1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-J081-112
Study Protocol Title:	Phase 1 Study of Lenvatinib in Combination with Everolimus in Subjects with Unresectable Advanced or Metastatic Renal Cell Carcinoma
Sponsor:	Eisai Co., Ltd.
Name of Active Ingredient:	E7080/Lenvatinib Mesilate
Indication:	Unresectable advanced or metastatic renal cell carcinoma
Phase of Development:	Phase 1
Approval Date:	V 1.0 25 Mar 2015 (original protocol)

GCP Statement: This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement: This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.;E7080
Name of Active Ingredient: Lenvatinib Mesilate
Study Protocol Title Phase 1 Study of Lenvatinib in Combination with Everolimus in Subjects with Unresectable Advanced or Metastatic Renal Cell Carcinoma
Investigators: TBD
Study Regions (Country) or Center Country: Japan Study center(s): 3 to 5
Study Period and Phase of Development Jun 2015 – Sep 2017 (planned) Phase 1
Objectives **Primary Objective:** • To investigate tolerability and safety of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma (RCC). **Secondary objectives** • To assess the pharmacokinetic (PK) of lenvatinib and everolimus • To assess the preliminary anticancer effects of lenvatinib in combination with everolimus

Study Design

This is a Phase 1 study of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma (RCC).

Subjects will be enrolled in this study after obtaining informed consent and confirming the eligibility. One treatment cycle is defined as 28 days. Lenvatinib will be administered at starting dose of 18mg in combination with everolimus at starting dose of 5 mg both orally once daily continuously. Dose limiting toxicity (DLT) will be observed during Cycle 1 (28 days following the initial dosing) to investigate tolerability and safety. Treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue withdrawal of consent or study termination by sponsor.A total of six subjects will be initially enrolled. Enrollment will be interrupted when DLT is observed in two or more subjects. Investigators and sponsor will review the nature and severity of all the DLTs and make a decision if enrollment of up to six subjects and further additions of three to six subjects are feasible and necessary. The suggestions by the independent medical advisor can be collected, if necessary.The study sponsor and investigators will consider the nature and severity of DLT during cycle 1 and also unacceptable toxicities that cannot be managed with dose interruption and/or reduction and overall toxicities until Cycle 2 on the evaluation of the tolerability of combination therapy. The suggestions by the independent medical advisor can be collected, if necessary.If the dose level of lenvatinib 18 mg/everolimus 5 mg QD is not tolerable such that more than one-third of subjects experience DLTs during Cycle 1 and/or unacceptable toxicities that cannot be managed with dose interruption and/or reduction are observed until Cycle 2, it will be considered that additional subjects are enrolled to the next lower cohort (lenvatinib 14 mg and everolimus 5mg once daily administration).

If a subject has no DLT and fails to administer ≥ 75% of the planned dosage of lenvatinib and/or everolimus as a result of a reason other than treatment related toxicity up to Cycle 1 Day 28, this subject will not be included in the DLT assessment population and another subject will be added for replacement.Investigator and sponsor will make a decision for selection of subject to be included in DLT assessment population and additional subject will be considered as needed.DLT is defined as toxicity related to this combination therapy of the following indicated in below Table.**Table : Dose Limiting Toxicities (DLT)**

Toxicity Category	**Toxicity/CTCAE Grade**
Hematologic	• Grade 4 neutropenia lasting >7 days • Grade 3 febrile neutropenia (axillary temperature ≥38.5ºC and neutrophils $<1\times10^3/\mu L$ ($<1000/mm^3$) • Grade ≥3 thrombocytopenia lasting >7 days or requiring blood transfusion
Non-hematologic toxicity	• Grade 3 non-hematologic toxicities lasting >7 days except for the following: ➢ Clinically insignificant or transient abnormal laboratory findings ➢ Able to be controlled by maximal supportive therapy Grade ≥3 hyperamylasemia or hyperlipasemia without clinical or other evidence of pancreatitis are not regarded as a DLT. • Grade ≥3 Nausea, vomiting or diarrhea lasting >7 days despite maximal medical therapy • Hypertension uncontrolled by medication • Any thromboembolic event including cerebrovascular hemorrhage/events
Medication compliance	• Failure to administer ≥75% of the planned dosage of lenvatinib or everolimus as a result of treatment related toxicity

Number of Subjects

6 to 12 (planned)

Inclusion Criteria

1. Voluntary agreement to provide written informed consent of this study
2. Willing and able to comply with all aspects of the protocol after being fully informed of the content
3. Males or females aged ≥20 years at the time of informed consent
4. Histological or cytological confirmation of RCC
5. Subjects must have confirmed diagnosis of unresectable advanced and/or metastatic RCC
6. Disease progression following VEGF targeted therapy
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1
8. Adequately controlled blood pressure with or without the use of antihypertensive agents (defined as BP ≤150/90 mmHg at screening and no change in antihypertensive therapy within 1 week prior to the Cycle 1 Day 1
9. Subjects with adequate function of major organs:

a. Hemoglobin ≥9.0 g/dL
b. Neutrophil count $\geq 1.5\times10^3$ /μL
c. Platelets $\geq 10\times10^4$ /μL
d. Total bilirubin ≤1.5 mg/dL × upper limit of normal specified by the testing laboratory (ULN)
e. Alkaline phosphatase (ALP), AST and ALT ≤ 3.0 x ULN (≤ 5.0 x ULN for patients with the liver metastasis)
f. Creatinine clearance ≥40 mL/min calculated per the Cockroft and Gault formula

Male: (140–age)×weight (kg)÷72×Serum creatinine (mg/dL)

Female: 0.85×(140–age)×weight(kg)÷72×Serum creatine (mg/dL)

10. Adequate blood coagulation function, defined as international normalized ratio (INR) ≤1.5
11. Survival expectation of 3 months or longer after study enrollment
12. Washout period required from the end of prior treatment to the start of study drug administration will be as follows:
    a. Anticancer therapies:
    - Other investigational drug or antibody therapy: ≥4 weeks
    - Chemotherapy (except small-molecule targeted therapy), surgical therapy, radiation therapy: ≥3 weeks
    - Endocrine therapy, immunotherapy, small-molecule targeted therapy: ≥2 weeks.

    b. Supportive therapies:

    Blood transfusion, blood preparations, hematopietic growth factors including G-CSF preparations: ≥2 weeks
13. Females of childbearing potential must not have had unprotected sexual intercourse within 28 days before subject registration and must agree to use a highly effective method of contraception (e.g., use of an intrauterine device, condom with spermicide*, a contraceptive implant**, an oral contraceptive*, or have a vasectomized partner with confirmed azoospermia)[Note] throughout the entire study period and for 30 days after final administration of investigational drug. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during this study period or for 30 days after investigational drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before administration and must continue to use the same contraceptive during this study and for 30 days after investigational drug discontinuation.
    All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy or bilateral oophorectomy,

all with surgery at least one month before administration

Females of childbearing potential must not have had unprotected sexual intercourse within 28 days before subject registration and must agree to use a highly effective method of contraception (e.g., use of an intrauterine device, condom with spermicide*, a contraceptive implant**, an oral contraceptive*, or have a vasectomized partner with confirmed azoospermia)[Note] throughout the entire study period and for 30 days after final administration of investigational drug. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during this study period or for 30 days after investigational drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before administration and must continue to use the same contraceptive during this study and for 30 days after investigational drug discontinuation.
All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least one month before administration.

Note: Whether or not a pharmaceutical agent or medical device has been approved and certified in Japan (* : yes, ** : no)

14. Male subjects and their female partners must meet the criteria above (i.e., not of childbearing potential or practicing highly effective contraception throughout this study period and for 30 days after final administration of investigational drug)

Exclusion Criteria

1. Subjects with CNS metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
2. Prior exposure to lenvatinib
3. Subjects who have not recovered from toxicities to ≤ Grade 1 as a result of prior anticancer therapy, except alopecia
4. Major surgery within 3 weeks prior to the first dose of lenvatinib
5. Subjects having ≥2+ proteinuria on urine dipstick testing will undergo a 24-hour urine collection for quantitative assessment of proteinuria. Subjects with a urine protein ≥1 g/24 hours will be ineligible.
6. Uncontrollable diabetes as defined by fasting glucose >1.5×ULN
7. Fasting total cholesterol >7.75 mmol/L (>300 mg/dL)
8. Fasting triglycerides >2.5×ULN
9. Gastrointestinal malabsorption, a history of gastroenterostomy, inability of oral administration, or any other condition that might affect the absorption of lenvatinib

and/or everolimus

10. Significant cardiovascular impairment:
    a. Congestive heart failure than New York Heart Association (NYHA) Class II within 6 months of the first dose of study drug
    b. Unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug
    c. Prolongation of QTc (Friderica formula) interval >480 ms
    d. Cardiac arrhythmia requiring medical treatment for cardiovascular impairment
11. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin is permitted.
12. Active hemoptysis (bright red blood of at least 0.5 teaspoon or 2.5 mL) within 3 weeks of the first dose of study drug
13. Active infections that require systemic treatment
14. Human immunodeficiency virus (HIV) positive
15. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb and/or HBsAb positive, an HBV DNA test will be performed and if positive the subject will be excluded
16. A history of interstitial pneumonia with clinical manifestation or as confirmed by means of diagnostic imaging
17. Medical need for the continued use of potent or moderate inhibitors of CYP3A or P-gp, or potent or moderate inducer of CYP3A. Subjects are eligible if 7 days or longer have passed since the last use of such agents prior to the first dose of study drug.
18. Known intolerance to lenvatinib (or any of the excipients) or known hypersensitivity to everolimus (or any of the excipients) or rapamycins (sirolimus, temsirolimus and so on)
19. Alcohol or drug dependency or abuse, inability to comply with every aspects of the study protocol, or any physical or mental conditions that in the opinion of the investigators would preclude the subject's participation in the study
20. Females who are pregnant or breastfeeding (not eligible even she discontinues breastfeeding)
21. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial

Study Treatment(s)

Lenvatinib is provided as 4 mg and 10 mg capsules by the study sponsor. Study site will be responsible for obtaining everolimus tablets commercially from local source.

Administration

Lenvatinib and everolimus will be administered orally at the same time once a day in 28-day cycles.

In cycle 1, lenvatinib and everolimus will be administered orally on a fasting state in the morning, followed by a 1-hour food fast. In cycle 2 or later, lenvatinib and everolimus will be administered consistently either before or after food. The starting doses will be 18mg for lenvatinib and 5mg for everolimus.

Drug interruption and dose reduction

1. Cycle 1
   a. If DLT occurs:

   Lenvatinib and everolimus should be interrupted immediately. Treatment may be resumed in Cycle 2 at one lower dose level of lenvatinib and/or reduction of everolimus to 5 mg every other day or discontinuation of everolimus if toxicity is resolved to Grade 0–1 or baseline and investigator or subinvestigator decides to continue the study.

   b. No DLT

   Lenvatinib and everolimus will be interrupted if judged to be clinically needed by investigators, and may be resumed at the same dose level at appropriate timing. No dose reduction is permitted.
2. Cycle 2 and onward

   Dose reduction and interruption for subjects who experience lenvatinib and/or everolimus related toxicity will follow the instructions shown in below Table. Dose reductions occur in succession based on the previous dose level (14, 10, 8 mg/day). Any dose modification must be discussed with the sponsor when toxicities occur at the dose of 8 mg/day. Once the dose has been reduced, it cannot be increased at a later date. For management of hypertension and interstitial lung disease, refer to instructions '9.4.2 Management of Hypertension' and '9.4.7 Management of interstitial lung disease' before consulting the table below, as appropriate.

Table : Dose Reduction and Interruption Instructions for Lenvatinib/Everolimus Combination Treatment[a]

Lenvatinib/Everolimus Treatment-Related Toxicity[b,c,d]	During Therapy	Adjusted Dose
Grade 1or Tolerable Grade 2[b]	Continue treatment	No change
Intolerable Grade 2[b] or Grade 3	Interrupt lenvatinib and everolimus until resolved to Grade 0–1 or baseline	Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required. Dose reduction lenvatinib by one level and/or reduce everolimus to 5 mg every other day or discontinuation of everolimus and resume the treatment.
Grade4[c]	Discontinue study treatment	

a:. An interruption of study treatment for more than 28 days due to treatment-related toxicity will require a discussion with the sponsor before treatment can be resumed.

b: Tolerability Grade 2 toxicities will be judged by the study investigators to be intolerable.

c: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

d: Initiate optimal medical management for nausea, vomiting, diarrhea prior to any treatment interruption, or dose reduction. If uncontrolled, the management will be followed by this guideline.

Duration of Treatment

Treatment will continue until disease progression, development of unacceptable toxicity,

subject requests to discontinue, withdrawal of consent, or study termination by sponsor.

Concomitant Drug/Therapy

The following therapies are **prohibited:**

1. From the time of subject enrollment to off-treatment observation
   a. Anticancer treatment other than lenvatinib and everolimus (eg, surgery, chemotherapy, endocrine therapy, palliative radiotherapy, immunotherapy).
   b. Other investigational drugs
   c. Any agent that potently inhibits CYP3A or P-gp
   d. Live vaccine (freeze-dried live attenuated rubella, oral poliomyelitis vaccine, freeze-dried BCG, etc.)
2. Cycle 1
   a. Any agent that potently and moderately inhibits CYP3A or P-gp, or any agent that potently and moderately induces CYP3A

Assessments

Safety and Tolerability

Safety assessment will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs): periodic laboratory test value, vital signs, 12-lead ECGs, echocardiograms or multiple gated acquisition scan (MUGA) including left ventricular ejection fraction (LVEF), ECOG-PS, physical examination. Severity of AEs will be graded according to CTCAE v4.03. DLT will be evaluated for the tolerability of lenvatinib in combination with everolimus.

Pharmacokinetic (PK) Assessments

Plasma concentrations of lenvatinib and whole-blood concentrations of everolimus will be measured to assess pharmacokinetics.

Efficacy Assessments

Tumor assessment will be performed by investigator using RECIST 1.1 at Screening, every 8 weeks after start of the study treatment, and as clinically indicated. Best Overall Response (BOR) will be used for the assessment.

Bioanalytical Methods

Plasma concentrations of lenvatinib and whole-blood concentrations of everolimus will be measured by using validated methods.

Statistical Methods

Analysis Sets

DLT Analysis Set is the group of subjects who have completed treatment Cycle 1 without major protocol deviation with at least 75% of treatment compliance and were assessed for DLT, and subjects who have experienced DLT during Cycle 1. Subjects with less than 75% treatment compliance to lenvatinib or everolimus due to a reason other than toxicity up to Cycle 1 Day 28 will not be included in this analysis set. Safety Analysis Set/Efficacy Analysis Set is the group of subjects who received at least 1 dose of lenvatinib. Pharmacokinetic (PK) Analysis Set is the group of subjects who received at least 1 dose of lenvatinib and had sufficient PK data to derive at least one PK parameter.

Following analysis will be performed for total subjects or by initial dose group (if applicable).

Tolerability/Safety Analyses

All tolerability analyses will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity. The Safety Analysis Set will be used for all other safety analyses. The number and percentage of subjects with all AEs and SAEs observed after first dosing will be summarized and listed by SOC, PT, and severity. Summary statistics will be presented for laboratory test values, vital sign, and 12-lead ECG parameters. If needed, the changes from baseline will also be summarized.

Pharmacokinetic Analysis

Lenvatinib plasma concentrations and everolimus whole-blood concentrations will be summarized and listed for the subjects who have at least 1 evaluable data in the Safety Analysis Set. The PK Analysis Set will be used for all other analyses including summaries of lenvatinib plasma concentrations, everolimus whole-blood concentrations and PK parameters. Concentrations – time profiles of lenvatinib and everlolimus will be plotted and investigated. Using non-compartmental analysis methods, plasma concentrations of lenvatinib and whole-blood concentration of everolimus will be calculated to determine the PK parameters including C_{max}, t_{max}, AUC at first administration (Cycle 1 Day 1) and repeated administration (Cycle 1 Day 15).

E**fficacy Analyses**

Efficacy analyses will be based on the Efficacy Analysis Set. BOR will be summarized using RECIST 1.1. BOR consists of CR, PR, SD, PD and NE. Objective response rate (ORR) and disease control rate (DCR) will be calculated with an exact 2-side 95% CI. ORR is defined as the proportion of subjects who have BOR of CR or PR. DCR is defined as the proportion of CR, PR or SD. Subjects with non-target disease only will be assigned to SD category if the BOR is non-CR/non-PD. SD has to be achieved at ≥7 weeks after first dose. CR and PR do not have to be confirmed at ≥4-week assessment. If applicable, a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at postbaseline nadir. If applicable, time profiles of tumor marker will be plotted and investigated.

Interim Analysis

No interim analysis is planned in this study.

Sample Size Rationale

The primary objective of this study is to investigate the tolerability and safety of lenvatinib in combination with everolimus. Hence neither clinical hypothesis nor judgment criteria are set, the sample size is not based on statistical consideration. The 6 to 12 subjects per initial dose group are considered to be adequate to obtain some preliminary data for the assessment of safety.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ALP	alkaline phosphatase
ALT	alanine aminotransferase (GPT)
AST	aspartate aminotransferase (GOT)
AUC	area under the plasma concentration-time curve
BOR	best overall response
BUN	blood urea nitrogen
Cmax	maximum observed concentration
CPK	creatine phosphokinase
CR	complete response
CRP	C-reactive protein
CTCAE	Common Toxicity Criteria for Adverse Events
CYP/CYP3A	cytochrome P450/cytochrome P450 3A
DCR	disease control rate
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FT_4	Free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBs	hepatitis B virus surface
HBc	hepatitis B virus core
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IAP	immunosuppressive acidic protein
IFN	interferon
INR	international normalized ratio
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multiple-gated acquisition technique
NE	not evaluable
NYHA	New York Heart Association

Abbreviation	Term
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDGF	platelet derived growth factor
PDGFRα	platelet derived growth factor receptor α
PFS	progression free survival
P-gp	P-glycoprotein
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PT	preferred term
QT	QT interval
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumor
RTK	receptor tyrosine kinase
SD	stable disease
SOC	system organ class
SOP	standard operating procedures
SpO_2	oxyhemoglobin saturation measured by pulse oximetry
TEAE	treatment-emergent adverse event
TEMAV	treatment emergent markedly abnormal laboratory values
TKI	tyrosine kinase inhibitor
t_{max}	time at which the highest drug concentration occurs
TNM Classification	tumor, nodes, metastasis classification
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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) constituted and functioning in accordance with ICH E6 (Good Clinical Practice) and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB 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 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 chairman must be sent to the head of the medical institution) 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. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.Study progress is to be reported to IRBs annually (or as required) by the investigator or the head of the medical institution, depending on local regulatory obligations. The sponsor will submit, depending on local regulations, periodic reports and inform the IRB, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per GCP guidelines and local IRB standards of practice. Upon completion of the study, the investigator will provide the IRB with a brief report of the outcome of the study, if required.

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
- GCP
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceuticals, Medical devices and Other Therapeutic Products Act (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP

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-approved ICF must be prepared in accordance with GCP, 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 should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at three to five investigational sites in Japan.The name and telephone and fax numbers of the sponsor are listed in the Appendix 3.

7 INTRODUCTION

7.1 Indication

Renal Cell Carcinoma (RCC) is a rare tumor type representing 3% of all cancers in adults, accounting for 90% of the total renal cancers (National Comprehensive Cancer Network, 2015). In 2012, estimate of the worldwide incidence of renal cancers (renal pelvis and ureters included) was 330,000 of which 210,000 were men and 120,000 were women. The total of 140,000 deaths was estimated to have occurred, of which 90,000 were men and 50,000 were women (Ferlay J, et al., 2015). In Japan, annual incidence of renal cancers (renal pelvis, ureters, and other unknown site in the urinary system are included) is approximately 18,000 and the number of death (renal pelvis, ureters, and other unknown site in the urinary system are excluded) is approximately 4,500 (Foundation for Promotion of Cancer Research, 2013).There are three main histologic types of renal cell carcinoma; clear cell-type tumors account for approximately 80% of RCC, followed by papillary type (10 to 15%), and chromophobe cell type (3 to 5%) (National Comprehensive Cancer Network, 2015. , Rini BI, et al., 2009).The risk factors for RCC include obesity, smoking, hypertension, dialysis treatment, and von Hippel-Lindau disease. When a patient is initially diagnosed with RCC, localized tumor is present in 45% of cases, followed by 30% of metastasis, and 25% of locally-advanced tumor. The prognosis is poor at stage IV with locally-advanced or distant metastasis, with only 10% of 5-year survival (Molina AM and Motzer RJ, 2008, Motzer RJ, et al., 1996, National Cancer Center, Department of Internal Medicine, 2013).The treatment options for RCC are surgery and/or anti-cancer medication, depending on the disease stage. Anti-cancer medication commonly used to treat unrespectable or metastatic RCC include: agents targeting vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) such as bevacizumab, sunitinib, sorafenib, pazopanib, axitinib, and agents targeting mammalian target of rapamycin (mTOR) such as timsirolimus and everolimus (National Comprehensive Cancer Network, 2015., Escudier B, et al., 2014). Cytokine (eg, interferon) has been widely used in the treatment of RCC but tyrosine kinase inhibitors (TKI) that block VEGFR, such as sunitinib and pazopanib, are administered as the first-line treatment in recent years. Type of second-line and subsequent treatments vary depending on the drug administered in the previous treatment. Among these available agents, everolimus was confirmed to be efficacious with 1.8% ORR, median PFS of 4.9 months, and overall OS of 14.8 months when administered to metastatic RCC patients with disease progression following sunitinib or sorafenib treatment (Motzer RJ, et al., 2008).In a phase 3 study comparing the efficacy of axitinib and sorafenib as second-line treatment in RCC subjects who previously received cytokine or sunitinib treatment, axitinib demonstrated higher efficacy with the ORR 23.0% (12.0% for sorafenib), median PFS 6.7 months (4.7 months for sorafenib), and median OS 20.1 months (19.2 months for sorafenib) (Rini BI, et al., 2011).

Based on above findings, axitinib or everolimus would likely be the second-line treatment option for RCC patients who were previously treated with TKI.Although many treatment options are available for patients with incurable, unresectable or advanced RCC, the

prognosis remains poor and development of new agents and treatment to improve clinical outcome of the second or third line treatments are anticipated.

7.2 Lenvatinib Mesylate (Lenvatinib)

VEGFR is expressed in vascular endothelial cells, playing a vital role for physiological and pathological angiogenesis and lymphogenesis or in the malignant cells led by VEGF ligand stimulation (Ellis LM and Hicklin DJ, 2008， Ferrara N, et al., 2003， Hattori K, et al., 2002, Laakkonen P, et al., 2007, Tammela T and Alitalo K, 2010).Fibroblast growth factors receptor (FGFR), platelet-derived Growth Factor receptor-α (PDGFRα), RET, and KIT are also known to be associated with angiogenesis, proliferation, or both (St Bernard, et al., 2005, Turner and Grose, 2012， Matsui, et al., 2004， Hirota, et al., 1998， Williams, 2002, Kondo, et al., 2006， Phay and Shah, 2010, Gild, et al., 2011， Hirota, et al., 2003, Oseini and Roberts, 2009) and an effective anticancer treatment may be established if their receptors, tyrosine kinases (RTKs) are inhibited simultaneously. Lenvatinib Mesylate (E7080) was developed at Eisai Tsukuba Research Laboratories to explore agents that inhibit RTKs activities associated with tumor angiogenesis. It is a multikinase inhibitor that exhibits potent inhibitory effects not only on VEGFR1 to VEGFR 3 at the level of inhibition constant Ki 1 nmol/L, but also on FGFR 1 to FGFR4 and KITs.In nonclinical studies, lenvatinib showed inhibitory activities dose-dependently in VEGFR2-driven phosphorylation, tube formation and proliferation in human vascular endothelial cells (human umbilical vein endothelial cell – HUVEC) induced by VEGF. In vivo study where human cancer cells are transplanted in immune deficient mouse models, lenvatinib also demonstrated high anticancer effect in a wide variety of cancers including RCC. In addition, safety results in non-clinical studies showed lenvatinib was well tolerated within the therapeutic range.Three phase 1 studies were conducted in Japan, US, and Europe with different regimen to determine the safety, tolerability and pharmacokinetics of lenvatinib. Treatment regimen for each study was: continuous once daily for E7080-E044-101 (Europe), continuous twice daily for E7080-A001-102 (US), and twice daily for 2 weeks with dosing intervals of one week for E7080-J081-103 (Japan). Based on the results from these studies, a continuous dose of 24 mg once daily has been selected to treat solid tumors for ongoing lenvatinib development.The tolerability in 24 mg once daily continuous dose in Japanese subjects was confirmed in another study conducted in Japan (E7080-J081-105). There was no significant difference in tolerability and pharmacokinetics among subjects in Japan, Europe, and US.lenvatinib is expected to be efficacious regardless of cancer type; clinical studies are being conducted for various solid malignancies including thyroid carcinoma, hepatocellular carcinoma, RCC, non-small-cell lung cancer, endometrial cancer, glioma, malignant melanoma, and ovarian cancer. Based on the results from Phase 2 studies conducted in Japan and overseas, and multi-center global Phase 3 studies, lenvatinib was approved in February 2015 for the treatment of patients with locally recurrent or metastatic, progressive radioioactive iodine-refractory differentiated thyroid cancer. Approvals in Europe and Japan are also underway in 2015.

7.3 Concomitant use of Lenvatinib and Everolimus for RCC patients

Common treatment options for RCC patients include VEGF, VEGFR, or mTOR target agents as first or second-line treatment. However, most patients do not respond well and become resistant to the currently available drugs, resulting in disease progression. Therefore, combination of lenvatinib and everolimus to simultaneously inhibit VEGF and mTOR signaling pathways seem logical as they both play a key role in exacerbation and development of resistance. The treatment is expected to enhance effectiveness of each agent and overcome treatment-resistance.

As of today, combination therapy of existing TKI agent and mTOR inhibitor is yet to be approved.

7.3.1 Everolimus

Everolimus inhibits mTOR, a type of serine/threonine protein kinase. It is known that mTOR is a downstream factor of P13K/Akt, comprising PI3K/Akt/mTOR signaling pathway. Functional abnormalities of molecules comprising this pathway are associated with various human cancer pathophysiology and have been confirmed for its significance in tumor genesis (Seeliger H, et al., 2007). Everolimus blocks intercellular signaling by inhibiting mTOR. This is believed to suppress proliferation, VEGF production by tumor cell, and proliferation of vascular endothelial cells, thereby controlling neoangiogenesis and exert anticancer effect.In Japan, everolimus has been approved for following conditions: unresectable, non-curable or metastatic RCC, pancreatic neuroendocrine tumors, unresectable or recurrent breast cancer, renal angiomyolipoma associated with nodular sclerosis, subependymal giant cell astrocytoma associated with nodular sclerosis.

7.3.2 Overseas Phase 1/2 study

Phase 1 and 2 studies (Study 205) were conducted to compare efficacy and safety of lenvatinib alone, everlolimus alone, or combination of the two when administered to advanced or metastatic RCC patients following prior VEGF-targeted treatment.

7.3.2.1 Phase 1 part

In Phase 1 part, the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of lenvatinib was determined when administered in combination with everolimus in subjects with unresectable advanced or metastatic RCC following prior VEGF-targeted treatment. Recommended dose of lenvatinib in combination with everlolimus for Phase 2 was also determined (Molina AM, et al., 2014).

One treatment cycle was defined as 28 days. Lenvatinib was administered at starting dose of 12 mg/day in combination with everolimus at starting dose of 5 mg/day (Cohort 1). Lenvatinib was subsequently titrated to 18 mg/day (Cohort 2) and 24 mg/day (Cohort 3) while starting dose of everolimus (5mg/day) was maintained. In Cohort 4, everlolimus was

titrated to 10 mg/day. Subjects were enrolled in the treatment group at which MTD was determined, up to the minimum of 10 subjects.

Number of subjects enrolled in Cohorts 1, 2, and 3 were 7, 11, and 2, respectively.

DLTs seen in each cohort were: one subject in Cohort 1 (Grade 3 abdominal pain), one subject in Cohort 2 (Failure to administer ≥75% of planed dose due to Grade 3 increased creatine phosphokinase, Grade 2 fatigue, Grade 1 gastroesophageal reflux disease), two subjects in Cohort 3 (Grade 3 nausea and vomiting [1 subject], (Failure to administer ≥75% of planed dose due to Grade 2 stomatitis [1 subject]). Cohort 4 was not treated. Based on these findings, recommended doses for combination therapy in Phase 2 were determined to be lenvatinib 18 mg/day and everolimus 5 mg/day.

7.3.2.2 Phase 2 part

In Phase 2 part, subjects with unresectable advanced or metastatic RCC with disease progression following one prior VEGF-targeted treatment were randomized to one of the following treatment groups to compare the safety and efficacy. Primary endpoint was PFS.

- Arm A：envatinib 18 mg + everolimus 5 mg
- Arm B：lenvatinib 24 mg
- Arm C：everolimus 10 mg

Efficacy

Number of subjects assigned to each treatment groups were: 51 subjects for Arm A, 52 subjects for Arm B, and 50 subjects for Arm C. PFS in Arms A and B were prolonged as compared with Arm C. Median PFS of Arms A, B, and C were 14.6 months, 7.4 months, and 5.5 months, respectively. Hazard ratio (HR) of Arm A to Arm C was 0.40, $P<0.001$, and that of Arm B to Arm C was 0.61, $P=0.048$. ORR of each treatment group was 43.1% (Arm A), 26.9% (Arm B), and 6.0% (Arm C). Median overall survival (OS) of Arm A, Arm B and Arm C was 25.5 months, 18.4 months, and 17.5 months, respectively. Hazard ratio (HR) of Arm A to Arm C was 0.55, $P=0.062$, and that of Arm B to Group C was 0.74, $P=0.290$.

Safety

Treatment-emergent adverse events (TEAE) experienced by ≥20% of subjects in Arm A were: diarrhea, decreased appetite, fatigue, vomiting, hypertension, nausea, cough, hypertriglyceridaemia, hypercholesterolaemia, weight decreased, stomatitis, oedema peripheral, arthralgia, asthenia, dyspnea, hypothyroidism, proteinuria, and pyrexia.Grade 3 or higher TEAEs experienced by ≥5% of subjects in Arm A were: diarrhea, hypertension, fatigue, anaemia, hypertriglyceridaemia, vomiting, decreased appetite, dehydration, nausea, and thrombocytopenia. Grade 3 or higher TEAEs that were seen more often in Arm A than in Arms B or C by ≥2 subjects were: diarrhea, fatigue, vomiting, dehydration,

thrombocytopenia, back pain, and general physical health deterioration. Serious TEAEs (SAE) experienced by ≥5% of subjects in Arm A were: anaemia, thrombocytopenia, diarrhea, and dehydration. SAEs that were seen more often in Arm A than in Arms B or C by ≥2 subjects were: thrombocytopenia, diarrhea, dehydration, vomiting, hyperkalaemia, general physical health deterioration, and renal impairment. An AE that resulted in subject death was cerebral haemorrhage.Following events were more frequently observed in Arm A than in Arms B or C: diarrhea, fatigue, vomiting, dehydration, thrombocytopenia, back pain, general physical health deterioration, hyperkalaemia, and renal impairment. In general, they were all manageable by administering symptomatic treatment, dose interuption, or dose reduction of study drugs. The safety profile of combination treatment group (Arm A) was genellary similar to those of single-agent treatment Arms (B and C), and no newly discovered safety concerns were reported.Above results demonstrated that improved prolongation of PFS and OS can be expected in combination treatment of lenvatinib 18 mg/day and everolimus 5mg/day, compared with everolimus single-agent treatment. Although adverse drug reactions were observed in some patients they were manageable, therefore this combination therapy seemed promising for unresectable advanced or metastatic RCC with disease progression following prior one VEGF-target treatment.

7.4 Expected Adverse Events

For lenvatinib, important identified risk include: hypertension, hemorrhage, arterial thromboembolism, venous thromboembolism, liver disorder, renal disorder, gastrointestinal perforation/fistula, posterior reversible encephalopathy syndrome, cardiac disorder, hand and foot syndrome, infections, bone-marrow suppression, hypocalcaemia, delayed wound healing. Lenvatinib should be administered with caution to the patients with hypertension, severe liver disorder, cerebral metastasis, thromboembolism or history of thromboembolism, and incomplete wound healing following surgical procedure. Close monitoring are required after lenvatinib administration for: hypertension, uric protein, bone-marrow suppression, liver disorder associated with increased AST or ALT, cardiac dysfunction, delayed wound healing, fatigue and apathy, dizziness, muscle spasms, serum calcium concentration, and level of thyroid-stimulating hormone.For everolimus, important identified risk include: interstitial lung disease, infections, renal failure, hyperglycemia, development or exacerbation of diabetes, anemia, decreased hemoglobin, decreased leukopenia, decreased lymphopenia, decreased neutropenia, and thrombocytopenia, stomatitis, anaphylaxis, acute respiratory distress syndrome, malignancy (secondary), progressive multifocal leukoencephalopathy, BK virus nephropathy, thrombotic microangiopathy, pulmonary alveolar proteinosis, and pericardial effusion.

Everolimus should be administered with caution to patients with current conditions or history of interstitial pulmonary shadow, comorbid infections, liver dysfunction or hepatitis virus, tuberculosis, and elderly patients. Close monitoring will be required following administration of everolimus for: interstitial pulmonary disease, infection or opportunistic infection from bacteria, fungi, viruses, protozoa, severe renal disorder, hyperglycemia, decreased hemoglobin, decreased lymphopenia, decreased neutropenia, decreased platelet.In overseas study (Study 205), Grade 3 or higher cases of diarrhea, fatigue, vomiting, dehydration, thrombocytopenia, back pain, general physical health deterioration, hyperkalaemia, and renal impairment are more frequently seen in lenvatinib-everolimus combination therapy compared to

single-agent therapy each. Cautions should be exercised as effects on adverse events can be potentiated by co-administering the two agents.

7.5 Study Rationale

This is a Phase 1 study of lenvatinib in combination with everolimus in Japanese subjects with unresectable advanced or metastatic RCC.Lenvatinib will be administered at starting dose of 18 mg in combination with everolimus at starting dose of 5 mg both orally once daily continuously. DLT will be observed during Cycle 1 (28 days following the initial dosing) to determine the tolerability and safety. Treatment will continue until disease progression, development of intolerable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by sponsor.The same regimen, lenvatinib 18 mg/day and everolimus 5 mg/day, will be employed based on the results obtained in the overseas study (Study 205) and is also considered for future global studies including Japan.Single-agent treatment of lenvatinib was tolerated up to the dose of 24 mg/day continuous administration in Japanese patients with solid tumor and similar results were observed in Europe and US. Everolimus has been approved in Japan, US, and Europe, for treatment of RCC patients at dose of 10 mg/day once daily continuous administration. No significant difference in tolerability has been noted between Japanese and non-Japanese patients.However, this combination regimen has never been studied in Japan; the tolerability and pharmacokinetics in Japanese patients are unknown.

For this reason, this study was considered scientifically rational and designed based on the previous findings to evaluate the tolerability, safety, and pharmacokinetics of lenvatinib- everolimus combination therapy.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To investigate tolerability and safety of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma (RCC)

8.2 Secondary Objectives

- To assess the pharmacokinetic (PK) of lenvatinib and everolimus
- To assess the preliminary anticancer effects of lenvatinib in combination with everolimus

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a non-randomized, open-label, multi-center Phase 1 study (E7080-J081-112) of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic RCC. Subjects will be enrolled in this study after informed consent is obtained and eligibility is confirmed.

One treatment cycle is defined as 28 days. Lenvatinib will be administered at starting dose of 18 mg in combination with everolimus at starting dose of 5 mg both orally once daily continuously. DLT will be observed during Cycle 1 (28 days following the initial dosing) to investigate tolerability and safety. Treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by sponsor.

A total of six subjects will be initially enrolled. Enrollment will be interrupted when DLT is observed in two or more subjects. Investigators and sponsor will review the nature and severity of all the DLTs and make a decision if enrollment of up to six subjects and further additions of three to six subjects are feasible and necessary. Suggestions by the independent medical advisor will be collected, if necessary.

The study sponsor and investigators will consider the nature and severity of DLT during Cycle 1 as well as unacceptable toxicities that cannot be managed with dose interruption and/or reduction and overall toxicities up to Cycle 2 on the evaluation of tolerability in combination therapy. The suggestions by the independent medical advisor can be collected, if necessary.

Additional subjects maybe enrolled to the lower cohort (lenvatinib 14 mg and everolimus 5 mg once daily administration) in the following cases: over one-third of subjects experiences DLTs during Cycle 1, development of unacceptable, development of unmanageable toxicity with dose interruption and/or reduction up to Cycle 2, tolerability cannot be confirmed with dose level of lenvatinib 18 mg/everolimus 5 mg QD.

If a subject has no DLT but fails to receive ≥ 75% of the planned dosage of lenvatinib and/or everolimus up to Cycle 1 Day 21, due to a reason other than treatment related toxicity, this subject will not be included in the DLT assessment population and a new subject will be added for replacement.

Subjects will discontinue study treatment at the time of disease progression, development of unacceptable toxicity, withdrawal of consent, or qualifies any of the criteria described in '9.3.3.1 Discontinuation for Individual Subjects'. The discontinuation assessments will occur within 7 days and off-treatment visit on 30th day after the final dose of study treatment.

DLT is defined as toxicity related to this combination therapy as indicated below.

Table 1. Dose Limiting Toxicities (DLT)

Toxicity Category	**Toxicity/CTCAE Grade**
Hematologic	• Grade 4 neutropenia lasting >7 days • Grade 3 febrile neutropenia (axillary temperature ≥38.5ºC and neutrophils $<1\times10^3/\mu L$ ($<1000/mm^3$) • Grade ≥3 thrombocytopenia lasting >7 days or requiring blood transfusion
Non-hematologic toxicity	• Grade 3 non-hematologic toxicities lasting >7 days except for the following: ➢ Clinically insignificant or transient abnormal laboratory findings ➢ Able to be controlled by maximal supportive therapy Grade ≥3 hyperamylasemia or hyperlipasemia without clinical or other evidence of pancreatitis are not regarded as a DLT. • Grade ≥3 Nausea, vomiting or diarrhea lasting >7 days despite maximal medical therapy • Hypertension uncontrolled by medication • Any thromboembolic event including cerebrovascular hemorrhage/events
Medication compliance	• Failure to administer ≥75% of the planned dosage of lenvatinib or everolimus as a result of treatment related toxicity

Overall study design is presented below.

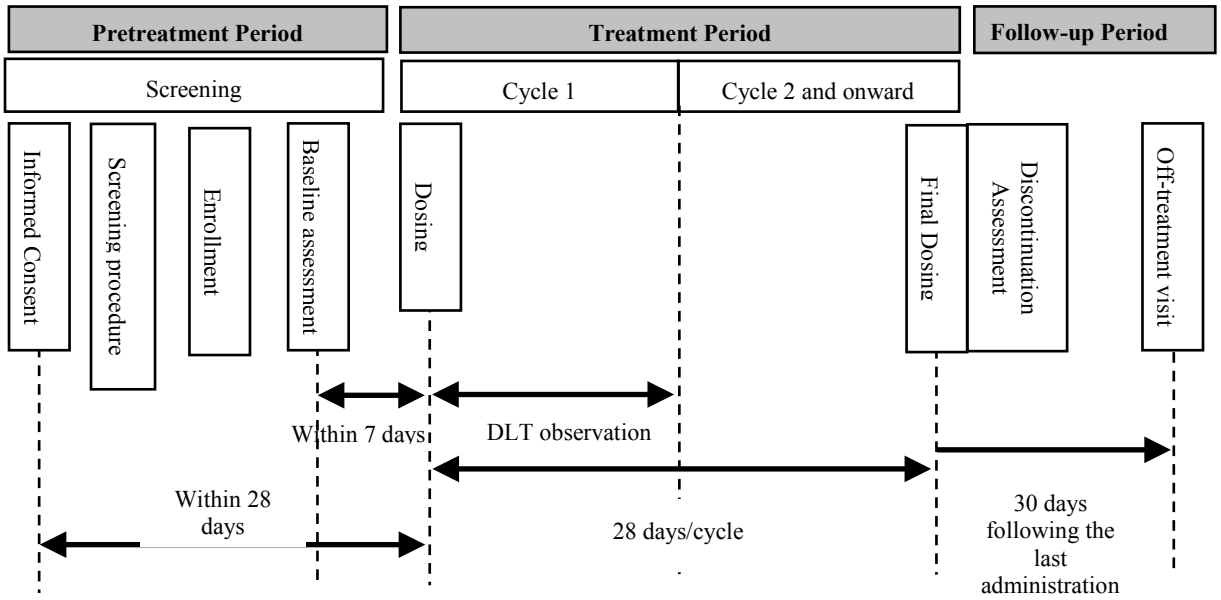


Figure 1 Study Design

9.1.1 Pretreatment Period

Pretreatment Period will consist of obtaining informed consent, screening procedures, subject enrollment and baseline assessments. Each subject must be explained the nature of the study and sign an informed consent form before any study-specific procedures are performed. Investigators must confirm the eligibility of each subject during screening procedures.

All Screening procedures are to be completed within 28 days prior to the Cycle 1 Day 1 and eligible subjects will be enrolled. All Baseline assessments are to be completed within 7 days prior to the Cycle 1 Day 1 and subjects' eligibility will be confirmed.

9.1.1.1 Treatment Period

Treatment Period will consist of two parts: Cycle 1 and following cycles.

One treatment cycle is defined as 28 days. Lenvatinib will be administered at starting dose of 18 mg in combination with everolimus at starting dose of 5 mg both orally once daily continuously. DLT will be observed during Cycle 1 (28 days following the initial dosing) to investigate tolerability and safety. Treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by sponsor.

Subjects will be required to stay at the clinic during Cycle 1 in principle, however, they may be allowed to go home temporarily, be discharged or receive treatment as outpatient per investigators' discretion.

9.1.1.2 Follow-up Period

Follow-up Period will include discontinuation assessments and off-treatment visit. Subject will discontinue study treatment if he/she qualifies for any of the criteria listed in Section 9.3.3.1. The discontinuation assessments will occur within 7 days and the off-treatment assessments on 30 days (+ 7 days) after the final dose of study treatment.

9.2 Discussion of Study Design, Including Choice of Control Groups

Control group is not employed in this study. Rationale of study design is described in Section 7.5 'Study Rationale' of this protocol.

9.3 Selection of Study Population

A total of 6 to 12 subjects will be enrolled in 3 to 5 investigational sites in Japan. Subjects who meet all of the inclusion criteria or none of the exclusion criteria will be eligible to receive study drug.

9.3.1 Inclusion Criteria

1. Subjects must meet all of the following criteria to be included in this study:Voluntary agreement to provide written informed consent of this study
2. Willing and able to comply with all aspects of the protocol after being fully informed of the content
3. Males or females aged ≥20 years at the time of informed consent
4. Histological or cytological confirmation of RCC
5. Subjects must have confirmed diagnosis of unresectable advanced and/or metastatic RCC
6. Disease progression following VEGF targeted therapy
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1
8. Adequately controlled blood pressure with or without the use of antihypertensive agents (defined as BP ≤150/90 mmHg at screening and no change in antihypertensive therapy within 1 week prior to the Cycle 1 Day 1
9. Subjects with adequate function of major organs:
   a. Hemoglobin ≥9.0 g/dL
   b. Neutrophil count $\geq 1.5\times10^3$ /μL
   c. Platelets $\geq 10\times10^4$ /μL
   d. Total bilirubin ≤1.5×upper limit of normal specified by the testing laboratory (ULN)
   e. Alkaline phosphatase (ALP), AST and ALT ≤ 3.0 x ULN (≤ 5.0 x ULN for patients with the liver metastasis)
   f. Creatinine clearance ≥40 mL/min calculated per the Cockroft and Gault formula

   Male: (140–age)×weight (kg)÷72×Serum creatinine (mg/dL)

   Female: 0.85×(140–age)×weight(kg)÷72×Serum creatine (mg/dL)

10. Adequate blood coagulation function, defined as international normalized ratio (INR) ≤1.5
11. Survival expectation of 3 months or longer after study enrollment
12. Washout period required from the end of prior treatment to the start of study drug administration will be as follows:

a. Anticancer therapies:

- Other investigational drug or antibody therapy: ≥4 weeks
- Chemotherapy (except small-molecule targeted therapy), surgical therapy, radiation therapy: ≥3 weeks
- Endocrine therapy, immunotherapy, small-molecule targeted therapy: ≥2 weeks

b. Supportive therapies:

Blood transfusion, blood preparations, hematopietic growth factors including G-CSF preparations: ≥2 weeks

13. Females of childbearing potential must not have had unprotected sexual intercourse within 28 days before subject registration and must agree to use a highly effective method of contraception (e.g., use of an intrauterine device, condom with spermicide*, a contraceptive implant**, an oral contraceptive*, or have a vasectomized partner with confirmed azoospermia)[Note] throughout the entire study period and for 30 days after final administration of investigational drug. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during this study period or for 30 days after investigational drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before administration and must continue to use the same contraceptive during this study and for 30 days after investigational drug discontinuation.
All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least one month before administration

Females of childbearing potential must not have had unprotected sexual intercourse within 28 days before subject registration and must agree to use a highly effective method of contraception (e.g., use of an intrauterine device, condom with spermicide*, a contraceptive implant**, an oral contraceptive*, or have a vasectomized partner with confirmed azoospermia)[Note] throughout the entire study period and for 30 days after final administration of investigational drug. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during this study period or for 30 days after investigational drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before administration and must continue to use the same contraceptive during this study and for 30 days after investigational drug discontinuation.
All females will be considered to be of childbearing potential unless they are

postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least one month before administration.

Note: Whether or not a pharmaceutical agent or medical device has been approved and certified in Japan (* : yes, ** : no)

14. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above (i.e., not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation).

9.3.2 Exclusion Criteria

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

1. Subjects with CNS metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
2. Prior exposure to lenvatinib
3. Subjects who have not recovered from toxicities to ≤ Grade 1 as a result of prior anticancer therapy, except alopecia
4. Major surgery within 3 weeks prior to the first dose of lenvatinib
5. Subjects having ≥2+ proteinuria on urine dipstick testing will undergo a 24-hour urine collection for quantitative assessment of proteinuria. Subjects with a urine protein ≥1 g/24 hours will be ineligible.
6. Uncontrollable diabetes as defined by fasting glucose >1.5×ULN
7. Fasting total cholesterol >7.75 mmol/L (>300 mg/dL)
8. Fasting triglycerides >2.5×ULN
9. Gastrointestinal malabsorption, a history of gastroenterostomy, inability of oral administration, or any other condition that might affect the absorption of lenvatinib and/or everolimus
10. Significant cardiovascular impairment:
    a. Congestive heart failure than New York Heart Association (NYHA) Class II within 6 months of the first dose of study drug
    b. Unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug
    c. Prolongation of QTc (Friderica formula) interval >480 ms
    d. Cardiac arrhythmia requiring medical treatment for cardiovascular impairment

11. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin is permitted.
12. Active hemoptysis (bright red blood of at least 0.5 teaspoon or 2.5 mL) within 3 weeks of the first dose of study drug
13. Active infections that require systemic treatment
14. Human immunodeficiency virus (HIV) positive
15. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb and/or HBsAb positive, an HBV DNA test will be performed and if positive the subject will be excluded
16. A history of interstitial pneumonia with clinical manifestation or as confirmed by means of diagnostic imaging
17. Medical need for the continued use of potent or moderate inhibitors of CYP3A or P-gp, or potent or moderate inducer of CYP3A. Subjects are eligible if 7 days or longer have passed since the last use of such agents prior to the first dose of study drug.
18. Known intolerance to lenvatinib (or any of the excipients) or known hypersensitivity to everolimus (or any of the excipients) or rapamycins (sirolimus, temsirolimus and so on)
19. Alcohol or drug dependency or abuse, inability to comply with every aspects of the study protocol, or any physical or mental conditions that in the opinion of the investigators would preclude the subject's participation in the study
20. Females who are pregnant or breastfeeding (not eligible even she discontinues breastfeeding)
21. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial

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 discontinues study treatment, the subject will enter the Follow-up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent.

The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The Subject Disposition CRF page will be completed indicating the primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from treatment. In addition, the date of last dose of study drug(s) will be recorded on the CRF.

9.3.3.1 Discontinuation for Individual Subjects

1. Subjects will continue to receive study treatment unless: Subject wishes to discontinue the treatment or withdraw the consent
2. Significant violation in eligibility is confirmed after subject's study enrollment
3. Subject experiences an AE that is difficult to continue the study treatment, in the opinion of investigator or subinvestigator.
4. Subject is pregnant
5. Disease progression is observed. Subject will be able to continue study treatment if investigator or subinvestigator judges that the clinical benefit will outweigh.
6. Investigator or subinvestigator's decision to discontinue the treatment.

When subject withdraws from lenvatinib, everlolimus will also be discontinued. Discontinuation assessments will be performed within 7 days and the final observation will be conducted on 30 days (+7 days) after the final dose of study treatment.

9.4 Treatments

Lenvatinib and everlolimus will be orally administered to subjects once daily in a 28-day cycle. During Cycle 1, subjects will receive the drugs in the morning after fasting with no food consumption for one hour postdose. In Cycle 2 and onward, subjects will receive study drug either fasted condition or at after meal and maintain the same dosing condition once it is decided.

Lenvatinib will be administered at starting dose of 18 mg in combination with everolimus at starting dose of 5 mg.

9.4.1 Drug interruption and dose reduction

1. Cycle 1

   a. If DLT occurs:

   Lenvatinib and everolimus must be interrupted immediately. Treatment may be resumed in Cycle 2 at one lower dose level of lenvatinib and/or reduction of everolimus to 5 mg every other day or discontinuation of everolimus if toxicity is resolved to Grade 0–1 or baseline and investigator or subinvestigator decides to continue the study.

   b. No DLT:

   Lenvatinib and everolimus will be interrupted if judged to be clinically needed by investigators, and may be resumed at the same dose level at appropriate timing. No dose reduction is permitted.

2. Cycle 2 and onward

   Dose reduction and interruption for subjects who experience lenvatinib and/or everolimus related toxicity will follow the instructions shown in Table 2. Dose

reductions occur in succession based on the previous dose level (14, 10, 8 mg/day). Any dose modification must be discussed with the sponsor when toxicities occur at the dose of 8 mg/day. Once the dose has been reduced, it cannot be increased at a later date. For management of hypertension and interstitial lung disease, refer to instructions '9.4.2 Management of Hypertension' and '9.4.7 Management of interstitial lung disease' before consulting the table below, as appropriate.

Table 2. Dose Reduction and Interruption Instructions for Lenvatinib/Everolimus Combination Treatment[a]

Lenvatinib/Everolimus Treatment-Related Toxicity[b,c,d]	During Therapy	Adjusted Dose
Grade 1or Tolerable Grade 2[b]	Continue treatment	No change
Intolerable Grade 2[b] or Grade 3	Interrupt lenvatinib and everolimus until resolved to Grade 0–1 or baseline	Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required. Dose reduction lenvatinib by one level and/or reduce everolimus to 5 mg every other day or discontinuation of everolimus and resume the treatment.
Grade4[c]	Discontinue study treatment	

a: An interruption of study treatment for more than 28 days due to treatment-related toxicity will require a discussion with the sponsor before treatment can be resumed.

b: Tolerability Grade 2 toxicities will be judged by the study investigators to be intolerable.

c: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

d: Initiate optimal medical management for nausea, vomiting, diarrhea prior to any treatment interruption, or dose reduction. If uncontrolled, the management will be followed by this guideline.

9.4.2 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

The following guideline should be followed for the management of hypertension:

1. Ensure that subjects have BP ≤ 150/90 mm Hg at the time of study entry
2. If known to be hypertensive, confirm that the subject has been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1.
3. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg) is confirmed on two assessments a minimum of 30 minutes apart. One BP assessment is defined as the mean value of two measurements at least 5 minutes apart. The choice of antihypertensive treatment

should be individualized to the subject's clinical circumstances and follow standard medical practice.

4. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg is first observed on two assessments a minimum of 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists. For subjects with hypertension and proteinuria, appropriate therapy, eg, angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred.
5. Lenvatinib and everolimus should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥ 160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same hypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.
6. The following guidelines should be followed for the management of systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg confirmed on repeat measurements after 30 minutes:

    - Continue lenvatinib and everolimus, and institute antihypertensive therapy for subjects not already receiving antihypertensive medication
    - For the subjects already on antihypertensive medication, dose or medication choice should be modified per investigators judgment.
    - If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib and everolimus administrations should be interrupted and restarted at a dose of one level lower for lenvatinib only when systolic BP ≤ 150 mm Hg and diastolic BP ≤ 95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours. Dose for everolimus will remain the same.
    - If systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg recurs with the reduced dose of lenvatinib despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib and everolimus administrations should be interrupted and restarted at a dose of another lower level for lenvatinib, only when systolic BP ≤ 150 mm Hg and diastolic BP ≤ 95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours. Dose for everolimus will remain the same.
    - During the Treatment Period, both in the Randomization Phase and in the Extension Phase, subjects with systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinical indicated) until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 3 consecutive months. If a repeat event of

systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 3 consecutive months.

7. If Grade 4 hypertension (life-threatening consequences) is observed, appropriate medical management will be introduced and lenvatinib and everolimus will be discontinued.

9.4.3 Management of Proteinuria

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments (Table 5) and as clinically indicated. Guidelines for assessment and management of proteinuria are summarized as follows:

- Initial episode of proteinuria: If proteinuria ≥ 2+ is detected on urine dipstick testing, lenvatinib and everolimus will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to CTCAE v4.03 (Appendix 6) will be based on the 24-hour urine collection for total protein result. Dosing will be managed based on the grade of proteinuria according to Table 2.
- Second and the subsequent episode of proteinuria：If proteinuria 3+ or 4+ is detected on urine dipstick testing, lenvatinib and everolimus will be continued and a 24-hour urine collection for total protein will be obtained to verify the grade of proteinuria. Dosing will be managed based on the grade of proteinuria according to Table 2. If proteinuria ≥2+ continues and is clinically indicated, a 24-hour urine collection for total protein will be obtained to verify the grade of proteinuria.
- Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (on Day 15 or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. If a new event of proteinuria ≥ 2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months.

9.4.4 Management of Hepatotoxicity

Regular monitoring of liver function tests (eg, alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the Schedule of Visits and Procedures (Table 5) and as clinically indicated. If signs occur indicating a decrease in liver function by 1 grade or more from baseline, the instructions contained in Table 2 of the protocol should be followed, “Study Treatment Dose Reduction and Interruption Instructions”. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs both lenvatinib and everolimus must be discontinued.

9.4.5 Management of Thromboembolic Events

Subjects should be advised to pay attention to the symptoms suggestive of venous thromboembolic events, which include acute onset of dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, redness and warmth to touch or tenderness. In case any of these signs or symptoms appears, subjects should be instructed to report such signs and symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 2 of the protocol should be followed, "Study Treatment Dose Reduction and Interruption Instructions." Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, both lenvatinib and everolimus must be discontinued.

9.4.6 Management of Posterior Reversible Encephalopathy Syndrome (PRES)

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In subjects with signs or symptoms of PRES, dose interruptions, reductions, or discontinuation of both lenvatinib and everolimus may be required per instructions included in Table 2.

9.4.7 Management of Interstitial Lung Disease

Interstitial lung disease (pneumonitis, lung disease, lung infiltration, alveolitis, pulmonary alveolar haemorrhage and pulmonary toxicity) is a frequently reported adverse reaction when treated with rapamycin derivative including everlolimus, and it can be fetal in rare cases. If breathing conditions of unknown cause are observed, the subject must be appropriately examined to rule out possible causes such as infection, neoplasm, and other nondrug related conditions to confirm diagnosis of lung disease.

Following procedures should be followed when determining dose of lenvatinib and everolimus for subject with lung disease.

- Radiology findings indicate lung disease but asymptomatic (Grade 1): Continue treatment without dose adjustment, however, study treatment may be discontinued depending on the subject's condition.
- Moderate (Grade 2) condition: Interrupt study treatment (lenvatinib and everolimus) and consider using adrenal cortical hormone. If it is resolved to Grade 0-1 or baseline, resume study treatment at the same dose level as before the interruption. If it does not resolve within 28 days, subject will treated with

lenvatinib alone after resolving to Grade 0-1 or baseline, according to his/her clinical condition. Investigator will make a decision on whether the subject can resume the treatment and if so, as well as the dose level. Everolimus must not be concomitantly administered.

- Consider using adrenal cortical hormone if Grade 2 lung diseasea recurs despite of appropriate management. If it is resolved to Grade 0-1 or baseline, resume study treatment at the same dose level as before the interruption. If it does not resolve within 28 days, subject will be treated with lenvatinib alone after resolving to Grade 0-1 or baseline, according to his/her clinical condition. Investigator will make a decision on whether the subject can resume the treatment and if so, as well as the dose level. Everolimus must not be concomitantly administered.
- Severe (Grade 3) condition: Interrupt study treatment (lenvatinib and everolimus) and consider using adrenal cortical hormone. If it is resolved to Grade 0-1 or baseline, resume study treatment with lenvatinib alone after resolving to Grade 0-1 or baseline according to his/her clinical condition. Investigator will make a decision on whether the subject can resume the study treatment and if so, as well as the dose level. Everolimus must not be concomitantly administered.
- If a subject experiences life-threatening (Grade 4) event, both lenvatinib and everolimus must be discontinued.

9.4.8 Management of Infectious Disease

Everolimus is known to decreases immune system activities while increasing the risk of developing infection. Subjects should be closely monitored for signs and symptoms of infections to immediately administer proper medical intervention. Dose adjustment of everlolimus may be required. Dose interruptions and reductions of lenvatinib and everolimus will be determined per instructions included in Table 2.

9.4.9 Management of Hyperglycemia and Hyperlipidemia

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia are commonly seen as an adverse reaction in patients treated with rapamycin, including everlolimus. Subjects need to have well regulated blood sugar level before being enrolled in the study.

Measurement of blood sugar level will be taken at subject visits as specified in Table 5. If sugar level exceeds standards specified by the study site, measurement should be taken after at least 6 hours of fasting (water is permitted). CTCAE Grade will be given to the sugar level measured at fasted condition. Insulin and/or oral antihyperglycemic drug may be administered (or dose increase if subject is already taking) as needed.

Antihyperglycemic drug will be selected according to individual clinical condition. Concomitant use of everolimus and CYP3A or P-gp inhibitors and inducers (see Appendix 2) should be avoided in accordance with the standard medical procedure.

Dose interruptions, reductions, or discontinuation of lenvatinib and everolimus will be determined per instructions included in Table 2.

9.4.10 Management of Stomatitis

Instruction for daily oral care should be given to subjects prior to study initiation and proper gargling and brushing should be continued throughout the study period. In general, sodium gualenate hydrate is recommended for mouth rinsing and gargling, and mouthwash products containing alcohol, hydrogen peroxide, or iodine should be avoided. For mild to moderate pain, a topical anesthetic such as lidocaine, acetaminophen, or Non-Steroidal Anti-Inflammatory Drugs can be used. To relieve moderate to severe pain, consider using narcotic-analgesic agents.

Dose interruptions, reductions, or discontinuation of lenvatinib and everolimus will be determined per instructions included in Table 2.

9.4.11 Points to Consider on Determination of DLT

1. Grade 4 neutropenia is observed
   a. Additional tests will be performed as needed to confirm duration of the event.
   b. If Grade 4 is present on Day 8 and beyond (Day 1 defined as the day the event was confirmed to be Grade 4), the event will be judged as 'duration ≥7 days'. If the event doesn't resolve and hematology tests cannot be performed on Day 8, the investigator will discuss with sponsor on handling of the event. Consult with independent medical advisor, as needed.
2. Grade 3 or Grade 4 thrombopenia is observed:
   a. Additional tests will be performed as needed to confirm duration of the event.
   b. If Grade 3 or 4 continues on Day 8 and beyond (Day 1 defined as the day the event was confirmed to be Grade 3 or 4), the event will be judged as 'duration ≥7 days'. If the event doesn't resolve and hematology tests cannot be performed on Day 8, the investigator will discuss with sponsor on handling of the event. Consult with independent medical advisor, as needed.
3. Grade 3 or Grade 4 noonhematologic toxicities is observed
   a. Additional tests will be performed as needed to confirm duration of the event.
   b. If Grade 3 or 4 continues on Day 8 and beyond (Day 1 defined as the day the event was confirmed to be Grade 3), the event will be judged as 'duration ≥7 days. If the event doesn't resolve and hematology tests cannot be performed on Day 8, the investigator will discuss with sponsor on handling of the event. Consult with independent medical advisor, as needed.
4. If a subject experiences unexpected AEs that is not listed on 'Table 1 Dose Limiting Toxicity (DLT)' and requires discontinuation from treatment, investigator will discuss with sponsor on handling of the event. Consult with independent medical advisor, as needed.

9.4.12 Identity of Investigational Products

Lenvatinib (study drug) will be provided as 4 mg and 10 mg capsules. Each investigational site will purchase commercially available everolimus (concomitant drug) for study treatment. Refer to the most updated prescribing information before administering everolimus to subjects.

9.4.12.1 Chemical Name, Structural Formula of Lenvatinib (E7080)

Test drug code: E7080

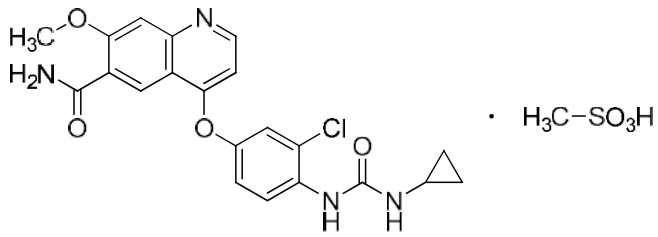
Generic name: Lenvatinib Mesilate

Chemical name:
4-{3-Chloro-4-[(cyclopropylcarbamoyl)amino]phenoxy}-7-methoxyquinoline-6-carboxamide monomethanesulfonate

Molecular formula: $C_{21}H_{19}ClN_4O_4 \bullet CH_4O_3S$

Molecular weight: 522.96

Structural formula:



9.4.12.2 Labeling for Study Drug

Both lenvatinib and everolimus will be labeled with the following information. Details are provided in Appendix 4.

- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.12.3 Storage Conditions

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

9.4.13 Method of Assigning Subjects to Treatment Groups

1. This is a non-blind study. Study drug will be administered to subjects who were confirmed for eligibility (see Section 9.3) and submitted a written consent form. This study will not be randomized. Procedure for subject enrollment is shown in Figure 2. Unique subject ID numbers prescribed by the sponsor will be assigned to subjects who signed ICF and their names and numbers will be recorded accordingly in the Subject Screening List.
2. Subjects will be screened for enrollment eligibility. The results will be recorded in the Subject Screening List by the investigator or subinvestigator.
3. Subjects' screening results and dispositions will be entered in the subject enrollment form (Appendix 5), which then will be faxed to the subject enrollment center.
4. Once the fax is received, the enrollment center will review subjects' eligibility. If ineligible subject is found, the center will fill in the designated form with details and fax to the investigators who will review the center's assessment, and remove the subject from the study.
5. If missing entries or discrepancies are found on the enrollment form, the center will check with investigators or study coordinator.
6. For subjects who were confirmed for eligibility, the center will fill in the enrollment form with subject ID number, date and dose, and the form will be faxed to investigators.
7. Investigators or study coordinator will review the enrollment form.

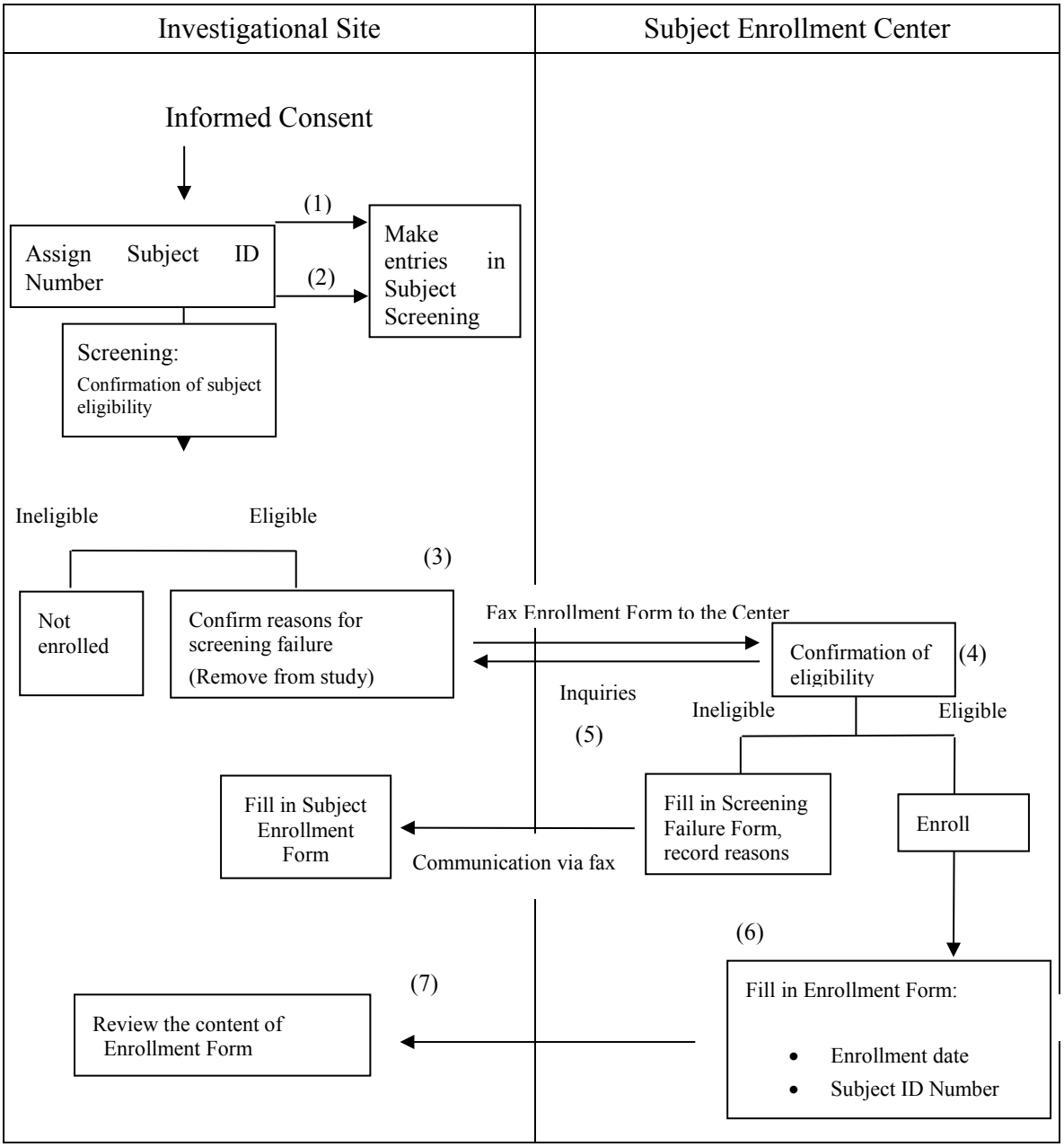


Figure 2 Subject Enrollment Procedure

9.4.14 Selection of Doses in the Study

See Section 7.5 ‘Study Rationale’ for selection of doses in this study.

9.4.15 Selection and Timing of Dose for Each Subject

See Section 9.4 'Study Treatment' for dose selection and timing for each subject.

9.4.16 Blinding

The study will not be blinded.

9.4.17 Prior and Concomitant Therapy

Any medications (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent and for 30 days after the last dose of study treatment) will be recorded on the CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. Name of the medication, the starting dose (for treatment of primary disease only), and dates of initial and last administration will be recorded on the CRF.

Medication or fluid infusion administered as pretreatment for surgery, examination, or drug administration will not be considered concomitant drugs. Name of concomitant therapy, dates of initial and last administration will be recorded on the CRF.

9.4.18 Concomitant Therapies

Investigator and subinvestigator will conduct study in compliance with prohibited concomitant drugs and therapies guidelines to ensure subject safety and accurately assess study treatment. Study treatment must be discontinued at once if any prohibited concomitant drug or therapy becomes necessary. Prohibited drug or therapy can be administered to subject per discretion of investigator or subinvestigator giving full attention to subject safety and development of AEs.

9.4.18.1 Prohibited Concomitant Drugs and Therapies

1. Prohibited from the time of subject enrollment for this study until discontinuation from this study
   a. Anti-cancer therapy other than lenvatinib and everolimus (surgery, anti-cancet medication, endocrine therapy, palliative radiotherapy or immunotherapy, etc.).
   b. Other investigational drugs.
   c. Any agent that potently inhibits CYP3A or P-gp
   d. Live vaccine (freeze-dried live attenuated rubella, oral poliomyelitis vaccine, freeze-dried BCG, etc.)
2. Prohibited during Cycle 1
   a. Any agent that potently or moderately inhibits CYP3A or P-gp, or potently or moderately induces CYP3A.

9.4.18.2 Limited Use of Concomitant Therapies and Drugs

Drugs that are not prohibited for concomitant use include drugs used to treat complications or AEs or drugs used to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, steroids, antidiarrheal drugs, and tranquilizers, etc.). These drugs and treatments can be concomitantly used, based on the judgment of the investigator or subinvestigator.In Cycle 2 and onward, agents that potently or moderately inhibit CYP3A or P-gp, and potently or moderately induce CYP3A will be allowed to a limited extent.

9.4.18.3 Drug–Drug Interactions

Lenvatinib is a substrate of P-gp and CYP3A, primarily metabolized by CYP3A and aldehyde oxidase while everolimus is a substrate of P-gp and CYP3A, primarily metabolized by CYP3A. Co-administration of drugs that potently or moderately induces CYP3A or P-pg with lenvatinib could affect the metabolism of lenvatinib and everolimus leading to possible development of toxic effect due to increase in plasma concentration.Drugs that potently or moderately induce CYP3A will accelerate metabolism of lenvatinib and everolimus causing decrease in plasma concentration and reduced therapeutic response.

Refer to Appendix 2 for drugs that can impact on activities of drug-metabolizing enzyme CYP3A.

9.4.19 Treatment Compliance

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

9.4.20 Drug Supplies and Accountability

The investigator and the study staff (or the designated pharmacist) will be responsible for the accountability of all study drugs/study supplies (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.Under no circumstances will the investigator allow the study drugs/study supplies 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.An accurate and timely record of the receipt of all study drugs, dispensing of study drug to the subject, collection of unused study drug returned by the subject (unused drug 1), collection of drug shipped to the site but not dispensed to subjects (unused drug 2) and subsequent return of unused study drug to the sponsor (sum of unused drugs 1 and 2) must be maintained.This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, and (d) documentation of returns to the sponsor.The study drugs/study supplies 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. As applicable, all unused study

drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigatorUnused study drugs that are to be returned from the site will be collected by sponsor's representative personally and will be returned to the sponsor's designated central or local depot(s). Drug accountability will be reviewed during investigational site visits and at the completion of the study.

9.5 STUDY ASSESSMENT

9.5.1 Assessments

9.5.1.1 Demography

Investigator, subinvestigator or clinical research associates will investigate the subjects who provided written informed consent for eligibility to fill out a 'Subject Registration Form'. In addition, patient characteristics will be collected for items below, which will be recorded on the CRF. Information available from the Subject Registration Form may be used for recording on the CRF without repeating the process.

1. Subject ID Number
2. Date of obtaining written Informed Consent
3. Sex
4. Ethnicity
5. Race
6. Date of birth

9.5.1.2 Baseline Assessments

MEDICAL HISTORY, CURRENT CONDITIONS, PHYSICAL EXAMINATION

All medical history and conditions confirmed at Screening will be documented in the CRF if they are judged by the investigators to have impact on the assessment of efficacy, safety or pharmacokinetic profile. Prior treatment and diagnosis on the primary disease will also be investigated.

1. Original tumor diagnosis (date of diagnosis, diagnostic method ［histology/cytology］, histological type, staging［TNM classification. See Appendix 6］)
2. Previous anti-cancer therapy for renal cell carcinoma
   a. Surgical therapy (date, modality)
   b. Radiotherapy (site of radiotherapy, end date of radiotherapy)
   c. Anti-cancer medication (medication name, initial dose, start/end date of medication, reason for discontinuation)
   d. Other anti-cancer procedure (procedure name, end date of procedure)

9.5.1.3 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs including CTCAE v4.03 grades (for increasing/decreasing severity), DLT, laboratory test value (hematology, blood chemistry, urine values), vital signs, 12-ECGs, and echocardiograms or MUGA scans including left ventricular ejection fraction (LVEF); chest CT scan, ECOG-PS and the physical examination as detailed in the Schedule of Procedures/Assessments (Table 5).

ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the study drug. For this study, the study drug is lenvatinib.

The criteria for identifying adverse events 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. If a diagnosis was made based solely on the sign and symptom, the identified medical condition or disease will be considered as AE.
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that results in a change in treatment or discontinuation from study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not

All AEs encountered during the clinical study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study consent through the last visit. Subjects may receive other anti-cancer treatment within 30 days after the final administration of study drug if his/her cancer conditions necessitate. In this case, off-treatment observation must be conducted before initiation of other anti-cancer treatment. For SAEs, all events occurred until 30 days

after the subject's last dose will be collected. If subject was withdrawn prior to and during screening evaluations due to findings meeting the definition of an AE, its severity will be recorded on the Adverse Events CRF.

All laboratory abnormalities meeting the criteria to qualify as an AE should be recorded on the CRF.

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

A laboratory result should be considered by the investigators to be an AE regardless of the presence of an abnormality laboratory test 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 (e.g., potassium supplement for hypokalemia)
- Results in any out of range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- Increases in severity compared to baseline by ≥ 2 CTCAE v4.03 grades, with the exception of lymphocytes, albumin, cholesterol, glucose. For these tests, a change of ≥ 2 grades will be evaluated by the investigator to determine if they are of clinical significance and, if so, will be considered an adverse event.

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

All AEs must be followed until resolution or for 30 days after the subject's last dose, whichever comes first. Serious adverse events will be followed until the event resolves or the event or sequelae stabilize.

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

Assessing Severity of Adverse Events

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

Assessing Relationship to lenvatinib or everolimus

Items to be considered when assessing the relationship of an AE to lenvatinib or everolimus are:

- Temporal relationship of the onset of the event to the initiation of lenvatinib or everolimus
- The course of the event, especially the effect of discontinuation of lenvatinib or everolimus or reintroduction of lenvatinib or everolimus, as applicable
- Whether the event is known to be associated with the lenvatinib or everolimus or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality to lenvatinib or everolimus

Related	A causal relationship between lenvatinib or everolimus and the AE is a reasonable possibility
Not Related	A causal relationship between lenvatinib or everolimus and the AE is not a reasonable possibility.

SERIOUS ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

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, other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; any treatment-emergent significant laboratory abnormality (Section 9.5.3and9.5.4). These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs (a case of normal births is excluded) associated with events of interest 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" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

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

PHYSICAL EXAMINATION

Physical examinations will be performed as designated on the Schedule of Procedures/Assessments (Table 5). A physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. Documentation of the physical examination will be included in the source documentation at the investigational site. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

VITAL SIGNS, WEIGHT AND HEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP］[mmHg], pulse [bpm], body temperature [°C], weight [kg] and height [cm, at Screening only]) will be obtained as designated in the Schedule of Procedures/Assessments (Table 5).

BP and pulse will be obtained after subjects have been resting. BP will be measured on the same arm and, preferably by the same clinical staff at each timepoint as far as possible.

One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. For subjects with an elevated BP (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg), confirmation should be obtained by performing another measurement after 30 minutes.

LABORATORY MEASUREMENTS

Clinical laboratory tests include hematology, blood chemistry and urinalysis (Table 3). The Schedule of Procedures/Assessments (Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3.Clinical Laboratory Tests

Category	Tests
Hematology	RBC, hemoglobin, hematocrit, platelet count, WBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood coagulation	INR[a]
Blood chemistry	
Liver function tests	ALP, AST, ALT, total bilirubin, conjugated (direct) bilirubin
Renal function tests	BUN, creatinine
Other	glucose [b], albumin, total cholesterol [b], triglycerides [b], LDH, total protein, Na, K, Cl, Ca, Mg, inorganic phosphorus, amylase [c], lipase, CPK [c]
Endocrinology[d]	TSH, FT4
Viral tests[e]	HIV antibodies, HCV antibodies, HBs antigen, HBs antibodies, HBc antibodies, (HBV-DNA as needed)
Urinalysis[f]	pH, protein, glucose, occult blood (or hemoglobin)
Pregnancy test	hCG or β-hCG (urine or serum)

a: INR should be performed as part of the screening assessment and when clinically indicated

b: Will be measured under fasted conditions at Screening and Baseline. If glucose level exceeds ULN, glucose measurement will be taken after being fasted for at least 6 hours (water is permitted) in the following assessments.

c: Amylase isoenzymes (pancreatic and salivary type) and CPK isoenzymes (CK-MM and CK-MB) should be evaluated if amylase or CPK is greater than 3 x the upper limit of normal

d: Thyroid antibody test should be performed if clinically indicated.

e: At screening evaluation only

f: If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (Section 9.5.1.3.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

If AEs were assessed during unscheduled clinic visits, all the data corresponding to the laboratory abnormality will be recorded on the CRF.

ELECTROCARDIOGRAMS

Twelve-lead ECG will be performed as designated in the Schedule of Procedures/Assessments (Table 5).

Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format may be used.

ECG parameters (HR, PR interval, QRS interval, QRS axis, QT interval, QTcF interval, RR interval) will be recorded on the CRF.

ECG findings (normal, abnormal, not clinically significant, abnormal clinically significant) will also be recorded on the CRF.

QTc will be corrected using Fridericia's formula (QTcF).

An ECG abnormality may meet the criteria of an AE as described in this protocol (Section 9.5.1.3.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

NYHA CLASSIFICATION FOR CARDIAC FUNCTION

Subjects will be assessed for cardiac function at Screening using NYHA classification system (Appendix 1).

ECOG-PS

ECOG-PS will be assessed as designated on the Schedule of Procedures/Assessments (Table 5). See Appendix 9.

ASSESSMENT OF INTERSTITIAL LUNG DISEASE

Subjects will be evaluated for interstitial lung disease by means of chest X-ray, CT and SpO_2 level, as designated on the Schedule of Procedures/Assessments (Table 5). The result will be documented in the medical record at the site. Changes from screening findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

OTHER SAFETY ASSESSMENTS

Echocardiogram or A multiple gated acquisition (MUGA) scan

A multiple gated acquisition (MUGA) scan (using technetium-99mpertechnetate) or an echocardiogram to assess LVEF will be performed during the Screening Visit, every 16 weeks or sooner if clinically indicated), at discontinuation (within one week or sooner). Echocardiogram or MUGA scans should be performed locally in accordance with the institution's standard practice. Whichever modality is used for an individual subject at baseline should be repeated for all subsequent LVEF assessments for that subject. Left ventricular ejection fractions as assessed by the institution will be entered onto the CRF.

Viral Tests

A blood sample will be taken for HIV antibodies, HCV antibodies, HBs antigen, HBs antibodies, HBc antibodies at Screening. HBV-DNA test will be performed as needed. HBV-DNA data acquired within 28 days of initial dosing or before obtaining informed consent may be used if available.

Pregnancy Tests

An hCG or β-hCG test (serum or urine) will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months as designated on the Schedule of Procedures/Assessments (Table 5).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic and Other Biomarker Assessments

PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected at the time points shown in Table 4 from each subject for measuring plasma lenvatinib concentration and whole blood everolimus concentration, using a validated analytical method. For subjects who discontinued study, samples should also be collected as far as possible. Total volume to be drawn at each timepoint will be 6 mL (3 mL for plasma lenvatinib concentration, 3 mL for whole blood everolimus concentration). Collection, handling and logistic procedures of obtained samples will be detailed in Appendix 8. The actual time of each sample collection will be recorded on the CRF. Dosage and time of lenvatinib and everolimus administration on the day before and the day of PK analysis sampling will be recorded on the CRF (Section 9.5.1.6 Treatment Compliance). Date and time of last food intake before study drug administration on Cycle 1 Day 1 and Day 15 will also be recorded on the CRF.

Table 4.Pharmacokinetic Sampling Time Points

Days	Time (on each Day)	Acceptable time-window (approximate)	Total Volume Collected (mL)
Cycle 1 Day 1	Predose	≤–60 min	6 mL each (3 mL x 2)
	1 h postdose	≤±15 min	
	2 h postdose	≤±15 min	
	4 h postdose	≤±15 min	
	8 h postdose	≤±60 min	
Cycle 1 Day 2	Predose (24 hours after dosing on Day 1)	≤–60 min	
Cycle 1 Day 15	Predose	≤–60 min	6 mL each (3 mL x 2)
	1 h postdose	≤±15 min	
	2 h postdose	≤±15 min	
	4 h postdose	≤±15 min	
	8 h postdose	≤±60 min	
Cycle 1 Day 16	Predose (24 hours after dosing on Day 1)	≤–60 min	

PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Efficacy Assessments

Tumor assessments will be performed using RECIST 1.1 (Appendix 7) by the investigators. Anti-tumor effect will be assessed by appropriate imaging modality such as CT or MRI, with images taken under the same conditions at screening. Tumor assessments will be performed at screening and recorded on the CRF for: overall (presence of target lesion［tumor and/or lymph node］and non-target lesion); target lesion (lesion site, diameter, date of assessment, modality); non-target lesion (lesion site, diameter, date of assessment, modality). Subsequently, target and non-target lesion, the presence or absence, location, date of emergence and diagnosis modality of new lesion as well as overall response will be investigated and recorded in the CRF.

Evaluations of the anti-tumor effect or safety may be performed by a third party as required. In this case, image data, if requested by the sponsor, will be provided by the investigator, subinvestigator, or clinical coordinator via an electronic medium.

TUMOR EVALUATIONS

Chest X-rays will not be used for the evaluation of target lesions.

Modality used for involved body part is indicated below:

- Brain：CT or MRI
- Chest：CT
- Abdomen：CT or MRI
- Pelvis：CT or MRI
- Bone：bone scintigraphy or whole-body MRI (screening), CT or MRI
- Others：CT , MRI, etc.
- Lesions that are visible or palpable: Clinical evaluation

1. CT or MRI

CT or MRI will be performed with contrast enhancement unless the subject is allergic to oral/IV contrast, in which case CT without contrast will be performed. Low-dose CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner, CT images for attenuation correction, or ultrasound should not be used for tumor assessment.

a. Screening

- Brain, chest, abdomen, pelvis, and known or newly suspected lesion will be evaluated
- Data acquired prior to subject's informed consent may be used as screening data if the assessment was conducted within 28 days of initial study drug administration.

b. Cycle 1 and onward

- Chest, abdomen, pelvis, site where lesion was observed at screening or any areas of newly suspected lesion should be assessed.

2. Assessment of bone lesion

Perform bone scan (scintigraphy or whole-body bone MRI) at screening. If the subject has had a bone scan performed within 6 weeks of initial study drug administration, the data may be used even if it is prior to obtaining informed consent. If a bone lesion is to be followed as a non-target lesion, it is preferable that this be done using CT or MRI. For non-target bone lesions that can be followed only on bone scans, bone scans should be performed every 24 weeks or sooner as clinically indicated. A time point response other than not evaluable (NE) will be allowed despite an individual lesion assessment of NE for

weeks when bone scans are not required. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability, unless tracer becomes unavailable.

3. Clinical evaluation

For evaluation of visible lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. Palpable lesions will be assessed by clinical evaluation and the results will be recorded on the source document. Where color digital photos of skin lesions are to be recorded, a millimeter scale ruler and a label showing the Subject ID Number and the date should be included in the photo. Measurements should be performed with calipers.

Tumor lesion will be assessed at screening, every 8 weeks starting from Cycle 1 Day 1 (i.e., Day 1 of odd-numbered Cycle, with time windows of +/- 7 days) and at discontinuation (+ 7 days), by the same modality every time. Additional assessments will be conducted if clinically indicated. Data obtained within 28 days prior to discontinuation will be used as discontinuation data if available.

TUMOR MARKERS

Tumor marker tests such as C-reactive protein (CRP) and immunosuppressive acidic protein (IAP) will be conducted at screening if clinically indicated, however, evaluation is not required if appropriate marker does not exist.

Following the evaluation at screening, tumor marker will be assessed every 8 weeks starting from Cycle 1 Day 1 (i.e., Day 1 of odd-numbered Cycle, with time windows of +/- 7 days) and at discontinuation (+/- 7 days). Data obtained within 28 days prior to discontinuation will be used as discontinuation data.

9.5.1.6 Assessments of Study Drug Administration

Investigator, subinvestigator, or clinical research associates will provide subjects with dosing instruction. Treatment compliance including the dosage and date of lenvatinib and Everolimus administration will be reviewed and recorded on the CRF. Dosing time will also be recorded on the day and the day before PK assessment date as shown on Table 4.

9.5.1.7 Assessments of Concomitant Drugs and Therapies

Investigator, subinvestigator, or clinical research associates will instruct subjects to comply with requirements indicated in ‘Section 9.4.18.1 Prohibited Concomitant Drugs and Therapies’. Compliance status will be reviewed as follows:

1. Concomitant medication

All medications that started after the date of informed consent up to completion of the last observation period will be investigated for the following items at each clinic visit and

recorded on the CRF. If subjects receive medical care by another physician at other department or medical institution, investigators may inquire the attending physician about the treatment given to the subject concerned.

Subjects may receive other anti-cancer treatment within 30 days after the final administration if his/her cancer conditions necessitate. In this case, off-treatment observation must be conducted before initiation of other anti-cancer treatment.

Concomitant medication name, Reason for use (indication), Start and end date (if continuing after the off-treatment observation, indicate as such)

2. Concomitant therapies

All therapies that started after the day of informed consent up to completion of last observation period will be investigated at each clinic visit and recorded on the CRF.

If subjects receive medical care by another physician at other department or medical institution, investigators may inquire the attending physician about the treatment given to the subject concerned.

Concomitant therapies name, Reason for use (indication), Start and end date (if continuing after the off-treatment observation, indicate as such)

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

The Schedules of Procedures/Assessments are shown in Table 5.

Table 5.Schedule of Procedures/Assessments in Study E7080-J081-112

	Pre-Treatment		Treatment Period										Follow-up Period	
	Screening[a]	Baseline[b]	Cycle 1				Cycle 2				Cycle 3～		Discontinuation	Off-treatment observation[e]
Day	Within 28 days predose	Within 7 days predose	1	8 (±2)	15 (±2)	22 (±2)	1 (±3)	8[c] (±3)	15 (±3)	22[e] (±3)	1 (±3)	15[d] (±3)	(+7)	30 days after last dosing (+7)
Informed consent	X													
Enrollment		X												
Inclusion/exclusion criteria	X	X												
Demographic data/Medical record	X													
NYHA	X													
Diagnosis/medical history	X													
Viral test	X													
Blood coagulation test(INR)	X													
Height	X													
Weight	X	X					X				X		X[m]	
ECOG-PS	X	X					X				X		X[m]	
12- Lead ECG	X						X				X[l]		X[m]	
Vital signs	X	X		X	X	X	X	X	X	X	X	X	X[m]	X
Physical Examination	X	X		X	X	X	X	X	X	X	X	X	X[m]	X
Hematology	X	X		X	X	X	X	X	X	X	X	X	X[m]	X
Blood chemistry	X	X		X	X	X	X	X	X	X	X	X	X[m]	X
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	X[m]	X
Pregnancy test (if applicable)	X	X												X
Endocrinology test	X	X					X				X		X[m]	
Blood sample for PK analysis			X[j]		X[j]									
Tumor assessment	X[g]		X[k]										X[n]	
Assessment of interstitial lung disease	X[h]		X[h]										X[n]	

MUGA or echocardiogram	X[i]		X[i]										X[n]		
lenvatinib/everolimus administration			←									→			
AEs/SAEs[f]	←														→
Concomitant medications/therapies	←														→

a: Screening tests are performed only if subject gives consent

b: For assessments scheduled for both at screening and baseline, the screening data can serve as the baseline data, if performed within 7 days prior to the initial dosing

c: Assessments/procedures on Cycle 2 Day 8 and Day 22 can be skipped only if subject's safety is assured by investigator/subinvestigator.

d: Assessments/procedures on Day 15 of Cycle 3 or later can be skipped only if subject's safety is assured by investigator/subinvestigator. Subjects with systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 3 consecutive months. If a repeat event of systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 3 consecutive months. Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (on Day 15 or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. If a new event of proteinuria ≥ 2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months. Subjects will return to the clinic for the Day 15 visit if BP monitoring or urine dipstick testing is required as specified above.

e: Subjects may receive other anti-cancer treatment within 30 days after the final administration if his/her cancer conditions necessitate. In this case, off-treatment observation must be conducted before initiation of other anti-cancer treatment.

f: SAEs, regardless of relationship to study drug treatment, must be reported as soon as possible within 1 working day. AEs will be recorded for 30 days after last dose. During cycle 1 and if clinically indicated, repeat AE assessments at least every 7 days until restarting administration during treatment interruption due to AEs.

g: Data obtained prior to informed consent as well as within 28 days prior to start of study treatment may be used. Assessments on the brain, chest, abdomen, pelvis or any other areas of known or suspected disease will be performed. Bone Scan will be performed within 6 week prior to start of study treatment. If clinical indicated, tumor markers such as CRP and IAP will be measured.

h: Assessment of interstitial lung disease will be performed by chest X-ray and CT, and SpO_2. X-ray and CT will be performed at screening and every 8 weeks (±7days) from Cycle1 Day1. SpO_2 will be performed at screening and Day1 of each cycle from Cycle2. Additional assessments maybe performed if clinically indicated.

i: MUGA or echocardiogram will be performed at screening and every 16 weeks (ie, Day 1 of every 4 cycles［±7days］) from Cycle1 Day1. Additional assessments maybe performed if clinically indicated.

j: Cycle 1 Day1/Day15: Samples collected at predose, 1,2,4,8, and 24 (predose on the following day) hours postdose.

k: Tumor assessments will be performed every 8 weeks (ie, Day 1 of odd-number Cycles［±7days］). Additional assessments maybe performed if clinically indicated. Assessments on the chest, abdomen, pelvis, and other areas of known disease at Screening plus newly suspected disease will

be performed every time. Bone scan will be performed every 24 weeks (ie, Day 1 of every 6 cycles［±14days］) if needed. Additional assessments maybe performed if clinically indicated. Tumor marker will be measured if the marker is measured in screening.

l: 12- Lead ECG will be performed every 8 weeks (ie, Day 1 of odd-number Cycles［±7days］) from Cycle 3.

m: Data obtained within 7 days prior to the study discontinuation can serve as discontinuation data, if available

n: Data obtained within 28 days prior to the study discontinuation can serve as discontinuation data, if available.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of RCC.

The assessments of safety and tolerability to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, vital signs, 12-lead ECG, ECOG-PS, chest CT scan, physical examinations and assessment of AEs, are standard evaluations to ensure subject safety.

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

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, irrespective of relationship to study treatment, must be reported on a completed SAE form by email, fax, or spoken communication as soon as possible, but no later than one business day from the date the investigator becomes aware of the event.

Deaths and life-threatening events should be reported by telephone immediately but no later than one business day. Other SAEs must be reported to the sponsor on a completed SAE form no later than 5 business days.

Serious adverse events, regardless of causality assessment, must be collected through the termination visit and for 30 days following study drug discontinuation, whichever is longer. 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 (and/or protocol-specified 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 Appendix 3.

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

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy 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 or within 30 days of last study treatment, must be reported. If an

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

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

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in Appendix 3. The Pregnancy Report Form (Appendix 11) must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported using the prescribed format (Appendix 12) as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

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

9.5.4.3 Reporting of Events Association with Special Situations

REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

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

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

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

9.5.4.4 Expedited Reporting

The sponsor must inform investigators, the head of the medical institution and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner detailed in Section 9.5.4.1

9.5.4.5 Breaking the Blind

Not applicable

9.5.4.6 Regulatory Reporting of Adverse Events

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

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue from the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 5).

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

Subjects who discontinue early from the study will be discontinued for 1 reason. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

9.5.6 Abuse or Diversion of Study Drug (or recreational use)

Not applicable

9.5.7 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 GCP 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 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

Statistical analyses will be performed after database has been locked, using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock. All analyses will be performed for total subjects and by initial dose group (if applicable).

9.7.1.1 Study Endpoints

PRIMARY ENDPOINTS

Dose limiting toxicity (DLT)

Safety variables (AEs, clinical laboratory results, vital signs, weight, ECG, ECOG-PS, LVEF)

SECONDARY ENDPOINTS

PK parameters including C_{max}, t_{max}, AUC of lenvatinib and everolimus

Best overall response (BOR), objective response rate (ORR), DCR, disease control rate (DCR) and change from baseline in sum of diameters of target lesion (if appropriate)

9.7.1.2 Definitions of Analysis Sets

DLT Analysis Set is the group of subjects who have completed treatment Cycle 1 without major protocol deviation with at least 75% of treatment compliance and were assessed for DLT, and subjects who have experienced DLT during Cycle 1. Subjects with less than 75% treatment compliance to lenvatinib or everolimus due to a reason other than toxicity up to Cycle 1 Day 28 will not be included in this analysis set.

Safety Analysis Set/Efficacy Analysis Set is the group of subjects who received at least 1 dose of lenvatinib.

Pharmacokinetic (PK) Analysis Set is the group of subjects who received at least 1 dose of lenvatinib and had sufficient PK data to derive at least one PK parameter.

9.7.1.3 Handling of Data

Details of handling on missing data, rejected data, and abnormal data will be provided in the SAP.

9.7.1.4 Subject Disposition

Screening subjects table will include the number of subjects who are enrolled (ie, subjects who signed informed consent), are eligible, failed screening, the primary reason, and other reason for screen failures. Subject disposition table will include the number of subjects who are treated/not treated, completed/discontinued the study, the primary reason, and other reason for the study discontinuation. Similarly, the number of subjects who completed/discontinued the study treatment, the primary reason, and, other reason for the study treatment discontinuation will also be summarized.

A subject who completed the study is defined as whose DLT assessment has been completed adequately. A subject who completed the study treatment is defined as who discontinued study treatment due to disease progression or study cut-off.

9.7.1.5 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safe Analysis set will be summarized. Continuous demographic and baseline variables include age, weight; categorical variables include sex, race, ethnicity, ECOG-PS, diagnostic information (site of primary lesion, histological type, disease stage), and prior therapy (surgery, radiotherapy, anti-cancer medication, and other therapies), if any.

9.7.1.6 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set), Anatomical Therapeutic Chemical (ATC) class (ie, <specify relevant ATC classes> *[eg, anatomical class, therapeutic class, pharmacologic class, chemical class]*), and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.7 Efficacy Analyses

ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

Since this study is phase 1, primary endpoint is not defined.

Efficacy analyses will be based on the Efficacy Analysis Set. Best overall response (BOR) will be summarized using RECIST 1.1. BOR consists of CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease) and NE (not evaluable). ORR (objective response rate) and DCR (disease control rate) will be calculated with an exact 2-side 95% CI. ORR is defined as the proportion of subjects who have BOR of CR or PR. DCR is defended as the proportion of CR, PR or SD.

Subjects with non-target disease only will be assigned to SD category if the BOR is non-CR/non-PD. SD has to be achieved at ≥7 weeks after first dose. CR and PR do not have to be confirmed at ≥4 week's assessment. If applicable, a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at postbaseline nadir. If applicable, time profiles of tumor marker will be plotted and investigated.

ANALYSIS OF THE SECONDARY EFFICACY ENDPOINT

Not applicable.

ANALYSIS OF THE EXPLORATORY EFFICACY ENDPOINT

Not applicable

9.7.1.8 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

PHARMACOKINETIC ANALYSES

Lenvatinib plasma concentrations and everolimus whole-blood concentrations will be summarized and listed for the subjects who have at least 1 evaluable data in the Safety Analysis Set. The PK Analysis Set will be used for all other analyses including summaries of lenvatinib plasma concentrations, everolimus whole-blood concentrations and PK parameters. Concentrations – time profiles of lenvatinib and everlolimus will be plotted and investigated. Using non-compartmental analysis methods, plasma concentrations of lenvatinib and whole-blood concentration of everolimus will be calculated to determine the PK parameters including C_{max}, t_{max}, AUC at first administration (Cycle 1 Day 1) and repeated administration (Cycle 1 Day 15).

PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.9 Safety Analyses

All tolerability analyses will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity. The Safety Analysis Set will be used for all other safety analyses. The number and percentage of subjects with all AEs and SAEs observed after first dosing will be summarized and listed by SOC, PT, and severity. Summary statistics will be presented for laboratory test values, vital sign, and 12-lead ECG parameters. If needed, the changes from baseline will also be summarized.

EXTENT OF EXPOSURE

The number of cycles, duration of treatment, total exposure time, total number and dose of the drug administered, dosing strength, and total ratio of dosage administered/total dosage planned will be summarized for both lenvatinib and everolimus in each subject.

ADVERSE EVENTS

1. Analysis of DLT

Tolerability analyses will be performed using the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity.

2. Analyses of AEs

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

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during and up to 30 days of treatment, having been absent at pretreatment (Baseline) or:

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

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

The number (percentage) of subjects with TEAE will be summarized by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will be summarized by highest grade according to CTCAE ver. 4.03.

The number (percentage) of subjects with treatment-related (lenvatinib or everolims) TEAEs will be summarized by MedDRA SOC and PT. The number (percentage) of subjects with treatment-related TEAEs will be summarized by highest CTCAE grade.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) or TEAEs leading to death, study drug withdrawal, and dose reduction or dose interruption will be summarized by MedDRA SOC and PT. Subject data listings of all serious adverse

events, AEs leading to death, leading to discontinuation from study treatment, dose reduction and dose interruption will be provided.

LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters listed in Section 9.5.1.3.3, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using descriptive statistics. Qualitative parameters will be summarized by number and percentage of subjects, and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. CTCAE v4.03 will be used to identify subjects with treatment emergent markedly abnormal laboratory values (TEMAV). A TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

VITAL SIGNS

Summary statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, and temperature), and weight and changes from baseline will be presented by visit.

ELECTROCARDIOGRAMS

The results of ECG assessments performed at each visit will be evaluated. Summary statistics for ECG parameters and changes from baseline will be presented by visit.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit.

In addition, the number (percentage) of subjects who met below criteria at least once in QTcF will be presented:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

OTHER SAFETY TESTS

1. LVEF

Electrocardiograms or multiple-gated acquisition technique will be performed at each site. LVEF and change from baseline will be summarized at each visit.

2. ECOG-PS

ECOG PS will be summarized by scale at each visit and by highest postbaseline scale.

9.7.2 Determination of Sample Size

The primary objective of this study is to investigate the tolerability and safety of lenvatinib in combination with everolimus. Hence neither clinical hypothesis nor judgement criteria are set, the sample size is not based on statistical consideration. The 6 to 12 subjects per initial dose group are considered to be adequate to obtain some preliminary data for the assessment of safety.

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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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 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 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 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.

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 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 IRB/IEC review.

In accordance with GCP, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, QOL, 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 source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

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

11.5 Identification of Source Data

All medical records (1) to (8) will not be considered source data.

1. For the followings, data recorded directly on the CRF are to be considered source data
   - Demographic data (age, race, etc.)
   - NYHA cardiac function classification – date of evaluation, NYHA class
   - Treatment history: Name, starting and ending date of the medication, starting dosage and reason for discontinuation
   - ECG results- normal/abnormal
   - Results of follow-up evaluation in subject who discontinued – in all categories

- Tumor evaluation : TNM classification
- Tumor assessment: presence of target and non-target lesion
- Target lesion: location, size in diameter, evaluation date and time
- Non-target lesion: location, evaluation date and time
- Newly discovered lesion : location and date of confirmation, if present
- Dose and dosing date of lenvatinib and everolimus
- Drug concentration measurement : dates and time of dosing, blood sampling, and food consumptions
- Discontinuation : reason for discontinuation
- Information concerning AEs: CTC AE Grade (for items not specified in CTC), outcome, causal relationship to lenvatinib and/or everolimus, severity of the AE, relation to overdose
- Concomitant drug (s) : reason for administration
- Concomitant therapy(ies): type of therapy, condition for which are being treated
- Other relevant information

2. Source data for informed consent

Informed consent form

3. Source data for tests and examinations

Test results sheet (and/or electronic data)

4. Source data for pathological assessment

Test results sheet (and/or electronic data)

5. Source data for tumor assessment

Imaging record (and/or electronic form). CSR is to be considered source data for assessment if it includes measured values

6. Source data for ECG recordings

Recorded ECG charts (and/or electronic data)

7. Shipping record of samples to outside laboratories

Shipping slip

8. Source data for subject enrollment

Subject enrollment form, list of enrolled subjects, list of ineligible subjects, etc.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator, 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, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 3 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications 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 the 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. A government regulatory authority may request inspections during the study or after its completion.

11.8 Handling of Study Drug

All study drugs will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing 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.

12 APPENDICES

Appendix 1: NYHA Cardiac Disease Classification

Appendix 2: Names of Drug Affecting Drug Metabolizing Enzyme CYP3A4 and P-gp Activities

Appendix 3: Study Administrative Structure

Appendix 4: Drug Labeling and Packaging

Appendix 5: Subject Enrollment Form

Appendix 6: TNM classification for renal cell carcinoma

Appendix 7: RECIST-Based Tumor Assessment

Appendix 8: Procedures for Collecting, Handling, and Shipping Blood Samples for Drug Concentration Measurements

Appendix 9: ECOG Performance Status

Appendix 10: Serious Adverse Event Report

Appendix 11: Pregnancy Report

Appendix 12: Pregnancy Outcome Report