medications and procedures, pregnancy test (serum or urine) in women of childbearing

potential within 72 hours prior to the first dose of study treatment, blood coagulation test, ECOG PS (see Appendix 5), Child-Pugh score (see Appendix 4), vital signs and weight, clinical chemistry and hematology, and urine dipstick testing.

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening and Baseline Visits. All medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations (comprehensive or symptom directed) will be performed as designated in the Schedule of Assessments (Table 3). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at screening will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.3 Efficacy Assessments

All efficacy endpoints, other than OS, will be based on the tumor response evaluation as determined by investigator assessment according to mRECIST (and including the RECIST 1.1 conventions for non-hepatic lesions). Tumor assessments will be performed at the site by appropriately qualified personnel. Treatment decisions will be based on tumor response assessments determined by the investigator.

9.5.1.3.1 TUMOR ASSESSMENTS

Tumor assessments will be performed during the Screening/Baseline phase (standard of care scans performed up to 28 days before the first dose of study treatment are acceptable) and then every 8 weeks (±1 week), or sooner if clinically indicated, during the Lenvatinib Treatment Period until disease progression (Table 3).

Subjects who discontinue lenvatinib treatment without disease progression should have tumor assessments performed (within 1 week of the lenvatinib Off-Treatment Visit) if more than 4 weeks have passed since the previous assessment and if the subject will not continue with follow-up scans.

Subjects entering the subsequent TPC period should have TPC baseline tumor assessments performed unless the last tumor assessment performed in the Lenvatinib Treatment Period is less than 28 days before the subsequent treatment starts, in which case those scans may be used as the TPC period baseline. A new tumor assessment baseline (selection of target and non-target lesions and calculation of a new baseline sum of diameters (SOD) must be established before beginning TPC. Subjects will continue tumor assessments during the subsequent TPC period every 8 weeks (±1 week), or until disease progression, subject death, withdrawal or loss to follow-up.

Tumor assessments will utilize mRECIST based on Lencioni and Llovet (Appendix 2, Lencioni and Llovet, 2010). Copies of all tumor imaging scans will be sent to an imaging core laboratory designated by the sponsor for potential future review. All subjects are required to undergo chest, abdomen, and pelvis imaging at baseline and all follow-up time points. Contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis, and any other areas of disease, as clinically indicated, will be acquired at Screening and at all imaging time points. Liver CT or MRI must be performed using triphasic scanning technique optimized to capture precontrast, arterial and portal venous phase.

Screening tumor assessments using triphasic liver CT/MRI (optimized for pre-contrast, arterial phase, and portal venous phase), contrast-enhanced CT of the chest, and contrast-enhanced CT or MRI of abdomen, pelvis, and other areas of known disease plus suspected disease should be performed within 28 days prior to treatment.

Screening CT of the brain with contrast or MRI of the brain pre- and post-gadolinium should be performed within 28 days prior to treatment. During the Treatment Phase, CT/MRI of the brain should be performed if clinically indicated. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability.

During the Treatment Phase, tumor assessments using triphasic liver CT/MRI (optimized for pre-contrast, arterial phase, and portal venous phase), contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis, and other areas of known disease at Screening plus newly suspected disease should be performed every 8 weeks (during the eighth week; starting from the date of the first treatment of lenvatinib), or sooner, if clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques, including use and timing of IV contrast, should be used as for the screening assessments. Tumor assessment at the lenvatinib Off-Treatment Visit is only necessary if more than 4 weeks have passed since the previous assessment (window for these assessments is within 1 week of the lenvatinib Off-Treatment Visit).

If a subject discontinues from the study prior to the Week 8 scan, then a CT/MRI scan should be performed as close as possible to 8 weeks after treatment. If a subject discontinues prior to Week 8, the scans for tumor assessment should be performed as close as possible to Week 8 but before another anticancer therapy is initiated.

Target lesions in bone may not receive palliative radiotherapy. A maximum of 2 bone metastases that become painful and are being followed as bone non-target lesions on CT or MRI scans (using bone windows/sequences) may be treated with palliative radiotherapy. The lesion(s) should be considered as not evaluable (NE) for all subsequent time points, unless they later progress unequivocally.

If a subject is unable to undergo a contrast CT due to allergy or renal insufficiency during follow-up, a chest CT without contrast, combined with MRI images of the remaining anatomy with gadolinium contrast, is preferred if tolerated by the subject. If it is determined

that neither CT nor MRI IV contrast can be tolerated by the subject during follow-up, a chest CT without contrast combined with high quality T1 and T2 weighted MRI images of the remaining anatomy should be provided. Importantly, such a modality switch will render the subsequent measurements of target lesions, especially typical hepatic target lesions, inadequate and the target lesion disease should be followed as NE or potentially progressing (if sufficient evidence is available).

The tumor assessment schedule should not be affected by interruptions in therapy, or any other events that might lead to imbalance between the treatment groups with regard to the timing of disease assessments.

CT and MRI scans should be of diagnostic quality acquired on spiral or multidetector CT with oral and IV contrast. Low dose noncontrast CT transmission scans from positron emission tomography (PET)/CT scanner are not acceptable. Spiral or multidetector CT should be performed with a 5 mm contiguous slice reconstruction algorithm. If MRI scans are acquired, contiguous 5 mm slice thickness with minimal gap are also recommended. Ultrasound should not be used for radiographic assessment. A chest x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

Brain scans should be performed by MRI pre- and post-contrast enhancement or CT with contrast enhancement, with 5-mm contiguous slices recommended (maximum inter-slice gap of 1 mm on MRI).

In order to be eligible for this study, all subjects must have at least one measurable lesion visible on screening CT or MRI scans. To adequately determine lesion progression and response, the investigator will categorize the baseline disease burden on the screening image into typical, atypical, and nonhepatic target and nontarget lesions. Lesions previously treated with radiotherapy or surgical therapy should not be considered suitable as target lesions, unless they show radiographic evidence of disease progression. The investigator will follow each of the selected lesions at each subsequent imaging time point until radiological progression is determined. If a lesion that was not present at baseline is detected on a follow-up scan, it will be identified as a new lesion. At every time point, the investigator will determine the overall tumor response of a subject as CR, PR, stable disease (SD), NE, or PD, as appropriate (see Appendix 2 for further details).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Not applicable.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Pharmacodynamic Blood Biomarkers

Blood serum samples for pharmacodynamic and exploratory biomarkers analysis will be collected at the following time points:

Treatment Period 1: Before dosing (predose) lenvatinib on Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of all subsequent cycles, and at the off-treatment assessment.

Treatment Period 2: Subjects entering the subsequent TPC period should have TPC baseline sample collected unless the lenvatinib Off-Treatment visit in the lenvatinib treatment period is ≤28 days before the subsequent treatment starts, in which case those samples may be used as the TPC period baseline. Samples will then be collected at week 8 and week 16 (±1 week).

A detailed biomarker analysis plan will be prepared separately.

Pharmacogenetic Biomarker Assessments

Archived, fixed tumor tissue from the most recent surgery or biopsy will be collected (if available) from all enrolled subjects for potential assessment of mutations and other genetic alterations or genes and/or proteins that may be important in the development and progression of cancer as well as in response to study drug treatment for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available. Note that in order to understand tumor-specific mutations, it may be necessary to compare the tumor genome with the germline genome.

A blood sample will be collected for potential genetic analysis from all enrolled subjects to evaluate whether genetic variation within a clinical study population correlates with response to the study treatment. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

A blood plasma sample to isolate circulating cell-free nucleic acids will be collected at the following time points:

Treatment Period 1: Before dosing (predose) lenvatinib on Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of all subsequent cycles, and at the off-treatment assessment.

Treatment Period 2: Subjects entering the subsequent TPC period should have TPC baseline sample collected unless the lenvatinib Off-Treatment visit in the lenvatinib treatment period is ≤28 days before the subsequent treatment starts, in which case those samples may be used as the TPC period baseline. Samples will then be collected at week 8 and week 16 (±1 week).

A detailed biomarker analysis plan will be prepared separately.

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to study treatment, cancer and/or for potential diagnostic development.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Biomarker correlative analyses may be performed to explore blood or tumor biomarkers that may be useful to predict subject's response in a retrospective manner. The results of these studies are to gain further insight into the clinical mechanism of action for study drug but not foreseen to result in commercially valuable products.

This study will collect biomarker samples in all enrolled subjects who have consented for participation of the biomarker assessments. Participation of any future exploratory research of leftover material will be optional.

9.5.1.5 Safety Assessments

Safety assessments consisted of monitoring and recording of all AEs, including all CTCAE v4.03 grades (for increasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine dipstick values; periodic measurement of ECOG PS, Child-Pugh score, vital signs, 12-lead electrocardiograms (ECGs), and echocardiograms or MUGA scans including LVEF; and the performance of physical examinations as detailed in Table 3.

Safety assessments will be performed at intervals as indicated in Schedule of Procedures/Assessments (Table 3) in both Treatment Periods. .

9.5.1.5.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease (HCC) should be captured under efficacy assessments as disease progression rather than as an AE. If the disease progression leads to an untoward medical occurrence, then this medical occurrence should be recorded as an AE.

- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug.
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline).
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit and for 28 days after the last dose of lenvatinib treatment if subjects do not enter TPC period, or for 8 weeks after the start of TPC period. SAE information should be collected for 8 weeks after the start of the TPC, or for at least 28 days after the last dose of lenvatinib/TPC if subjects do not continue into the TPC period or do not stay in the TPC period for the 8 weeks of safety monitoring.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03. Investigators will report CTCAE grades for all AEs (for increasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments

- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed are summarized in Table 2. All clinical laboratory tests during the study will be performed by local laboratories. All hematology, blood chemistry (including pregnancy test, as applicable) are to be obtained prior to study drug administration and sent to the local laboratory on the day of collection, unless otherwise instructed. Subjects should be in a seated or supine position during blood collection.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), INR[a], PT[a]
Chemistry	Blood urea nitrogen (BUN), creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, lactate dehydrogenase, potassium, chloride, sodium, calcium total, cholesterol, total protein, albumin, total amylase, lipase, serum gamma glutamyl transpeptidase, C-reactive protein, ammonia.
Urinalysis/Urine Dipstick Testing	Glucose, hemoglobin (or blood), ketones, pH, protein, specific gravity
Other	α-Fetoprotein and thyroid-stimulation hormone Pregnancy test (serum or urine β-hCG)

INR = International Normalized Ratio, PT = prothrombin time, RBC = red blood cell, WBC = white blood cell,

a: INR and prothrombin time (PT) should only be performed as part of the screening assessment and when clinically indicated.

The Schedule of Procedures/Assessments (Table 3) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study (refer to the Laboratory Manual for a list of tests). All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle.

Laboratory tests at baseline may be performed up to 72 hours prior to start of study treatment. Hematology and clinical chemistry results will be reviewed within 48 hours after receiving quick estimation. Assessments scheduled may be performed within 72 hours prior to the visit. If subjects experience ≥Grade 3 hematologic or clinical chemistry toxicities, repeat laboratory tests and AE assessments at least every 7 days until improvement to <Grade 3. Refer to Table 1 for the management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

For laboratory abnormalities meeting the criteria of SAEs (Section 9.5.1.5.2), the site must send the SAE report including the laboratory report (as regionally required) to the SAE fax number or email provided in the Investigator File.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, BP [systolic and diastolic; mmHg], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]) and BW (kg) will be obtained at the visits designated on the Schedule of Procedures/Assessments (Table 3) by a validated method. Blood pressure and heart rate will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory BP assessment at least 30 minutes later should be obtained by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Starting dose of lenvatinib is determined based on measurement of BW at the Baseline Visit. Subsequent measurements of BW are not relevant for dose determination.

9.5.1.5.5 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 3). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.6 Electrocardiograms

A single resting 12-lead ECG will be performed as designated in the Schedule of Procedures/Assessments (Table 3). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a

minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

Echocardiograms or MUGA scans will be obtained as designated on the Schedule of Procedures/Assessments (Table 3). A MUGA scan (using technetium-99m-pertechnetate) or an echocardiogram to assess LVEF will be performed during the Screening Visit and at the lenvatinib Off-Treatment Visit of the Lenvatinib Treatment Period (or sooner if clinically indicated). MUGA scans and echocardiograms should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at baseline should be repeated for all subsequent LVEF assessments for that subject.

LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

Pregnancy Test

A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) at designated time points as specified in the Schedule of Procedures/Assessments (Table 3).

9.5.1.6 Other Assessments

Subjects perceived burden post lenvatinib treatment in the subsequent TPC period will be measured by completed PRO-CTCAE questionnaires. PRO-CTCAE data will be collected only at the lenvatinib Off-Treatment Visit in Treatment Period 1, and every 2 weeks for the first 4 weeks, and then at week 8 and week 16 (±1 week) in the TPC period. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed within 7 days prior to the first TPC treatment.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the study.

Table 3 Schedule of Procedures/Assessments in Study E7080-M001-222

Period	Screening[a]	Baseline[a]	Lenvatinib (Treatment Period 1) (All cycles are 28 days in duration)								TPC (Treatment Period 2)					Survival FU
Visit	1	2	3	4	5	6	7	8, 9, etc		99						
Day	-21 to -2	-1	Cycle 1[b]			Cycle 2[c]		Cycle 3 – Last[c]		Lenvatinib Off-Treatment Visit	TPC Baseline	Week 2	Week 4	Week 8	Week 16[aa]	Every 12 weeks
			1	8	15	1	15	1	15							
Procedures/ Assessments																
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Demographic data	X															
ECOG-PS[d]	X	X				X		X		X	X[d]	X	X	X		
NYHA[d]	X															
BCLC staging	X															
Medical/surgical history	X	X														
Gastroenterological endoscopy[e]	X															
Virus tests (HIV Ab, HCV Ab, HBsAg)[f]	X															
Phone contact or visit[g]				X												
Vital signs and weight[h,i]	X	X	X		X	X	X	X	X	X	X[h]	X	X	X		
Physical examination[j]	X	X[k]			X	X		X		X	X[j]	X	X	X		
12-Lead ECG[l]	X					X		X		X	X[l]	X	X	X		
MUGA scan or echocardiogram[m]	X									X						

Period	Screening[a]	Baseline[a]	Lenvatinib (Treatment Period 1) (All cycles are 28 days in duration)								TPC (Treatment Period 2)					Survival FU
Visit	1	2	3	4	5	6	7	8, 9, etc		99						
Day	-21 to -2	-1	Cycle 1[b]			Cycle 2[c]		Cycle 3 – Last[c]		Lenvatinib Off-Treatment Visit	TPC Baseline	Week 2	Week 4	Week 8	Week 16[aa]	Every 12 weeks
			1	8	15	1	15	1	15							
Procedures/ Assessments																
Hematology and chemistry[n]	X	X			X	X	X	X		X	X[n]	X	X	X		
Urinalysis[o,i]	X	X			X	X	X	X	X	X	X[i]	X	X	X		
Pregnancy test[p]	X	X														
Child-Pugh score[d]	X	X				X		X		X	X[d]	X	X	X		
PRO-CTCAE questionnaires[q]										X	X[q]	X	X	X	X	
Blood coagulation test (PT/INR)	X	X				X		X		X						
Special chemistries[r]	X	X			X	X		X		X	X[r]			X	X	
Biomarker (whole blood)[s]		X														
Biomarker (serum/plasma) sample[s]			X		X	X		X		X	X[s]			X	X	
Tumor assessments CT/MRI[t]	X		CT of the chest and CT or MRI of the abdomen, pelvis, and other areas of known disease at screening plus newly suspected disease will be performed every 8 weeks from the first dose of study treatment, or sooner if clinically indicated, until disease progression. Triphasic CT/MRI of liver is							X	X[t]			X	X[t]	

Period	**Screening**[a]	**Baseline**[a]	**Lenvatinib (Treatment Period 1)** (All cycles are 28 days in duration)								**TPC (Treatment Period 2)**					**Survival FU**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9, etc**		**99**						
Day	**-21 to -2**	**-1**	**Cycle 1**[b]			**Cycle 2**[c]		**Cycle 3 – Last**[c]		**Lenvatinib Off-Treatment Visit**	**TPC Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 16**[aa]	**Every 12 weeks**
			1	**8**	**15**	**1**	**15**	**1**	**15**							
Procedures/ Assessments																
			mandatory at screening and all subsequent time points.													
Brain scan[u]	X		Brain scans will be performed if clinically indicated.													
Archive tumor block or slides[v]	X															
Survival[w]		Throughout														X
Study treatment			QD for lenvatinib								TPC[x]					
Prior/Concomitant medication[y]	Throughout															
AEs/SAEs[z]	Throughout															

AE = adverse event, BCLC = Barcelona Clinic Liver Cancer, CT = computed tomography, ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status, FU = Follow up, HBsAg = Hepatitis B surface antigen, HBV = hepatitis B virus, HCV Ab= hepatitis C virus antibody, HIV Ab = human immunodeficiency virus antibody, INR = international normalized ratio, MRI = magnetic resonance imaging, NYHA = New York Heart Association, MUGA = multigated acquisition, PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, PT = prothrombin time, SAE = serious adverse event, TPC = treatment of physician choice.

a: Subjects must be screened within 21 days prior to the first dose of study treatment. The screening assessment can serve as the baseline assessment, if performed within 72 hours before the first dose of study treatment. The baseline assessments can be performed on C1D1, prior to the first dose of study treatment. Informed consent may be taken up to 4 weeks prior to C1D1.

b: Efforts should be made to conduct study visits on the day scheduled (± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Procedures/Assessments.

c: Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures.

d: See protocol appendices for ECOG assessments, NYHA Cardiac Disease Classification, and Child-Pugh assessments. NYHA cardiac disease classification should be only performed at Screening if needed. For ECOG and Child-Pugh assessments, a TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment.

e: Gastroenterological endoscopy at screening is necessary only if more than 3 months have passed since the previous assessment. Gastroenterological endoscopy must have been performed within 3 months prior to receiving first dose of the study treatment.

f: Subjects who are receiving antiviral therapy for hepatitis B virus (HBV) may continue to receive this therapy at the discretion of the investigator.

g: Telephone contact on or visit on C1D8 to assess subjects for development of early toxicity. An unscheduled visit will occur prior to C1D15 if deemed necessary by the investigator.

h: Assessments will include vital signs (resting BP, heart rate, respiratory rate, and body temperature), and weight measured at Screening, Baseline, Day 1 and Day 15 of every cycle, lenvatinib Off-Treatment visit in Treatment Period 1, and at week 2, week 4, and week 8 (±1 week) in TPC period. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory BP assessment at least 30 minutes later should be obtained by performing 2 measurements (at least 5 minutes apart) to yield a mean value. Starting dose is determined based on measurement of body weight at the Baseline Visit. Subsequent measurements of body weight not relevant for dose determination. See dose adjustment table for management of hypertensive subjects.

i: Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 15) or more frequently as clinically indicated until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles. If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 2 consecutive treatment cycles.

Urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks (on Day 15) or more frequently as clinically indicated until the results have been 1+ or negative for 2 consecutive treatment cycles. If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles.

Note: During Cycle 3 and subsequent cycles in Treatment Period 1, subjects will return to the clinic for the Day 15 visit only if BP monitoring or urine dipstick testing is required as specified above. The Day 15 visit is mandatory in Cycles 1 and 2. In TPC period, a baseline urine dipstick testing should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment, and then the testing should be done at week 2, week 4, and week 8 (±1 week) .

j: A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visit, on C1D15, on Day 1 of each subsequent cycle, and at the lenvatinib Off-Treatment Visit in Treatment Period 1 and at week 2, week 4, and week 8 (±1 week) in TPC period. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment. A symptom-directed physical examination will be performed on C1D1 and at any time during the study as clinically indicated. Height will be measured at the Screening Visit only.

k: Required if screening physical examination is performed >7 days prior to C1D1.

l: Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG will be performed at week 2, week 4, and week 8 (±1 week) in TPC period. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment.

m: MUGA or echocardiogram during screening and at lenvatinib Off-Treatment Visit or sooner if clinically indicated. Assessment should utilize the same methodology (MUGA or echocardiogram).

n: Clinical laboratory tests (hematology and clinical chemistry) will be performed at local laboratory. Laboratory tests at Baseline may be performed up to 72 hours prior to first dose of lenvatinib treatment. Review hematology clinical chemistry results within 48 hours after receiving quick estimation. Assessments scheduled may be performed within 72 hours prior to the visit. If ≥ Grade 3 hematologic or clinical chemistry toxicities, repeat laboratory test and AE assessment at least every 7 days (until improvement to <Grade 3). Clinical laboratory tests will be performed at week 2, week 4, and week 8 (±1 week) in TPC period. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment.

o: For subjects with proteinuria ≥2+ (see the dose adjustment table for management of proteinuria).

p: A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

q: PRO-CTCAE data will be collected at the following time points: lenvatinib Off-Treatment Visit during Treatment Period 1, every 2 weeks for the first 4 weeks, and then at week 8 and week 16 (±1 week) in Treatment Period 2. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment.

r: α-Fetoprotein (AFP) and thyroid-stimulation hormone (TSH) will be measured at screening visit, Baseline, on C1D15, C2D1, C3D1, and every 2 cycles thereafter (C5D1, C7D1, C9D1, etc) in Treatment Period 1, and week 8 and week 16 (±1 week) in TPC period. A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit is completed ≤7 days prior to the first TPC treatment.

s: Collection of blood sample to obtain serum and plasma to be used for biomarker studies. Samples will be obtained on C1D1 (predose), predose on C1D15, Day 1 of and all subsequent cycles, and the lenvatinib Off-Treatment Visit in Treatment Period 1, and at week 8 and week 16 (±1 week) in Treatment Period 2 (TPC period). A TPC baseline assessment should be performed unless the lenvatinib Off-Treatment visit in Treatment Period 1 is ≤28 days before the first TPC treatment. A whole blood sample for genetic analysis will be obtained at baseline. If sampling is not performed predose, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur.

t: Screening Period: Tumor assessments using triphasic liver CT/MRI (optimized for precontrast, arterial phase and portal venous phase), contrast-enhanced CT of the chest, and contrast-enhanced CT or MRI of the abdomen, pelvis, and other areas of known disease plus suspected disease should be performed within 28 days prior to first dose of study treatment.

Treatment Period: Tumor assessments using triphasic liver CT/MRI (optimized for precontrast, arterial phase and portal venous phase), contrast-enhanced CT of the chest, and contrast-enhanced CT or MRI of the abdomen, pelvis, and other areas of known disease at screening or newly suspected disease should be performed every 8 weeks (during the 8th week) (±1 week) or sooner if there is evidence of progressive disease. The same methodology (CT or MRI) and scan acquisition techniques should be used as for the screening assessments.

Tumor assessments will be performed during the Screening/Baseline Phase (standard of care scans performed up to 28 days before the first dose of study treatment are acceptable) and then every 8 weeks, or sooner if clinically indicated, during lenvatinib treatment phase until disease progression. Subjects

who discontinue lenvatinib treatment without disease progression should have tumor assessments performed (within one week of the lenvatinib Off-Treatment Visit) if more than 4 weeks have passed since the previous assessment and if the subject will not continue with follow-up scans.

Subjects entering subsequent treatment period (TPC period) should have TPC period baseline tumor assessments performed unless the last tumor assessment performed in lenvatinib treatment period is less than 28 days before the subsequent treatment starts, in which case those scans may be used as the TPC period baseline. A new tumor assessment baseline (selection of target and non-target lesions and calculation of a new baseline sum of diameters (SOD) must be established before beginning TPC. **Subjects will continue tumor assessments during subsequent TPC every 8 weeks (±1 week) or until disease progression, subject death, withdrawal or loss to follow-up**. Detailed image acquisition guidelines will be provided by the imaging core laboratory.

u: Screening CT of the brain with contrast or MRI of the brain pre- and post-gadolinium should be performed within 28 days prior to the first dose of study treatment. During the study drug treatment period, CT/MRI of the brain should be performed if clinically indicated. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.

v: An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected at screening or at any time during the study, unless no such material is available.

w: Subjects who do not take subsequent TPC will be followed for survival every 12 weeks after the Off-Treatment visit. Otherwise, subjects will be followed for survival every 12 weeks after the final Visit in the subsequent TPC period. If a clinic visit is not feasible, follow up information may be obtained via telephone or email. Subjects' survival status and all additional anticancer treatments received will be recorded.

x: Treatment dose and schedule on Prescribing Information of commercially available TPC should be followed.

y: Concomitant meds will be recorded for 28 days after last dose of lenvatinib treatment if subjects do not enter TPC period, or for 8 weeks after the start of TPC period or up to 28 days after last dose of TPC if subject does not stay in the TPC period for the 8 weeks of safety monitoring. All anticancer therapy will be recorded until time of death or termination of survival follow-up. Prior medication information before screening should be collected at the screening period.

z: SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 1 business day. AEs will be recorded for 28 days after last dose of lenvatinib treatment if subjects do not enter TPC period, or for 8 weeks after the start of TPC period. During treatment interruption due to AEs, repeat AE assessment at least every 7 days (until restarting administration). SAE information should be collected for 8 weeks after the start of the TPC, or for at least 28 days after the last dose of lenvatinib/TPC if subjects do not continue into the TPC period or do not stay in the TPC period for the 8 weeks of safety monitoring.

aa: After week 16, only tumor assessment and TPC dose information will be collected until the end of TPC (disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor).

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Procedures/Assessments (Table 3).

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in HCC studies.

Tumor assessments by the investigator will be done using mRECIST criteria (as opposed to RECIST 1.1) as it more appropriately reflects changes in intrahepatic lesions by measuring only the viable portions of the lesions. Other differences between mRECIST and RECIST 1.1 include requiring interval growth for new atypical hepatic lesions before considering them as unequivocal and requiring cytologic evidence of malignancy to consider ascites/effusions as malignant given that underlying cirrhosis is common in HCC subjects (Lencioni and Llovet, 2010).

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, ECGs/echocardiograms, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, should be collected for 8 weeks after the start of the TPC, or for at least 28 days after the last dose of lenvatinib/TPC if subjects do not continue into the TPC period or do not stay in the TPC period for the 8 weeks of safety monitoring. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to lenvatinib treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 24 hours by emailing or faxing the completed SAE form.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the

subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject (or partner of a male subject) in which the estimated date of conception is either before the last visit or within 30 days of last dose of study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last dose of study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 3).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

9.5.6 Abuse or Diversion of Study Drug

Not applicable

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint is the safety and tolerability of subsequent systemic TPC following the first-line lenvatinib treatment in uHCC subjects, and will be analyzed by summarizing the incidence of treatment-emergent adverse events (TEAEs) and SAEs.

9.7.1.1.2 SECONDARY ENDPOINTS

- Overall survival (OS), measured from the date of first dose of study treatment until date of death from any cause. Subjects who are lost to follow-up will be censored at the last date the subject was known to be alive, and subjects who remain alive will be censored at the time of data cutoff.
- Progression-free survival (PFS), defined as the time from the date of first dose of first-line lenvatinib treatment to the date of first documentation of disease progression, or date of death, during the subsequent systemic TPC, whichever occurs first.
- Time to progression (TTP), defined as the time from the date of first dose of first-line lenvatinib treatment to the date of first documentation of disease progression during subsequent systemic TPC.

9.7.1.1.3 EXPLORATORY ENDPOINT

Patient-reported outcome (PRO) results from a well-defined PRO instrument (PRO-CTCAE) will be determined by scores in the subsequent TPC period.

9.7.1.2 Definitions of Analysis Sets

The **Safety Analysis Set (Full Analysis Set)** is the group of subjects who received at least 1 dose of study drug. This will be the analysis set for all safety and efficacy evaluations.

The **Pharmacodynamic Analysis Set** is all the subjects who have received at least 1 dose of lenvatinib and had sufficient pharmacodynamic data to derive at least 1 pharmacodynamic measurement and with documented dosing history.

9.7.1.3 Subject Disposition

The number (percentage) of subjects who completed the study treatment/study and discontinued from the study treatment/study and reasons for discontinuation will be provided.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, BW, and height; categorical variables include sex, age group, BW group, race, region, macroscopic portal vein invasion and/or extra hepatic spread, ECOG-PS, NYHA cardiac disease classification, BCLC staging, and Child-Pugh score.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms (verbatim terms) for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized, using Anatomical Therapeutic Chemical (ATC) class and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 28 days after last dose of lenvatinib treatment if subjects do not enter TPC period, or for 8 weeks after the start of TPC period or up to 28 days after last dose of TPC if subject does not stay in the TPC period for the 8 weeks of safety monitoring. All medications will be presented in subject data listings. All anticancer therapy will be recorded until time of death or termination of survival follow-up.

9.7.1.6 Efficacy Analyses

Efficacy analyses will be performed based on the Safety Analysis Set.

OS

The median OS and the cumulative probability of OS at selected time points will be calculated and presented with 2-sided 95% CIs. The selected time points will depend on the

OS times that are observed during the study and will be specified in the SAP. Kaplan-Meier (KM) estimates of OS will be plotted over time.

PFS

Median PFS time and the cumulative probability of PFS at selected time points will be calculated, and presented with corresponding 2-sided 95% CIs. The selected time points will depend on the PFS times that are observed during the study and will be specified in the SAP. KM estimates of PFS will be plotted over time.

TTP

TTP (based on the tumor response evaluation as determined by investigator assessment according to mRECIST) will be evaluated using same procedure as used for PFS.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Not applicable

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The effect of study treatment on soluble, tissue, genetic and/or other relevant biomarkers will be summarized using descriptive statistics using the Pharmacodynamic Analysis Set and correlated with clinical outcomes-related endpoints for safety and/or efficacy as appropriate. Details will be included in a separate analysis plan.

9.7.1.8 Safety Analyses

All safety analyses based on Safety Analysis Set will be performed for each treatment period. Safety data will be summarized on an "as treated" basis. The incidence of TEAEs and SAEs will be summarized. Laboratory test results, vital signs and their changes from baseline, and 12-lead ECG and echocardiogram results including LVEF, will be summarized using descriptive statistics. Abnormal values will be flagged.

9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to AEs will be summarized.

Additionally, the following data will be summarized: percentage of subjects that receive TPC, average dose intensity and relative dose intensity of lenvatinib treatment and TPC, and feasibility rate (defined as the percentages of subjects completing the first 2, 4, and 6 cycles of lenvatinib treatment without requiring dose reduction due to AE).

9.7.1.8.2 ADVERSE EVENTS

Adverse Events will be graded using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (baseline) or

- Reemerges during treatment, having been present at pretreatment (baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

TEAE will be defined and summarized for each treatment period separately.

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade. The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (probably related, possibly related, and not related).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug or leading to study drug dose changes will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug or leading to study drug dose changes will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects).

Percentages will be based on the number of subjects with both nonmissing baseline and at least 1 postbaseline results.

Laboratory parameters will be categorized according to CTCAE v4.03 grades, and shift tables from baseline CTCAE grades to the maximum/worst and final postbaseline grades will be provided.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, heart rate, respiratory rate, temperature, weight) and changes from baseline will be presented by visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit. Change from baseline to each postbaseline visit and to end of treatment in ECG findings will be summarized by visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive statistics and changes from baseline for LVEF assessed on echocardiogram or MUGA scans will be presented.

9.7.1.9 Other Analyses

PRO-CTCAE questionnaire results will be summarized descriptively.

9.7.2 Determination of Sample Size

With the sample size of 100 subjects, assuming that more than 50% subjects will go on to receive TPC, and that the rate of TEAE with CTCAE Grade ≥3 is 75%, the half width of 95% CI for the rate of TEAE with CTCAE Grade ≥3 will be no more than 12%.

Table 4 provides the 95% CI estimates for the rate of TEAEs with CTCAE Grade ≥3, when the percentages of subjects receiving TPC range from 100% to 50%.

Table 4 Half width of 95% CI estimates for Rate of TEAE with CTCAE Grade≥3 for Subjects Receiving TPC (Range from 100% to 50%)

Percentage of subjects receiving TPC	The half width of 95% CI for the rate of TEAE with CTCAE Grade ≥3
100%	8.5%
90%	8.9%
80%	9.5%
70%	10.1%
60%	11%

50%	12%

CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, TEAE = treatment emergent adverse events, TPC = treatment of physician choice

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:56–66.

Cheng A, Finn R, Qin S, Han K, Ikeda K, Piscaglia F, et al. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). ASCO Annual Meeting, Chicago IL, June, 2017.

El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017; 389:2492–502.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

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Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol. 2017;52:512–9.

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Lencioni R., Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.

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Marrero JA, Kudo M, Venook AP, Ye SL, Bronowicki JP, Chen XP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 2016;65(6):1140–1147.

Study E7080-G000-304 (Clinical Study Report). 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. May, 2017.

CTCAE Reference

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- Study drug compliance (eg, the reason for any change of dosage)
- Indication for prior/concomitant medication (drug/therapy)
- Discontinuation information (eg, in the case of lost to follow-up due to the subject choice)
- Sampling date and time for the drug concentration

- Sampling date for the clinical laboratory tests
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing, returns and destruction of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form

to the sponsor's CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the

sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 American Association for the Study of Liver Diseases (AASLD) Criteria

Diagnosis of hepatocellular carcinoma is to be clinically confirmed according to AASLD practice guidelines as described in: Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-2. Available from: http://www.aasld.org/practiceguidelines.

The diagnostic algorithm is shown below.

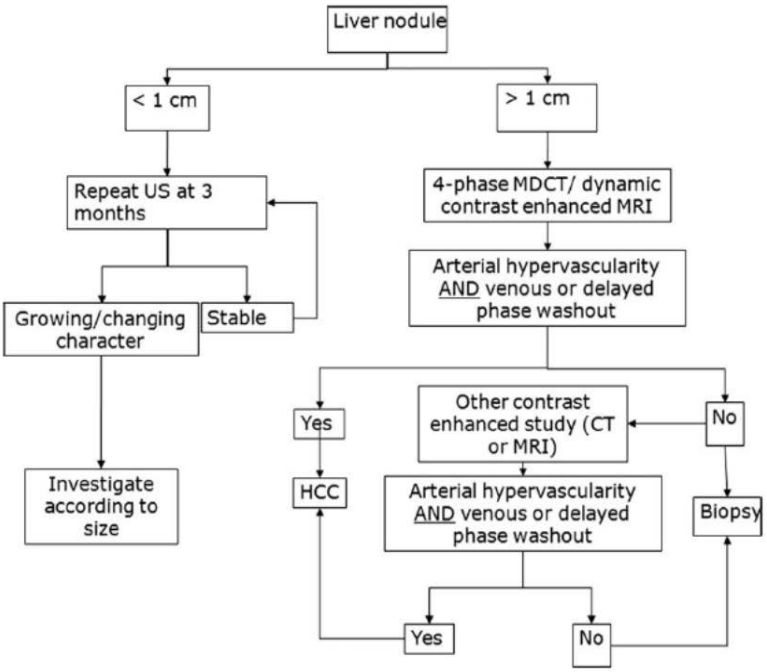


Fig. 1. Diagnostic algorithm for suspected HCC. CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound.

Appendix 2 Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

Tumor response assessments in this clinical study will use modified Response Evaluation Criteria in Solid Tumors (mRECIST) based on Lencioni and Llovet, 2010 and incorporating elements of RECIST 1.1 based on Eisenhauer, et al., 2009.

QUANTITATIVE AND QUALITATIVE ASSESSMENTS OF TUMOR BURDEN

The disease burden at Baseline will be categorized into target and nontarget lesions. Within the target and nontarget categories are typical hepatic lesions, atypical hepatic lesions, and nonhepatic lesions.

- Typical hepatic lesions are lesions that display hypervascularity in the arterial phase and "wash-out" in the portal venous phase of contrast-enhanced CT or MRI imaging.
- Atypical hepatic lesions are lesions that are not showing the distinctive enhancement pattern but are considered to be malignant.
- Nonhepatic lesions are all nodal and non-nodal lesions outside of the liver.

SELECTION AND MEASUREMENT OF TARGET LESIONS

A maximum of 2 target lesions per organ and 5 target lesions in total, representative of all involved organs, may be selected. Target lesions are lesions that can be accurately measured in at least one dimension and whose minimum lesion size is as follows:

- Typical hepatic target lesions: The longest diameter of the viable tumor must measure ≥1 cm or ≥ two times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Atypical hepatic target lesions: The longest diameter must measure ≥ 1 cm or ≥ two times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Nonhepatic non-nodal target lesions: The longest diameter must measure ≥1 cm or ≥ two times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Nonhepatic nodal target lesions (lymph nodes): The short axis must measure ≥1.5 cm (regardless of modality/scanner type and slice thickness/reconstruction interval).

If typical and atypical liver lesions are present, preference should be given to typical liver lesions when selecting targets. Target lesions are measured at every time point and a single Sum of Diameters (SOD) will be determined by adding the longest diameters of all non-nodal lesions and short axes (ie, widest dimensions perpendicular to the long axis) of nodal nonhepatic lesions. For typical hepatic lesions the longest diameters will include only the viable tissue, while for all other target lesions all tumor tissue (whether necrotic or not) will be included in the SOD. Note that hypovascular tissue should not be considered as necrotic (nonviable) tissue. While hypovascular tissue will still show contrast uptake (although less than what would be observed in a hypervascular lesion), necrotic tissue will show complete

absence of any contrast enhancement. Quantitative determinations of average Hounsfield Units (HU) in the tissue of interest both pre-contrast and post-contrast may be used, if needed, to support the subjective assessment: necrotic (nonviable) tissue will show no change in HU between the phases, while hypovascular tissue will yield an increase in HU (although less than what would be observed in a hypervascular lesion) between pre-contrast and post-contrast images of the same region. Please refer to the Image Interpretation Guidance Manual for the use of mRECIST for HCC for further details regarding differentiating hypovascular from necrotic (nonviable) tissue.

Target lesions are assessed as CR, PR, SD, PD, or NE at every time point based on the SOD.

SELECTION AND ASSESSMENT OF NONTARGET LESIONS

Nontarget lesions are all other lesions, including malignant portal vein thrombosis, infiltrative type, and diffuse type HCC with ill-defined lesion borders and truly nonmeasurable lesions, malignant pleural effusions, malignant ascites, and malignant porta hepatis lymph nodes (≥2.0 cm in short axis). Nontarget lesions will be assessed qualitatively, and the possible assessments are CR, NonCR/Non-PD (NN), and PD.

If a hepatic nontarget lesion exhibits an enhancement pattern that is consistent with HCC, the determination of CR, NN, PD, or NE will be dependent on the enhancing portion of the lesion. All other nontarget lesions will be assessed following the conventional RECIST 1.1 criteria.

If pleural effusions or ascites selected as nontarget lesions at Baseline are stable in size or minimally enlarging, they will be assessed as NN. A cytopathological confirmation of any effusion that appears or worsens on treatment is required when the measurable tumor has met criteria for response or SD.

NEW LESIONS

New lesions are defined as:

- Unequivocally new nonhepatic lesions seen at follow-up, without a corresponding lesion on the baseline imaging
- New typical hepatic lesions displaying intratumoral arterial enhancement (hypervascularization in the arterial phase and washout in the portal venous phase on contrast-enhanced CT or MRI) that measure ≥1 cm in the longest diameter
- New atypical hepatic lesions ≥1 cm in the longest diameter that show interval growth in subsequent scans of at least 1 cm

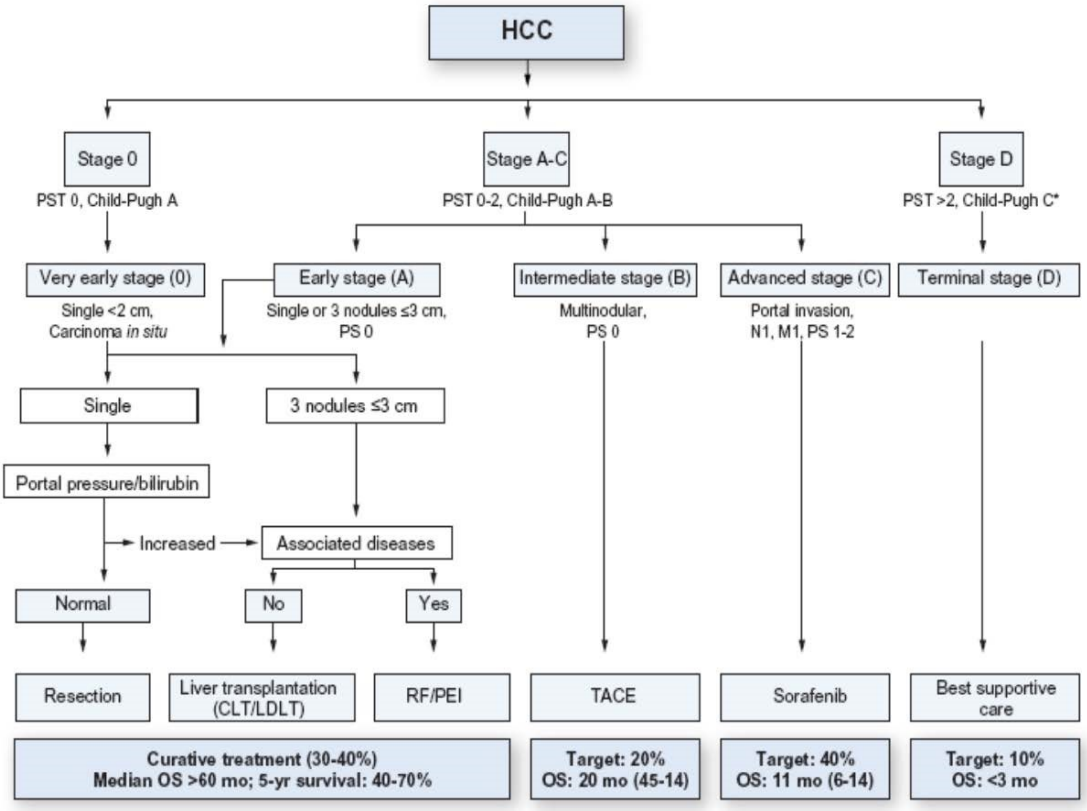
Any lesion that meets the requirements for unequivocal new lesions will trigger PD. Any lesion that does not meet the above criteria (eg, <1 cm in longest diameter and/or does not show typical HCC vascular enhancement pattern) should be considered an equivocal new lesion. If an equivocal lesion is later determined to be unequivocal, the time point of progression will be the time point the lesion was first noted as equivocal.

OVERALL RESPONSE ASSESSMENTS

Target Lesions	Nontarget Lesions	New Lesions	Overall Time Point Response
CR	CR	No	CR
CR	NN	No	PR
CR	NE	No	PR
PR	NE	No	PR
PR	CR	No	PR
PR	NN	No	PR
SD	NE	No	SD
SD	CR	No	SD
SD	NN	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
CR	No nontarget lesions identified	No	CR
PR	No nontarget lesions identified	No	PR
SD	No nontarget lesions identified	No	SD

CR = complete response, NE = not evaluable, NN = NonCR/Non-PD, PD = progressive disease, PR = partial response, SD = stable disease.

Appendix 3 Barcelona Clinic Liver Cancer (BCLC) Staging System



BCLC = Barcelona Clinic Liver Cancer, CLT = cadaveric liver transplantation, HCC = hepatocellular carcinoma, LDLT= living donor liver transplantation, OS = overall survival, PEI = percutaneous ethanol inject, RF = radiofrequency ablation, TACE = transarterial chemoembolization.

European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer.

EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012 Apr;56(4):908-43. Erratum to: EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2012;56:908-43.

Appendix 4 Child-Pugh Classification

Parameter	Score[a]		
	1	**2**	**3**
Ascites	**Absent**	**Mild (Respond to treatment)**	**Moderate (Refractory)**
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.30	>2.30
Encephalopathy[b]	0	1–2	3–4

INR = international normalized ratio.

a: Child-Pugh A: 5 or 6 points; Child-Pugh B: 7–9 points; Child-Pugh C: >9 points.

b: Encephalopathy grades defined as follows:

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per second) waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cps delta activity

Appendix 5 Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

Scale	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Adapted from Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Appendix 6 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

The Common Terminology Criteria for Adverse Events (CTCAE v4.03, published 14 Jun 2010) provides descriptive terminology to be used for adverse event reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE v4.03 have been correlated with single-concept Medical Dictionary for Regulatory Activities (MedDRA) terms.

The Common Terminology Criteria for Adverse Events v4.03 grading refers to the severity of the AE. The Common Terminology Criteria for Adverse Events grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	CTCAE Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL[b]
4	Life-threatening consequences: urgent intervention indicated
5	Death related to adverse event

ADL = activities of daily living, CTCAE = Common Terminology Criteria for Adverse Events.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03.

For further details regarding MedDRA, refer to the MedDRA website at:
http://www.meddramsso.com

Appendix 7 New York Heart Association (NYHA) Cardiac Disease Classification

The New York Heart Association Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac subjects. Based on NYHA definitions, subjects are to be classified as follows:

Class	NYHA Status
Class I:	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV:	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

NYHA = New York Heart Association.

Adapted from The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. New York: Little Brown; 1994. p.253-6.

Appendix 8 Clinical Studies Evaluating Drug–Drug Interactions with Lenvatinib

Nonclinical studies identify CYP3A4 as a potentially important enzyme responsible for human hepatic metabolism of lenvatinib. Clinical studies were conducted to test these findings.

Simultaneous CYP3A4/P-glycoprotein (P-gp) inhibition by ketoconazole slightly (15% to 19%) increases systemic exposure to lenvatinib. Since no change was observed in half-life, t_{max}, or lag time (t_{lag}), the slight increase in systemic exposure is probably related to a decrease in first pass metabolism. However, since the magnitude of change is small, co-administration of lenvatinib with CYP3A4/P-gp inhibitors is not of clinical concern.

The influence of P-gp inhibition on lenvatinib PK has been investigated. P-gp inhibition was accomplished by co-administering a single dose of rifampin with a single dose of lenvatinib. Preliminary results suggest P-gp inhibition increases systemic exposure to lenvatinib 26% to 32%. Thus, co-administration of lenvatinib with P-gp inhibitors only causes a small increase in lenvatinib exposure.

The influence of simultaneous P-gp and CYP3A4 induction on lenvatinib PK has been investigated. Examination of simultaneous P-gp and CYP3A4 induction on lenvatinib PK was accomplished by administering rifampin QD for 21 days. A single dose of lenvatinib was coadministered with the 15th dose of rifampin. Based on preliminary data, simultaneous P-gp and CYP3A4 induction minimally altered lenvatinib exposure as mean C_{max} increased about 8% while AUC decreased about 7%. Co-administration of lenvatinib with CYP3A4/P-gp inducers is not of clinical concern.

Please refer to http://medicine.iupui.edu/clinpharm/ddis/ for the most current information regarding co-administration of lenvatinib and CYP3A4 substrates, inhibitors, and inducers.

Appendix 9 Pharmacogenomic and Biomarker Research

Subjects enrolled in this clinical study will have samples collected for pharmacogenomic and biomarker analysis. The aim of the analysis is to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or noncoding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response. Similarly, biomarker discovery and validation may be performed to identify blood or tumor biomarkers that may be useful to predict subject response to lenvatinib and the subsequent treatment.

Collection of the samples for pharmacogenomic and biomarker analysis will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacogenomic and biomarker analysis is required per the study protocol unless the collection and use of the samples is prohibited by specific country laws or the subject declines participation.

SAMPLE COLLECTION AND HANDLING

The samples will be collected according to the schedule of Procedures/Assessments. If, for operational or medical reasons, the blood sample for pharmacogenomic analysis cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

SECURITY OF THE SAMPLES, USE OF THE SAMPLES, RETENTION OF THE SAMPLES

Sample processing, including DNA/RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol by the sponsor. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report [CSR] to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a Health Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single- or double-coded (according to the ICH15 guidelines) in order to maintain subject privacy.

RIGHT TO WITHDRAW

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples if they can still be identified (not anonymized). Once samples have been anonymized, it will not be possible to identify which samples have come from a particular individual. Therefore, it will not be possible to destroy subject samples after anonymization. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

SUBJECT PRIVACY AND RETURN OF DATA

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. Samples that are processed for analysis (DNA/RNA extracted) may be double-coded. Double-coding involves removing the initial code and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample identification (ID) to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded (the first code being the subject number) as long as the initial tube does not carry any personal identifiers or the random code assigned by the central laboratory or biorepository. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

Sample anonymization may occur by destruction of the "key." Once the "key" is destroyed, it will not be possible to trace the pharmacogenomics assay results back to an individual. The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share anonymized data with persons and organizations involved in the conduct or oversight of this research. These include:

• Clinical research organizations retained by the sponsor

• Independent ethics committees or IRBs that have responsibility for this research study

• National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report, which can include part or all of the anonymized data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the planned analysis, it will not be possible to return individual data to subjects participating in the pharmacogenomic and biomarker analysis.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-M001-222

Study Protocol Title: A Single-Arm, Multicenter, Phase 2 Trial to Evaluate Safety and Efficacy of Treatment of Physician Choice (TPC) Following First-Line Treatment of Lenvatinib in Subjects With Unresectable Hepatocellular Carcinoma (uHCC)

Investigational Product Name: LENVIMA® (E7080/Lenvatinib)

IND Number: 115650

SIGNATURES

Authors:

PPD

9/27/18
Date

Oncology Business Group, Eisai Inc.

PPD

27 Sept. 2018
Date

Oncology Business Group, Eisai Inc.

PPD

9/27/18
Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-M001-222
Study Protocol Title:	A Single-Arm, Multicenter, Phase 2 Trial to Evaluate Safety and Efficacy of Treatment of Physician Choice (TPC) Following First-Line Treatment of Lenvatinib in Subjects With Unresectable Hepatocellular Carcinoma (uHCC)
Investigational Product Name:	LENVIMA® (E7080/Lenvatinib)
IND Number:	115650

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date