1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-G000-604		
Study Protocol Title:	An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials		
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA	Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK	Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Lenvatinib (E7080) and additional investigational agents as per Eisai parent study if applicable		
Indication:	Indication(s) for solid tumors as per Eisai parent study		
Phase:	2		
Approval Date(s):	02 Aug 2017	Original Protocol	
	25 Jan 2018	Protocol Amendment 01	
	18 Oct 2018	Protocol Amendment 02	
	10 Mar 2021	Protocol Amendment 02 CHN-1 Local Protocol Amendment China Only	
IND Number:	072010		
EudraCT Number:	2017-003668-11		
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for 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

DATE	Highlights of Major Changes Section/Change
10 Mar 2021	**Amendment 02 CHN-1** **Local Protocol Amendment China Only:** Section 9.4.1 Treatment(s) Administered: Text added to allow for the local procurement of commercial comparator treatments as necessary. Appendix 4: To add the standard of care that is recommended by sponsor.
18 Oct 2018	**Amendment 02:** Title page: The IND number was added. Synopsis (Study Design) and Section 9.1: Clarity was added regarding the study design, process of ICF signing, and intention of non-interruption of treatment during a subject's transitioning from the parent study to Study E7080-G000-604. Section 9.1 (Figure 1): The figure was updated to clarify that the screening period for the study will overlap with the end of the parent study, and accordingly, subjects may remain on the parent study during the screening period. Also, the footnote was updated to state that the Screening Period is "Approximately from Day −30 to Day −1)." Section 9.4.1: It was clarified that subjects must not be dispensed more than a 3-months (formerly, 2 months) supply of study drug(s) at any particular time during participation in this study. Section 9.5.10: Study discontinuation criteria were harmonized with the synopsis. Synopsis (Inclusion Criteria): The statement "Subjects must be rolled over within 30 days of termination from their parent study" was deleted to harmonize with inclusion criteria in the protocol, since this was left in the previous amendment in error. The ICH definition was updated to match the current ICH definition on the title page, abbreviation list, Section 5.2, and investigator signature page.
25 Jan 2018	**Amendment 01:** The main reason for the protocol amendment is to align the safety data collection in the study with the FDA guidance for long-term safety data collection for oncology studies. • Accordingly, the protocol has been updated to define that only treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) will be collected for all patients. • It has been clarified that all safety related examinations (including vital signs, physical examination, electrocardiogram [ECG], echocardiogram [ECHO], multigated acquisition scan [MUGA], laboratory investigations should be performed as per local standard of care or as clinically indicated, and should be reported in the case report form (CRF) only if associated with an adverse event (AE/SAE) (ie, only the AE should be recorded in the CRF). Accordingly, all

DATE	Highlights of Major Changes Section/Change
	references to these procedures providing specific guidance on conduct of these procedures and statistical reporting in the study were deleted. • Routine reporting of concomitant medications in the study CRF has been deleted. Other global updates were made to the protocol as follows: • The terminology "study" has been used throughout to replace "trial." • AE has been updated throughout the protocol to TEAE. Major revisions to individual sections are presented below:
	The abbreviation list was updated.
	The approximate number of sites and investigators initially planned for the study was updated from 100 sites and 100 investigators to 50 sites and 50 investigators (Synopsis).
	The primary objective was harmonized between the Synopsis and Section 8.1, and the term "Eisai-sponsored lenvatinib studies" was harmonized globally in the protocol.
	The definition of "Parent study" was added in Section 9.1 and the Synopsis. Figure 1 was updated in Section 9.1 to present all criteria for discontinuation. It was emphasized that the subject will not be without study drug during transition from the parent study to the roll-over study. Also, the timeline of 30 days from termination in the parent study to enrollment in the roll-over study was deleted (Synopsis and Section 9.1)." It was clarified in Section 9.1 and Synopsis that the SAE management and reporting requirements specific to study drugs will be as per the parent study protocol. It was also clarified that ongoing adverse events (AEs) in the parent study will remain ongoing at the time of discontinuation in the parent study, and that the roll-over study will only capture new or worsening TEAEs occurring after signing the ICF for the roll-over study.
	The number of subjects expected to initially roll over into the study was updated from 200 to 50 in Section 9.3 and Synopsis.
	Inclusion criterion 2 "Demonstrate compliance with study drug(s), treatment visit schedules, requirements and restrictions listed in the consent form" in Section 9.3.1 and Synopsis was deleted, and the following inclusion criterion was added "Must be able and willing to comply with the current roll-over protocol requirements."
	All references to parent study protocols being included in the protocol appendices for E7080-G000-604 were deleted since the parent study protocols are not included in the protocol appendices for E7080-G000-604 (Sections 9.1.1, 9.5.9.1, 9.5.9.2, and Synopsis).

DATE	Highlights of Major Changes Section/Change
	Added statement that the study drug(s) administered and dispensed (kit number) will be recorded in the CRF (Section 9.4.1 and Section 9.4.4, respectively). Also, the following was added in Section 9.4.1: Subject must not be dispensed more than 2 months supply of study drug(s) at any particular time during participation in Study E7080-G000-604.
	Recording in the study of all prior medications administered 30 days before first dose of study drug, any concomitant therapy until 30 days after the final dose of study drug, and any other diagnostic, therapeutic, or surgical procedures relating to malignancy was deleted, and it was clarified that if concomitant medication/therapy is administered for an AE, investigators will record that AE on the Adverse Event CRF (Section 9.4.2.4 [Prior and Concomitant Therapy] and Synopsis).
	The prohibited concomitant therapies and drugs in Section 9.4.2.6 and Synopsis were harmonized. Also, it was clarified that palliative radiotherapy of painful pre-existing non-target bone metastases will be permitted without being considered progressive disease. This is in line with the current lenvatinib protocols.
	The requirement for 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 was deleted since laboratory tests are not mandatory per protocol and will be performed as per local standards or only when clinically indicated [Section 9.4.4 (Drug Supplies and Accountability]).
	Clarified in Section 9.4.1 and Section 9.2 that subjects rolling over to the study will continue receiving (in addition to lenvatinib or lenvatinib combination regimen) any other comparator therapy (except placebo). It was also added in Section 9.5.7.1 that, for this study, the study drugs include any other comparator therapy (except placebo) (in addition to lenvatinib or lenvatinib combination therapy).
	Study assessments: Deleted recording of baseline characteristics, since only demography information will be recorded (Section 9.5.1). Clarified that initial physical examination and any therapeutic area-specific assessments will be performed as per local standard of care or as clinically indicated (Section 9.5.2). Clarified that tumor assessments will be performed as per local standard of care (Section 9.5.3). Clarified that laboratory parameters, vital signs and physical examination should be performed as per local standard of care or as clinically indicated. Also, added that long term safety information will be collected at the time drug is dispensed to the subject (Section 9.5.7 and Synopsis).

DATE	Highlights of Major Changes Section/Change
	Clarified that only TEAEs will be collected in the study and definition of TEAE added (Section 9.5.7.1). Specific guidance and details on conduct of laboratory tests (including the names of the laboratory parameters [formerly Table 2]), procedure for vital signs and weight measurements, conduct of physical examination, and ECG recording was deleted (Sections 9.5.7.5, 9.5.7.6, 9.5.7.7, and 9.5.7.8, respectively, and Synopsis) and it has been mentioned that these procedures and assessments should be performed per local standard of care or as clinically indicated. It was also specified that for vital signs and ECG, only changes from screening vital signs or ECG findings that meet the definition of a TEAE will be recorded on the AE CRF (Section 9.5.7.6 and 9.5.7.8).
	Table 3 (Schedule of Procedures and Assessments; Section 9.5.8.1) was deleted and replaced with the following statement: All assessments for efficacy and safety will be performed as per local standard of care or as clinically indicated
	Reasons for discontinuation of the subjects from the study were harmonized between Section 9.1.1, Section 9.5.10, Figure 1 (Section 9.1) and Synopsis. Additional criterion of pregnancy mentioned in Section 9.5.10 was deleted (as it was added in error).
	Reporting for TEAEs and SAEs throughout the protocol was harmonized in Sections 9.1, 9.5.7.1, and Synopsis as follows: All TEAEs and SAEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the roll-over study informed consent form (ICF) for up to 28 days after the last dose of study drug(s) (or 5 × half-life of the study drug[s], whichever is longer).
	Statistical analysis: The study analysis set was updated from the "all treated population" to the "Safety Analysis Set" in Section 9.7 and the Synopsis, and the set was defined as the group of subjects who received at least 1 dose of study drug(s). It was clarified that only demographic characteristics will be reported in the study and "other baseline characteristics" was deleted (Section 9.7.1.3). Former Section 9.7.1.3 (Prior and Concomitant Therapy) was deleted since this data will not be collected in the study. Section 9.7.1.6 (Safety Analyses) was modified to reflect that only TEAE and SAEs will be summarized. Laboratory test results, physical examination findings, vital signs, and echocardiogram results were deleted as these assessments will not be summarized in the study report (also deleted from Section 9.7).

DATE	Highlights of Major Changes Section/Change
	Accordingly Section 9.7.1.9 (Laboratory Values), Section 9.7.1.10 (Vital signs), Section 9.7.1.11 (Electrocardiogram), and Section 9.7.1.12 (Other Safety Analyses) were deleted. The definition of TEAE was updated in Section 9.7.1.8 as follows: An AE that emerges during treatment in the roll-over study, having been absent before the time the subject signs the roll-over study ICF or • Re-emerges during treatment in the roll-over study, having been present before signing the ICF but stopped before signing the ICF, or • Worsens in severity during treatment in the roll-over study relative to the pre-ICF state, when the AE is continuous. It was added that for the TEAEs, the incidence, severity, duration and timing in relation to the start of study medication will be summarized.
	Since the subjects are not required to adhere to a specific visit schedule, the following sentence was deleted from Section 9.5.10, "All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments found in Table 3." Also, reasons for discontinuation were added.
	Section 11.5 (Identification of Source Data): Recording of sampling date and time for drug concentration and sampling date and time for the clinical laboratory test in the CRF was deleted since these procedures will not be done in the study.
	Appendix 3 – Updated Sponsor's Grading for Laboratory Values Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for alkaline phosphatase and γ-glutamyl transpeptidase.
02 Aug 2017	Original Protocol

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredient: lenvatinib and additional investigational agents as per Eisai parent study if applicable

Study Protocol Title

An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials

Investigators

Approximately 50 investigators worldwide are initially planned to participate in the roll-over study. It is anticipated that additional investigators may also participate in future.

Sites

Approximately 50 sites globally are initially planned to participate in the roll-over study. It is anticipated that additional sites may also participate in the future.

Study Period and Phase of Development

- **Study Period:** From the date the consent form for roll-over study is signed by first subject until 30 days following the last dose of study drug(s) by last subject
- **Phase:** 2 (Extension Study)

Objectives

Primary Objective

The primary objective is to assess long-term safety of study drug(s) in subjects who are enrolled in Eisai-sponsored lenvatinib studies.

Secondary Objectives

None

Study Design

This is an open-label extension study to roll-over eligible subjects from Eisai sponsored lenvatinib studies. The subject can be enrolled in the roll-over study for the purpose of long-term safety data collection. The subjects may roll-over no sooner than the primary completion dates in their parent study or after all study data for primary outcome measure were collected for the parent study. The parent study is defined as the Eisai-sponsored lenvatinib clinical study in which the subject was receiving lenvatinib either as monotherapy or as combination therapy or was receiving any other comparator therapy. The subjects willing to participate in the roll-over study have to sign the ICF for Study E7080-G000-604. The "End of Treatment" assessments in the parent study are to be completed and reviewed by the investigator prior to enrollment of the subject into Study E7080-G000-604. Eligibility for the roll-over study is to be established based on meeting all inclusion and exclusion criteria for Study E7080-G000-604. The intention is that the subject will not be without study drug during transition from the parent study to the roll-over study. The subjects in Study E7080-G000-604 should receive the first dose of the study drug the following day after the last dose of the study drug in the parent study. All treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the roll-over study ICF for up to 28 days after the last dose of study drug(s) (or 5 × half-life of the study drug[s], whichever is longer).

Treatment Cohorts:

After signing the consent form for the study and meeting all inclusion and exclusion criteria, subjects will be assigned to a treatment cohort as described below to continue treatment with study drug(s) in the study protocol.

Cohorts	Interventions
Cohort A Subjects who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study will continue to receive lenvatinib monotherapy	Lenvatinib
Cohort B Subjects who received lenvatinib combination therapy or who crossed over from a comparator arm to receive lenvatinib combination therapy in their parent study will continue to receive lenvatinib combination therapy	Lenvatinib combination therapy
Cohort C Subjects who received comparator treatment in their parent study will continue to receive comparator treatment, with exception of subjects receiving placebo*	Comparator treatment arm

* Subjects who received placebo in their parent study and who were either not permitted to crossover or who opted not to crossover to active treatment, will not be eligible to enroll in this study.

Treatment Period:

Subjects will continue study drug(s) until disease progression as confirmed by clinical judgment of the investigator and/or radiological assessment, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, use of non-permitted concomitant drug(s), unacceptable non-compliance with the protocol, or lost to follow-up.

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

Tumor/Disease assessment: Clinical activity will be assessed by using local standard of care imaging practices and as per appropriate response criteria as determined by the investigator. Sites should utilize the local imaging methodology and imaging acquisition techniques as per local standard of care.

In situations where the investigator judges that alternative therapy(s) must be instituted immediately for a subject's safety, study drug(s) may be discontinued as per investigator's discretion. Before the subject is discontinued from this roll-over study, the investigator should consult with the sponsor, if possible.

Safety assessments may consist of (but are not limited to) monitoring and recording TEAEs and SAEs, using Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03.

The other assessments including vital signs, physical examinations, ECG, and clinical laboratory assessments should be performed as per local standard of care and as per discretion of the investigator. For urgent safety issues, all appropriate medical care is to be administered to the subject and the appropriate study team member listed in the Investigator Study File should be contacted. All TEAEs and SAEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the roll-over study ICF for up to 28 days after last dose of study drug(s) (or 5 × half-life of the study drug[s], whichever is longer). Any exposure to study drug(s) through breastfeeding during the roll-over study or within 120 days of the last study drug(s), or 30 days following the last study drug(s) if the subject initiates a new anticancer therapy, whichever occurs first, must be reported. SAE management and reporting requirements specific to study drugs will be addressed as per instructions in the parent study protocol.

Number of Subjects

It is expected that approximately 50 subjects will be initially rolled over into the study. It is anticipated that additional subjects may also roll over into the study in the future.

Inclusion Criteria

It is required for all subjects currently participating in other lenvatinib studies to meet the following eligibility criteria.

1. Provide signed written informed consent for the roll-over study
2. Currently enrolled in an Eisai sponsored lenvatinib clinical study and still receiving at least one of the study drugs from that protocol
3. Currently deriving clinical benefit from at least one of the study drug(s) as determined by the investigator
4. Must be able and willing to comply with the current roll-over protocol requirements
5. Continued ability to swallow and retain orally administered study drug(s)
6. Does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels
7. Women of childbearing potential and men with reproductive potential (if specified by the parent study) must be willing to continue to use highly effective methods of contraception as per local practices of standard of care during the period of the study
8. Women of childbearing potential must have a negative serum pregnancy test at the time of transition to the study and before continuing study drug(s)

Exclusion Criteria

1. Permanent discontinuation of all study drug(s) in the parent study due to toxicity or disease progression and without clinical benefit
2. Receiving any prohibited medication(s) as described in the parent study
3. Any unresolved toxicity that meets the criteria for study drug(s) discontinuation or withdrawal criteria from the parent study at the time of transition to this study
4. Uncontrolled diabetes, hypertension or other medical conditions at the time of transition to the roll-over study that may interfere with assessment of toxicity
5. Pregnant or lactating female

6. Any serious and/or unstable pre-existing medical condition, psychiatric disorder or other conditions at the time of transition to the roll-over study that could interfere with subject's safety in the opinion of the investigator

Study Treatment

Eligible subjects from Eisai sponsored studies for lenvatinib will be rolled over to the appropriate cohort and continue receiving the study drug(s) as described in the above-mentioned sections.

Dose Modifications

Dose reduction and interruption to study drug(s), will be in accordance with the parent study protocol. If a subject is receiving more than one study drug, the investigator will decide the probability and causality of the event being related to one or both drugs. The investigator will also decide if dose modification of one or both drugs is required.

Dose reductions will apply to individual subjects only. Once the dose has been reduced, it cannot be increased at a later date unless the dose was mistakenly decreased; in this situation, the sponsor's approval is required to increase the dose.

Details regarding the management of important identified risks associated with the use of study drug(s) will be in accordance with the parent study protocol.

Duration of Treatment

A subject will remain on study drug(s) until 1 or more of the following events occur(s):

- Progressive disease (PD) (as confirmed by treating investigator)

  Note: Subjects will be permitted to continue study drug(s) beyond initial disease progression as long as investigator-assessed clinical benefit is observed after discussion and approval by the sponsor and if the subject is tolerating study drug(s). Subjects will discontinue study drug(s) upon evidence of further progression and/or loss of clinical benefit as judged by the investigator
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by sponsor
- Use of non-permitted concomitant drug(s)
- Unacceptable non-compliance with the protocol
- Lost to follow-up

Concomitant Drug/Therapy

Any medication which is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the investigational product, may be given at the discretion of the investigator.

The concomitant therapies that are permitted and prohibited therapies that are not allowed during the study will be in accordance with the local prescribing information and/or investigator brochure for study drug(s).

The following therapies are prohibited during the study:

- Concurrent other anticancer therapies such as chemotherapy, tyrosine-kinase inhibitor (TKIs), antitumor interventions (surgical resection, surgical de-bulking of tumors, etc.), or cancer immunotherapy
- Radiotherapy except for palliative radiotherapy: palliative radiotherapy of painful pre-existing non-target bone metastases will be permitted without being considered progressive disease
- Concurrent other investigational drugs

If subjects receive antitumor therapies listed above, or any additional antitumor therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued.

Assessments

Efficacy Assessments

Only disease progression will be recorded in the study case report forms (CRFs).

Pharmacokinetic Assessments

Not applicable

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all TEAEs and SAEs using Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Long term safety information will be collected at the time drug is dispensed to the subject.

Safety Reporting Requirements

All serious adverse events (SAEs) and all other events of interest as described in the parent study protocol must be captured in the CRFs and must be reported to sponsor's safety representative (or sponsor's dedicated local safety and pharmacovigilance contact personnel) and site's ethics committee as per local regulatory requirements. The safety reporting plan will be provided to participating sites outlining country specific requirements for safety reporting.

Bioanalytical Methods:

Not applicable

Statistical Methods

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug(s). The Safety Analysis Set will be used in all analyses of safety. The following safety tables and listings will be available for review:

• Extent of exposure, TEAEs, SAEs, TEAEs/SAEs related to study drug(s), TEAEs leading to discontinuation of study drug(s)/withdrawal, fatal TEAEs and deaths. • Other TEAEs that the investigator deemed important to report and reasons for discontinuation of study drug(s).
Interim Analyses Not applicable
Sample Size Rationale Not applicable

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BP	blood pressure
CA	competent authorities
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	Clinical Research Organization
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
DTC	differentiated thyroid cancer
EC	European Communities
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration
g-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Term
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IVRS/IWRS	interactive voice/web response system
LLN	lower limit of normal
LMWH	low-molecular-weight-heparin
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MUGA	multigated acquisition scan
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
PD	progressive disease
PR	partial response
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PRT	palliative radiotherapy
PSC	Protocol Steering Committee
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RR-DTC	radioiodine-refractory differentiated thyroid cancer
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
TKI	tyrosine kinase inhibitor
TTP	time to progression
ULN	upper limit of normal

Abbreviation	Term
US/USA	United States of America
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell (count)

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 ICH E6 (Good Clinical Practice), Section 3, and any local regulations. 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 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 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 (CA) within 90 days. The definition of the end of the study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA 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 2014

- 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 for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- Title 21 of the United States 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

- A waiver from the IRB(s)/IEC(s) will be obtained before study initiation for non-US studies conducted under an Investigational New Drug (IND) application.

- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.

- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP

- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or guardian/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 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. 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 physicians under the sponsorship of Eisai (the sponsor) at an unspecified number of treatment sites.

The name and contact information of the sponsor's study team members and any Contract Research Organizations (CROs) used for this study are listed in the Physician Information Package provided to each site.

7 INTRODUCTION

Lenvatinib is an investigational tyrosine kinase inhibitor (TKI) agent and it has completed clinical registration studies for the treatment of radioiodine-refractory differentiated thyroid cancer (RR-DTC) and unresectable Hepatocellular Carcinoma. Moreover, a multicenter, open-label, randomized, Phase 3 trial is ongoing to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma (E7080-G000-307). Based on its efficacy and safety profile, lenvatinib was granted approval to treat patients with progressive, DTC whose disease progressed despite receiving radioactive iodine therapy disease (Lenvima approval for DTC,13 Feb 2015). Moreover, lenvatinib was approved for use in combination with everolimus (Afinitor®) in the treatment of advanced renal cell carcinoma following one prior antiangiogenic therapy (FDA Approved Drugs, 13 May 2016).

The activity of lenvatinib for treatment of patients with advanced, progressive DTC unresponsive to conventional radioiodine therapy has been initially established in a Phase 2 trial E7080-G000-201, which enrolled 58 patients with RR-DTC (Cabanillas, et al., 2015) and 59 patients with medullary thyroid cancer. The primary efficacy endpoint of this study was the objective response rate (ORR) based on the assessments by the independent imaging review using modified Response Evaluation Criteria in Solid Tumors (RECIST). In the RR-DTC cohort, the ORR was 50%; 59% in patients with prior VEGF/VEGFR-targeted treatment and 46% in patients without prior vascular endothelial growth factor (VEGF)/ vascular endothelial growth factor receptor (VEGFR)-targeted therapy. The median estimate of progression-free survival (PFS), at a minimum follow-up of 14 months, was 12.6 months. The 6-months PFS rate was 78% and the 12-months PFS rate was 55%. The overall survival

(OS) rate was 86% at 12 months and was 78% at both 18 and 24 months. The most frequently reported (>40% of all patients) treatment-emergent adverse events (TEAEs) were diarrhea, hypertension, proteinuria, fatigue, weight decreased, decreased appetite, nausea, headache, cough, and dysphonia. In the DTC cohort, the most commonly reported Grade 3 TEAEs (occurring in approximately 10% of patients) were hypertension, weight decrease, diarrhea, and proteinuria.

The efficacy and safety of lenvatinib treatment has also been evaluated in the multicenter, randomized, double-blind, placebo-controlled Phase 3 trial E7080-G000-303 (SELECT trial) in patients with RR-DTC with documented disease progression within 13 months. Patients were stratified by age (≤65, >65 years), region and ≤1 prior VEGFR-targeted therapies and randomized 2:1 to lenvatinib or placebo arms (24 mg a day, 28-day cycle). The primary endpoint was PFS assessed by Independent Radiologic Review; the secondary endpoints included ORR (ie, complete response [CR] + partial response [PR]), OS, and safety. A total of 392 patients (63.0 years median age; 51.0% male) were randomized at over 100 sites in Europe, North and South America, and Asia. Patients in the lenvatinib arm had a significantly prolonged PFS (hazard ratio = 0.21, 95% confidence interval [CI] = 0.14–0.31; P<0001) with a median PFS for the lenvatinib arm of 18.3 months (95% CI = 15.1–not evaluable) vs the placebo arm: 3.6 months (95% CI = 2.2–3.7). The lenvatinib arm PFS benefit was observed in all predefined subgroups: median lenvatinib arm PFS for patients with prior vs no prior VEGF-therapy was 15.1 months (n=66) and 18.7 months (n=195), respectively; rates (n) of CRs for the lenvatinib arm vs placebo arm were 1.5% (4) and 0, respectively; PRs for the lenvatinib arm vs the placebo arm were 63.2% (165) and 1.5% (2), respectively. Median exposure durations for the lenvatinib arm vs the placebo arm were 13.8 months and 3.9 months, respectively; median time to lenvatinib response was 2.0 months. Median OS has not been reached; deaths for the lenvatinib arm were 71 (27.2%) and for the placebo arm were 47 (35.9%). The 5 most common lenvatinib treatment-related adverse events (AEs) (any grade) were hypertension (68%), diarrhea (59%), appetite decreased (50%), weight loss (46%), nausea (41%). The most common Grade ≥3 lenvatinib treatment-related AEs (≥5%) were hypertension (42%), proteinuria (10%), weight loss (10%), diarrhea (8%), and appetite decreased (5%). The lenvatinib dose was reduced in 78.5% of patients and lenvatinib was discontinued due to AEs in 14.2% of patients (Schlumberger, et al., 2014). Based on the efficacy and safety information to date, patients with RR-DTC may benefit from lenvatinib treatment.

In regards to efficacy and safety in RCC, the Phase 2 portion of Study E7080-G000-205 enrolled 153 patients with advanced or metastatic, clear- cell, RCC who had a history of receiving 1 prior VEGF agent. A total of 153 patients were randomized in a 1:1:1 ratio to receive treatment with lenvatinib plus everolimus, lenvatinib (24 mg once daily [QD]), or everolimus (10 mg QD). The safety profile for lenvatinib plus everolimus was consistent with the known toxic effects of each individual agent, with no unexpected TEAEs observed. The most common TEAEs of any grade in the lenvatinib plus everolimus arm were diarrhea and fatigue or asthenia. Grade 3 and 4 events occurred in fewer patients allocated single-agent everolimus (25 [50%]) compared with those assigned lenvatinib alone (41 [79%]) or lenvatinib plus everolimus (36 [71%]). The most common Grade 3 or 4 TEAEs in patients allocated lenvatinib plus everolimus was diarrhea (10 [20%]), in those assigned single-agent

lenvatinib it was proteinuria (10 [19%]), and in those assigned single- agent everolimus it was anemia (6 [12%]). Two deaths were deemed related to study drug,1 cerebral hemorrhage in the lenvatinib plus everolimus group and 1 myocardial infarction with single-agent lenvatinib (Motzer, et al., 2015a).

In regards to efficacy and safety in unresectable HCC, lenvatinib has been evaluated in the Phase 3 study of "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" (E7080-G000-304). This was a non-inferiority study of patients who had unresectable HCC with ≥ 1 measurable target lesion, Barcelona Clinic Liver Cancer stage B or C, Child-Pugh class A, Eastern Cooperative Oncology Group (ECOG) PS ≤ 1, and with no prior systemic therapy. Among 954 enrolled patients, 478 patients received lenvatinib while 476 received sorafenib and were randomized 1:1 to lenvatinib (body weight ≥ 60 kg: 12 mg/day; < 60 kg: 8 mg/day) or the comparator arm of sorafenib 400 mg twice daily. The efficacy of lenvatinib has been demonstrated to be non-inferior in terms of OS, and achieved statistically significant and clinically meaningful improvements in PFS, time to progression (TTP) and ORR by modified RECIST as first line therapy for unresectable hepatocellular carcinoma. The TEAEs were consistent with the known lenvatinib safety profile. Most common lenvatinib TEAEs were hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%), and fatigue (30%) (Cheng, et al., 2017). As there are patients who are continuing treatment from several ongoing clinical studies of different phases in the lenvatinib program at Eisai, the "roll-over" study will allow those patients to continue to receive their treatments of lenvatinib as monotherapy or in combination regimen provided that they are deriving clinical benefit. Long-term safety will be assessed in patients in this study.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective is to assess long-term safety of study drug(s) in subjects who are enrolled in Eisai-sponsored lenvatinib studies.

8.2 Secondary Objective(s)

Not applicable.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open-label extension study to roll-over eligible subjects from Eisai sponsored lenvatinib studies. The subject can be enrolled in the roll-over study for the purpose of long-term safety data collection. The transition would occur after the completion and evaluation of the primary endpoint of the parent studies or after all study data for the primary outcome measure were evaluated for the parent study. The parent study is defined as the

Eisai-sponsored lenvatinib clinical study in which the subject was receiving lenvatinib either as monotherapy or as combination therapy, or was receiving any other comparator therapy. The subjects willing to participate in the roll-over study have to sign the ICF for Study E7080-G000-604. The "End of Treatment" assessments in the parent study are to be completed and reviewed by the investigator prior to subject enrollment into Study E7080-G000-604. The eligibility for the roll-over study is to be established based on meeting all inclusion and exclusion criteria described in Section 9.3. The intention is that the subject will not be without study drug during transition from the parent study to the roll-over study. The subjects in Study E7080-G000-604 should receive the first dose of the study drug the following day after the last dose of the study drug in the parent study. All TEAEs and SAEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the roll-over study ICF for up to 28 days after last dose of study drug(s) (or 5 × half-life of study drug[s], whichever is longer). SAE management and reporting requirements specific to study drugs will be addressed as per the instructions in the parent study protocol. Ongoing AEs in the parent study will remain ongoing at the time of discontinuation in the parent study, and the roll-over study will only capture new or worsening TEAEs occurring after signing the roll-over study ICF.

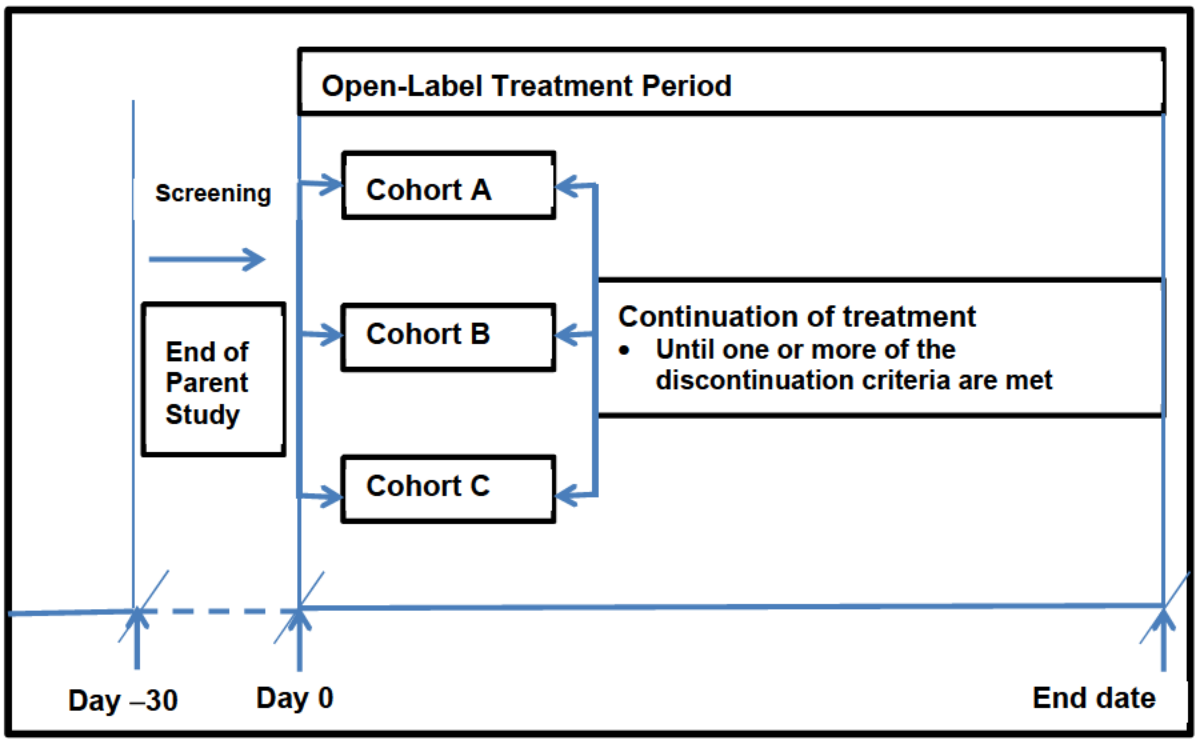

Figure 1 Study Design for Study E7080-G000-604

Screening period: From approximately Day –30 to Day –1, subjects may remain on the parent study.

Cohort A: Subjects who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study will continue to receive lenvatinib monotherapy

Cohort B: Subjects who received lenvatinib combination therapy or who crossed over from a comparator arm to receive lenvatinib combination therapy in their parent study will continue to receive lenvatinib combination therapy

Cohort C: Subjects who received comparator treatment in their parent study will continue to receive comparator treatment, with exception of subjects receiving placebo*
Discontinuation criteria: progression of disease, unacceptable toxicity, subject request, withdrawal of consent, termination of study by sponsor, use of non-permitted concomitant drugs, unacceptable non-compliance with the protocol, subject lost to follow-up.

Subjects will be permitted to continue study drug(s) beyond initial disease progression as long as the treating investigator considers that there is continued clinical benefit after discussing with the sponsor and if the subject is tolerating the study drug(s).
* Subjects who received placebo in their parent study and who were either not permitted to cross over or who opted not to cross over to active treatment will not be eligible to enroll in this study.

9.1.1 Treatment Phase

During the Treatment Phase, subjects still on treatment will continue the same treatment they received upon discontinuation of the parent study. Subjects will remain on treatment in consecutive cycles as per the parent study protocol until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, discontinuation of Study E7080-G000-604 by the sponsor, use of non-permitted concomitant drugs, unacceptable non-compliance with the protocol, or if the subject is lost to follow-up.

9.2 Discussion of Study Design, Including Choice of Control Groups

Subjects will enter the study at the same doses of study drug of lenvatinib or the combination regimen, or any other comparator therapy (except placebo), upon discontinuation of the parent study. This is a roll-over open-label study with no control group.

9.3 Selection of Study Population

It is expected that approximately 50 subjects will be initially rolled over to the study. It is anticipated that additional subjects may also roll over to the study in the future. Subjects who meet all of the inclusion criteria and none of the exclusion criteria, with no evidence of progressive disease, and who have tolerated study drug(s) in their parent study without significant toxicities will be rolled over to this study. Subjects with evidence of disease progression but who continue to derive clinical benefit as determined by the investigator would require discussion with the sponsor on an individual case-by-case basis prior to enrollment in this study.

9.3.1 Inclusion Criteria

It is required for all subjects currently participating in other lenvatinib studies to meet the following eligibility criteria prior to entry in the study.

1. Provide signed written informed consent for the roll-over study

2. Currently enrolled in an Eisai sponsored lenvatinib clinical study and still receiving at least one of the study drugs from that protocol
3. Currently deriving clinical benefit from at least one of the study drug(s) as determined by the investigator
4. Must be able and willing to comply with the current roll-over protocol requirements
5. Continued ability to swallow and retain orally administered study drug(s)
6. Does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels
7. Women of childbearing potential and men with reproductive potential (if specified by the parent study) must be willing to continue to use highly effective methods of contraception control as per local practices of standard of care during the period of the study
8. Women of childbearing potential must have a negative serum pregnancy test at the time of transition to the study and before continuing study drug(s).

9.3.2 Exclusion Criteria

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

1. Permanent discontinuation of study drug(s) in the parent study due to toxicity or disease progression and without clinical benefit
2. Receiving any prohibited medication(s) as described in the parent study
3. Have any unresolved toxicity that meets the criteria for study drug(s) discontinuation or withdrawal criteria from the parent study at the time of transition to this study
4. Uncontrolled diabetes, hypertension or other medical conditions at the time of transition to the roll-over study that may interfere with assessment of toxicity
5. Pregnant or lactating female
6. Any serious and/or unstable pre-existing medical condition, psychiatric disorder or other conditions at the time of transition to the roll-over study that could interfere with subject's safety in the opinion of the investigator

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. If a subject withdraws consent, the date will be documented in the CRF and source documents.

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

Subjects enrolled from parent study will enter the roll-over study and will continue the study drug of lenvatinib, or combination regimen, or any other comparator therapy (except placebo) at the same doses upon discontinuation of the parent study. Study drug(s) administered will be recorded in the case report form (CRF).

Subject must not be dispensed more than a 3-months supply of study drug(s) at any particular time during participation in Study E7080-G000-604.

For China Only:
Comparator Drug: Sorafenib

The subject(s) who receive the comparator in the parent study will be enrolled to Cohort C. In the event that comparator clinical supply is limited, the comparator treatment may be obtained commercially from local sources and reimbursed by the sponsor unless this is prohibited by specific country laws. Further instructions on acquisition procedures for commercial supply will be provided by the sponsor.

Criteria for Interruption of Treatment, Dose Reduction and Resumption

Dose reduction and interruptions for subjects who experience toxicity will be made according to the guidelines provided in the parent protocol.

9.4.1.1 Management of Toxicities

Management of toxicities including hypertension, proteinuria, hepatotoxicity, thromboembolic events, Posterior Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome and hypocalcemia and any other adverse events will be according to the parent study.

9.4.1.2 Chemical Name, Structural Formula of Lenvatinib

- Test drug code: E7080
- Generic name: lenvatinib, lenvatinib mesilate, lenvatinib mesylate
- Chemical name: 4-[3-Chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate
- Molecular formula: $C_{21}H_{19}ClN_4O_4 \bullet CH_3SO_3H$
- Molecular weight: 522.96
- Structural formula: (see Figure 2)

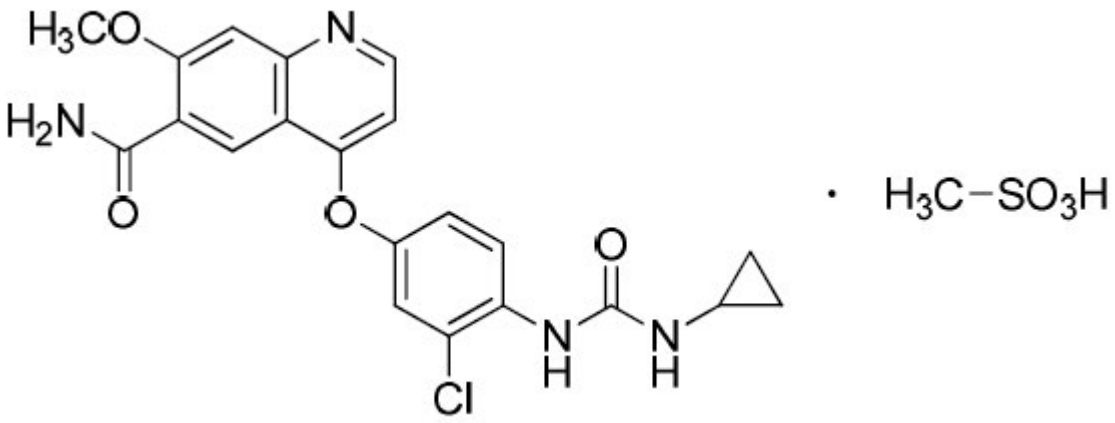

Figure 2 Structural Formula of Lenvatinib Mesilate

9.4.1.3 Chemical Name, Structural Formula of Study Drug in Combination Regimen other than Lenvatinib

The following information if applicable will be provided in the corresponding parent study.

9.4.1.4 Prior and Concomitant Therapy

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 lenvatinib or with the lenvatinib combination regimen as per the parent study 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) lenvatinib.

If a subject is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Granulocyte colony-stimulating factor (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.

If concomitant medication/therapy is administered for an AE, investigators will record that AE on the Adverse Event CRF.

9.4.1.5 Drug-Drug Interactions

Lenvatinib's weak in vitro inhibitory and induction potential on cytochrome P450 enzymes (CYP P450) (Study No. XT063020) suggests a low risk of lenvatinib interference with the PK of other drugs metabolized by CYP P450 enzymes which are co-administered in usual clinic practice. Nonclinical studies identify CYP3A4 as the important CYP isozyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted showed that co-administration of lenvatinib with CYP3A4/P-glycoprotein (P-gp) inhibitors or inducers is not of clinical concern. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (LENVIMA® Package Insert). Please refer to Appendix 1 and http://medicine.iupui.edu/clinpharm/ddis/ for the most current information.

For subjects receiving everolimus, drugs or substances (including herbal supplements or grapefruit juice) known to be potent inhibitors of CYP3A4/P-gp should not be used. Potent inducers of CYP3A4/P-gp should not be used unless there is no alternative treatment available. Moderate/ weak inhibitors or inducers or substrates of CYP3A4 and/or P-gp should be used with caution. Dose reduction of everolimus may be considered when coadministering moderate CYP3A4 or P-gp inhibitors. For further information please refer to the prescribing information. No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Pembrolizumab is a monoclonal antibody; pharmacokinetic interactions with lenvatinib (and vice-versa) are not expected. Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition or induction is recommended. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor. A dose increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity. In regards, to lenvatinib combination regimen, please refer to drug-drug interactions section in the parent study.

9.4.1.6 Prohibited Concomitant Therapies and Drugs

The following therapies are prohibited during the study:

- Concurrent other anticancer therapies such as chemotherapy, tyrosine-kinase inhibitor (TKIs), antitumor interventions (surgical resection, surgical de-bulking of tumors, etc.), or cancer immunotherapy
- Radiotherapy except for palliative radiotherapy: palliative radiotherapy of painful pre-existing non-target bone metastases will be permitted without being considered progressive disease
- Concurrent other investigational drugs

If subjects receive antitumor therapies listed above, or any additional antitumor therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued.

9.4.2 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.

9.4.3 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
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all sub-investigators 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

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 Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Study drug(s) dispensed (Kit #) will be recorded in the CRF.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study. 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 drug 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, Medicines and Healthcare Products Regulatory Agency [MHRA]). As applicable, all unused study drugs and empty and partially empty blister packages 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. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). 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 Demography

Subject demography information will be collected and recorded in the CRF. Demography information includes age, sex, and race/ethnicity.

9.5.2 Medical History and Physical Examinations

Initial physical examination and any therapeutic area-specific assessments will be performed as per local standard of care or as clinically indicated.

9.5.3 Efficacy Assessments

Tumor assessments will be performed as per local standard of care .

9.5.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

9.5.5 Pharmacokinetic Assessments

Not applicable.

9.5.6 Pharmacodynamic, Pharmacogenomic, and Other Biomarker, Assessments

Not applicable.

9.5.7 Safety Assessments

Safety assessments will consist of monitoring and recording all TEAEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for both increasing and decreasing severity), and SAEs. Long term safety information will be collected at the time drug is dispensed to the subject.

Monitoring of hematology, blood chemistry, and urine values; measurement of vital signs and performance of physical examinations should be performed per local standard of care or as clinically indicated

9.5.7.1 Adverse Events

An adverse event (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. For this study, the study drug(s) is/are lenvatinib, or lenvatinib combination regimen, or any other comparator therapy (except placebo) as per the parent study.

AEs collected in this study must be treatment-emergent adverse events (TEAE). This is defined as an AE that emerges during treatment in the roll-over study, having been absent before the time the subject signs the roll-over study ICF or

- Re-emerges during treatment in the roll-over study, having been present before signing the ICF but stopped before signing the ICF, or
- Worsens in severity during treatment in the roll-over study relative to the pre-ICF state, when the AE is continuous.

The criteria for identifying TEAEs 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
- Any new disease or exacerbation of an existing disease.

- 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 a TEAE 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

A laboratory result should be considered by the investigator to be a TEAE if it:

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia
- Results in any out-of-range laboratory value that in the investigator's judgment fulfills the definitions of a TEAE with regard to the subject's medical profile
- Increases in severity compared to the pre-ICF state by 2 or more CTCAE grades (Table 1 and Appendix 2 for CTCAE v4.03), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, any change of 2 or more grades will be evaluated by the investigator to determine if it is of clinical significance and, if so, will be considered a TEAE

All TEAEs and SAEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the roll-over study ICF for up to 28 days after the last dose of study drug(s) (or 5 × half-life of study drug[s], whichever is longer).

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 a TEAE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute a TEAE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as a TEAE. Any laboratory abnormality considered to constitute a TEAE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as a TEAE, should be considered a TEAE 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 a TEAE should be reported as such.

9.5.7.2 Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 Table 1. Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Table 1 Grading of adverse events as per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

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.

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 bed-ridden

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

CTCAE v4.03 is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

9.5.7.3 Assessing Relationship to Study Treatment(s)

Items to be considered when assessing the relationship of a TEAE to the study treatment(s) are:

- Temporal relationship of the onset of the event to the initiation of the study treatment(s)
- The course of the event, especially the effect of discontinuation of study treatment(s) or reintroduction of study treatment(s), as applicable
- Whether the event is known to be associated with the study treatment(s) 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 non-study, treatment(s)-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each TEAE to the study drug(s) will be recorded on the CRF in response to the following question:

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

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

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

9.5.7.4 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (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(s) through breastfeeding; TEAEs 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 TEAEs 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(s) or insertion of access for administration of study drug(s)
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry.

9.5.7.5 Laboratory Measurements

Clinical laboratory tests including hematology, chemistry, and urinalysis should be performed per local standard of care or as clinically indicated.

A laboratory abnormality may meet the criteria to qualify as a TEAE as described in this protocol (see Section 9.5.7.1 and the CRF Completion Guidelines). In these instances, the TEAE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.7.6 Vital Signs and Weight Measurements

Vital signs measurements (will be performed as per local standard of care or as clinically indicated. Only changes from screening vital signs findings that meet the definition of a TEAE will be recorded on the Adverse Events CRF.

9.5.7.7 Physical Examinations

Physical examinations will be performed as per local standard of care or as clinically indicated. Only changes from screening physical examination findings that meet the definition of a TEAE will be recorded on the Adverse Events CRF.

9.5.7.8 Electrocardiograms

Complete, standardized, 12-lead ECG recordings (if required) will be performed as per local standard of care.

Only changes from screening ECG findings that meet the definition of a TEAE will be recorded on the Adverse Events CRF.

9.5.7.9 Other Assessments

Not applicable.

9.5.8 Schedule of Procedures/Assessments

9.5.8.1 Schedule of Procedures/Assessments

All assessments for efficacy and safety will be performed as per local standard of care or as clinically indicated.

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

9.5.9.1 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 24 hours from when the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected as indicated in the parent protocol.

Regardless of treatment arm, all SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

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 24 hours 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.

9.5.9.2 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 study treatment, or any exposure to study drug through breastfeeding during study treatment(s) or within 30 days of last study treatment, must be reported as indicated by the parent study. For subjects receiving treatment with lenvatinib combination regimen, any pregnancy in which the estimated date of conception is either before the last visit or within the timeline (as indicated in the parent study protocol) of the last study treatment or 30 days following last study

treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Regardless of the treatment arm, 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 Reporting of Serious Adverse Events [Section 9.5.9.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours 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 24 hours from the date the investigator becomes aware of the outcome.

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

9.5.9.3 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 TEAEs 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 TEAEs 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 9.5.9.1) even if the TEAEs do not meet serious criteria. Abuse is always to be captured as a TEAE. If the TEAE 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.

9.5.9.4 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.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.10 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason.

Subjects who discontinue early from the study will be discontinued for 1 or more of these primary reasons: unacceptable toxicity, subject lost to follow-up, subject request, progression of disease (as confirmed by the clinical judgment of the investigator and/or radiological assessment), withdrawal of consent, study terminated by sponsor, use of non-permitted concomitant drug(s), or unacceptable non-compliance with the protocol.

Subjects will be permitted to continue study drug(s) beyond an initial disease progression as long as an investigator-assessed clinical benefit is observed after discussion and approval by the sponsor and if the subject is tolerating the study drug(s). Subjects will discontinue the study drug(s) upon evidence of further progression and/or the loss of clinical benefit as judged by the investigator.

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.

Study disposition information will be collected on the Subject Disposition CRF.

9.5.11 Abuse or Diversion of Study Drug

Not applicable

9.5.12 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another

physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

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

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug(s). The Safety Analysis Set will be used in all analyses of safety. The following safety tables and listing will be available for review:

Extent of exposure, TEAEs, serious AEs (SAEs), TEAEs/SAEs related to study drug(s), TEAEs leading to discontinuation of study drug(s)/withdrawal, fatal TEAEs and deaths, and other TEAEs that the investigator deemed important to report and reasons for discontinuation of study drug(s).

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 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug(s).

9.7.1.2 Subject Disposition

The number of subjects enrolled, treated, and prematurely discontinued from study treatment will be summarized. The reason for study drug discontinued will be summarized according to the categories in the CRF.

9.7.1.3 Demographic Characteristics

Demographic characteristics for the safety analysis set will be summarized using descriptive statistics.

9.7.1.4 Efficacy Analyses

PRIMARY EFFICACY ANALYSIS

Not applicable.

9.7.1.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

PHARMACOKINETIC ANALYSES

Not applicable.

PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. All safety analyses will be summarized separately by treatment group. TEAEs and SAEs will be summarized using descriptive statistics. Time to treatment discontinuation due to a TEAE, number of dose reductions, and time to first dose reduction will be summarized.

9.7.1.7 Extent of Exposure

The number of days on treatment, quantity of study drug administered, and the number of subjects requiring treatment interruption, and treatment discontinuation due to TEAEs will be summarized.

9.7.1.8 Adverse Events

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 most recent 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 treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment in the roll-over study, having been absent before the time the subject signs the roll-over study ICF or

- Re-emerges during treatment in the roll-over study, having been present before signing the ICF but stopped before signing the ICF, or
- Worsens in severity during treatment in the roll-over study relative to the pre-ICF state, when the AE is continuous.

All TEAEs will be presented in subject data listings.

An overview table, including the incidence of and the number of subjects with TEAEs, SAEs, deaths, and those TEAEs that led to study drug discontinuation, or dose interruption will be provided. The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

For the TEAEs, the incidence, severity, duration and timing in relation to the start of study medication will be summarized.

9.7.1.9 Other Analyses

Not applicable.

9.7.2 Determination of Sample Size

Not applicable for this study.

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.

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Cabanillas ME, Schlumberger M, Jarzab B, Martins RG, Pacini F, Robinson B, et al. A phase II trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: a clinical outcomes and biomarker assessment. Cancer. 2015;121(16):2749-56.

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Shumaker R, Aluri J, Fan J, Martinez G, Thompson GA, Ren M. Effects of ketoconazole on the pharmacokinetics of lenvatinib (E7080) in healthy participants. Clin Pharm Drug Dev. 2015;4(2):155-60.

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 *(*or appropriate study team member*)* 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 (or if regionally required the head of the medical institution) 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 (or, if regionally required, the head of the medical institution) 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 sponsor's/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 (or if regionally required, the head of the medical institution) 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, computed tomography 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 correction 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 dose reduction).
- Discontinuation information.
- 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 (or if regionally required, the head of the medical institution or the designated representative) 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(s) will be supplied to the principal investigator (or a designated pharmacist) by the sponsor, or when there is agreement between the PI and sponsor, the site can source study drug if it is commercially available in the country and be reimbursed 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 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, 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.

Appendix 1 Clinical Studies Evaluating Drug-Drug Interactions with Lenvatinib

Nonclinical studies identify CYP3A4 as a potentially important Cytochrome P450 isozyme responsible for metabolism of lenvatinib. Clinical studies were conducted to test these findings. Simultaneous CYP3A4/P-glycoprotein (P-gp) inhibition by ketoconazole slightly (15% to19%) increases systemic exposure to lenvatinib (Shumaker, et al., 2015). 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 (Shumaker, et al., 2014). A single dose of lenvatinib was co-administered 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%.

Coadministration of lenvatinib with CYP3A4/P-gp inducers is not of clinical concern. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (Lenvima® Package Insert).

Appendix 2 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

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 studies. 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.

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 NCI, Cancer Therapy Evaluation Program. CTCAE v4.03

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

Appendix 3 Sponsor's Grading for Laboratory Values Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 2.5×ULN	>2.5 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN	>2.5 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 4 For China only : Sponsor's Recommended Standard of Care

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E7080-G000-604
Study Protocol Title:	An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials
Investigational Product Name:	Lenvatinib (E7080) and additional investigational agents as per Eisai parent study if applicable
IND Number:	Not applicable
EudraCT Number:	2017-003668-11

SIGNATURES

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3/15/2021
Date

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-G000-604
Study Protocol Title:	An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials
Investigational Product Name:	Lenvatinib (E7080) and additional investigational agents as per Eisai parent study if applicable
IND Number:	Not Applicable
EudraCT Number:	2017-003668-11

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 for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

As regionally required

President of Japan/Asia Clinical Research Product Creation Unit	Signature	Date