- To explore blood biomarkers that correlate with efficacy-related endpoints of this study.
- To develop exposure/biomarker/clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data that will allow exploration of alternative dosing regimens with a better efficacy/safety profile than the lenvatinib 18-mg plus everolimus 5-mg dose.

Study Design

Originally, this was a multicenter, randomized, double-blind study conducted as a postmarketing requirement by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to evaluate an alternate dose regimen for lenvatinib in combination with everolimus. As of 14 Jul 2018, all ongoing subjects' treatment assignment has been unblinded to investigational site personnel, and the study will be conducted in an open-label fashion. The investigational site personnel and study subjects will be unblinded as to the treatment assignment for all newly enrolled subjects.

In subjects with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic treatment, the current approved lenvatinib dose is 18 mg daily in combination with everolimus 5 mg daily. This study will evaluate the combination of lenvatinib and everolimus in subjects with advanced predominant clear cell RCC following one prior vascular endothelial growth factor (VEGF)-targeted treatment at 14-mg starting dose of lenvatinib and allow up-titration of lenvatinib to determine whether this regimen provides comparable efficacy but has a better safety profile than the 18-mg starting dose. The 14-mg starting dose will be escalated to 18 mg if no Grade 2 (intolerable) or any ≥ Grade 3 treatment-emergent adverse events (TEAEs) that require dose reduction are observed in the first cycle (4 weeks) of treatment. If Grade 2 (intolerable) or Grade 3 or 4 TEAEs are observed, the lenvatinib dose will be reduced, as described below in the dose reduction section. Both lenvatinib and everolimus will be administered orally (PO) and once daily (QD).

Eligible subjects will have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and will be randomly assigned to each treatment arm in a 1:1 ratio. The total sample size will be approximately 338 subjects. Randomization will follow a predefined randomization scheme based on the following stratification factors: Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate, or poor risk); and whether subjects have had a prior PD-1/PD-L1 treatment (yes or no).

Subjects will receive study treatment as continuous 28-day cycles. Treatment cycles will be counted continuously regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments and in the Schedule of Assessments after the Data Cutoff for the Primary Analysis. After the data cutoff for the primary analysis subjects, will be eligible to receive study treatment as continuous 56-day cycles.

Subjects will discontinue study treatment upon evidence of progressive disease, as judged by the Investigator. After disease progression, subjects will be followed for survival and PFS2 until data cutoff for the primary analysis.

This study will consist of 2 phases, the Prerandomization Phase, and the Randomization Phase with treatment continuing after the data cutoff for the primary analysis.

The **Prerandomization Phase** will last no longer than 28 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the sponsor.

The **Randomization Phase** will consist of a Treatment Period and a Follow-up Period. It will begin at the time of randomization of the first subject and will end at the data cutoff for the primary analysis, which is defined as when all randomized subjects complete the Week-24 tumor assessments or discontinue study treatment before Week 24. Subjects will be randomly assigned to treatment in a

Abbreviation	Term
FKSI-DRS	Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms
GCP	Good Clinical Practice
HRQoL	Health-Related Quality of Life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICL	imaging core laboratory
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IxRS	Interactive voice and web response system
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MSKCC	Memorial Sloan-Kettering Cancer Center
MUGA	multigated acquisition scan
N	number of subjects
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	objective response rate
ORR_{24W}	objective response rate at 24 weeks
OS	Overall survival
PRES/RPLS	posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome
PD	progressive disease or pharmacodynamic
PFS	progression-free survival
PFS2	progression-free survival after next line of therapy
PI	principal investigator or package insert
PR	partial response
PRO	patient-reported outcomes

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess progression-free survival (PFS)
- To assess ORR
- To determine the tolerability and safety profile of lenvatinib in combination with everolimus
- To assess the proportion of subjects who discontinued treatment due to toxicity
- To assess time to treatment failure due to toxicity
- To assess pharmacokinetic (PK) profiles of lenvatinib and everolimus during combination therapy and to assess PK and pharmacodynamics (PD) drug-drug interactions
- To evaluate overall survival (OS)
- To evaluate the impact of disease and treatment on patients' Health-Related Quality of Life (HRQoL) as assessed by using the Functional Assessment of Cancer Therapy - Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L
- To evaluate the PFS after next line of treatment (PFS2)

8.3 Exploratory Objectives

The exploratory objectives of the study are:

- To explore tumor response parameters (ORR_{24W}, ORR, PFS) based on blinded independent imaging review (IIR) for efficacy assessment
- To explore blood biomarkers that correlate with efficacy-related endpoints of this study
- To develop exposure/biomarker/clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data that will allow exploration of alternative dosing regimens with a better efficacy/safety profile than the lenvatinib 18-mg plus everolimus 5-mg dose

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

Originally, E7080-G000-218 was designed as a multicenter, randomized, double-blind study, conducted as a postmarketing requirement of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to evaluate an alternate dose regimen for lenvatinib in combination with everolimus. As of 14 Jul 2018, all ongoing subjects' treatment assignment has been unblinded and the study will be conducted in an open-label fashion. The investigational site personnel will be unblinded as to treatment assignment for all newly enrolled subjects. Lenvatinib 18 mg daily in combination with everolimus 5 mg

daily is approved in the US and EU for the treatment of adult patients with advanced RCC following 1 prior VEGF-targeted therapy.

This study will evaluate the combination of lenvatinib and everolimus at a 14-mg starting dose of lenvatinib and allow up-titration of lenvatinib to determine whether this alternate dose regimen provides comparable efficacy but has a better safety profile than the 18-mg starting dose in this subject population. The 14-mg starting dose will be escalated to 18 mg if no Grade 2 (intolerable) or any ≥ Grade 3 TEAEs that require dose reduction are observed in the first cycle (4 weeks) of treatment. If Grade 2 (intolerable) or Grade 3 or 4 TEAEs are observed, the lenvatinib dose will be reduced, as described in the dose reduction section (Section 9.4.2). Both lenvatinib and everolimus will be administered orally (PO) and daily (QD).

Eligible subjects will have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and will be randomly assigned to each treatment arm in a 1:1 ratio. The total sample size will be approximately 338 subjects. Randomization will follow a predefined randomization scheme based on the following stratification factors: Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate, or poor risk); and whether subjects have had a prior PD-1/PD-L1 treatment (yes or no).

Subjects will receive study treatment as continuous 28-day cycles. Treatment cycles will be counted continuously regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 6) and in the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). After the data cutoff for the primary analysis subjects will be eligible to receive study treatment as continuous 56-day cycles.

Subjects will discontinue study treatment upon evidence of progressive disease, as judged by the investigator. After disease progression, subjects will be followed for survival and PFS2 until the data cut-off for the primary analysis.

This study will consist of 2 phases, the Prerandomization Phase and the Randomization Phase with treatment continuing after the data cutoff for the primary analysis. An overview of the study design is presented in Figure 8.

The data cutoff for the primary analysis will occur when all randomized subjects in the Randomization Phase have completed Week 24 assessments or have discontinued study treatment prior to Week 24. After the primary analysis is completed, subjects still receiving study treatment may continue taking lenvatinib and everolimus after the data cutoff for the primary analysis. Subjects will continue to receive investigational product after the data cutoff for the primary analysis until

they complete the Off-treatment visit. The definition of the **End of Study** is the last subject's last assessment (Off-Treatment Visit) after the data cutoff for the primary analysis.

The data obtained after the data cutoff for the primary analysis will be summarized and included in the CSR at the end of study as an addendum.

1. Histological or cytological confirmation of predominant clear cell RCC (original tissue diagnosis of RCC is acceptable).
2. Documented evidence of advanced RCC.
3. One prior disease progression episode on or after vascular endothelial growth factor (VEGF)-targeted treatment (for example, but not limited to, sunitinib, sorafenib, pazopanib, cabozantinib, bevacizumab, axitinib, vatalanib, AV951/ tivozanib) administered for the treatment of RCC. Prior PD-1/PD-L1 treatment in addition to 1 prior VEGF-targeted treatment is allowed.
4. At least 1 measurable target lesion according to RECIST 1.1 meeting the following criteria:
   - Lymph node (LN) lesion that measures at least 1 dimension as ≥1.5 cm in the short axis
   - Non-nodal lesion that measures ≥1.0 cm in the longest diameter
   - The lesion is suitable for repeat measurement using computerized tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.
5. Male or female subjects age ≥18 years (or any age >18 years if that age is considered to be an adult per the local jurisdiction) at the time of informed consent.
6. Karnofsky Performance Status (KPS) of ≥70.
7. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week before the Cycle 1/Day 1.
8. Adequate renal function defined as calculated creatinine clearance ≥30 mL/min per the Cockcroft and Gault formula (Appendix 1).
9. Adequate bone marrow function defined by:
   - Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 x 10^9/L)
   - Platelets ≥100,000/mm^3(≥100 x 10^9/L)
   - Hemoglobin ≥9 g/dL
10. Adequate blood coagulation function defined by International Normalized ratio (INR) ≤1.5 (except for subjects on warfarin therapy where INR must be ≤3.0 prior to randomization).
11. Adequate liver function defined by:
    - Total bilirubin ≤1.5 x ULN except for unconjugated hyperbilirubinemia of Gilbert's syndrome
    - Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN) Subjects with bone metastases with ALP values greater than 3 times can be included.
12. Subject must voluntarily agree to provide written informed consent.
13. Subject must be willing and able to comply with all aspects of the protocol.

At every dose change, the investigator or a designee will call the Interactive Voice and Web Response System (IxRS) to register the subject's visit (see the IxRS Manual for further instructions). At each of these postrandomization visits, the investigator will select the subject's appropriate treatment dose in accordance with the protocol. As of 01 Oct 2020, the IxRS will be discontinued. Refer to the revised Pharmacy Manual for complete instructions.

9.4.2.2 Management of Hypertension

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

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) is confirmed on 2 assessments a minimum of 30 minutes apart. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. After the data cutoff for the primary analysis, one BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is first observed on 2 assessments a minimum of 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib 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 mmHg, 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.

During the Treatment Period, subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently as clinically indicated until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 1 treatment cycle (ie, 56-day cycle). If a repeat event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day-15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 1 treatment cycle (ie, 56-day cycle).

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

1. Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving this.

Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity," should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

9.4.2.10 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS) were reported for less than 1% of lenvatinib-treated subjects. PRES/RPLS 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/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES/RPLS, instructions contained in Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity," should be followed.

9.4.2.11 Management of Hypocalcemia

Serum calcium should be monitored per the Schedule of Procedures/Assessments. Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v4.03, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] x 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

9.4.3 Identity of Investigational Products

The study drug under evaluation in this study is lenvatinib 14 mg and 18 mg in combination with everolimus 5 mg. Lenvatinib will be packaged in a double-blind configuration (until the current supply is exhausted) and will be supplied as 4-mg and 10-mg capsules (and matching placebo) by the sponsor. The sponsor may substitute drug supply without placebo capsules when resupplying study drug. In addition, the sponsor may make changes to the packaging of lenvatininb at its discretion. Changes may include the use of child-resistant bottles rather than child-resistant wallets. Child-resistant bottles will not include placebo. Lenvatinib is formulated with calcium carbonate, d-mannitol, microcrystalline cellulose,

Medical and surgical histories will be obtained during the Prerandomization Phase, along with a record of prior and concomitant medications.

Physical examinations (comprehensive or symptom-directed) will be performed as specified in the Schedule of Procedures/Assessments (Table 6) and the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination.

A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to the start of study drug will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Subjects must have measurable disease according to RECIST 1.1 as defined in Inclusion Criterion #4 (Appendix 8). Subjects must also fulfill the medical and physical characteristics identified in the inclusion criteria and not otherwise meet any of the exclusion criteria.

9.5.1.2 Efficacy Assessments

Tumor assessments will be performed using RECIST 1.1 (Appendix 8). Investigator-determined response assessments will be performed at each assessment time point and entered onto the case report form (CRF). Copies of all tumor assessment scans will be sent to an ICL designated by the sponsor for blinded independent efficacy assessment until the data cutoff for the primary analysis. For subjects enrolled after implementation of Amendment 06, tumor assessments will be carried out following the guidelines provided by the ICL.

Tumor assessments (computed tomography [CT] chest, and CT or MRI abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Prerandomization Phase and then, during the Randomization Phase, every 8 weeks (within the 8th week) until documentation of progressive disease as determined by the investigator and on a schedule as determined by the treating physician after the data cutoff for the primary analysis, but not less frequently than every 12 weeks or earlier if clinically indicated. Historical CT or MRI scans performed within 28 days of randomization but before informed consent may be used as screening scans provided they meet minimum standards as separately defined by the ICL. The same imaging modality and image-acquisition protocol (including use or nonuse of contrast) should be used consistently across all time points. All responses must be confirmed no less than 4 weeks following the initial indication of response. A chest x-ray or a skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

A bone scan (^{99}m-technetium-based scintigraphy, whole-body bone MRI, or ^{18}F-sodium fluoride positron emission tomography [NaF PET]) will be performed during the Prerandomization Phase to establish a baseline (a historical bone scan performed within 6 weeks prior to randomization is acceptable), every 24 weeks after randomization, within a

target of 1 week but no more than 2 weeks following a complete response (CR) as assessed by the investigator, and as clinically indicated after the data cutoff for the primary analysis. Lesions identified on bone scans should be followed at all tumor assessment time points with cross-sectional imaging.

A brain scan will be performed at screening and as clinically indicated thereafter, and within a target of 1 week but no more than 2 weeks following achievement of a confirmed CR. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all protocol-specified tumor assessment time points (eg, every 8 weeks). Subjects with protocol-eligible treated brain metastases should also have brain CT/MRI performed as per local standard of care. For other subjects, brain scans should be performed as clinically indicated.

Stable disease must be achieved at ≥7 weeks after randomization to be considered best overall response. Subjects going off treatment without disease progression in the Treatment Period will continue to undergo tumor assessments in the Follow-up Period per the above schedule until disease progression is documented, another anticancer therapy is initiated, or data cutoff for the primary analysis.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Sparse PK samples (plasma for lenvatinib and whole blood for everolimus) will be collected from all subjects and will be analyzed using a population PK approach (PopPK). The timing for obtaining the 7 PK sampling time points (one tube each for lenvatinib and everolimus PK) is shown in the Schedule of Procedures/Assessments (Table 6) and Table 4. See the Laboratory Manual for a description of collection, handling, and shipping procedures for PK samples. A separate statistical analysis plan will be developed for the PopPK analysis.

Table 4 Pharmacokinetic Sampling Time Points

Time Point	Sample Number	Time (h)
Cycle 1/Day 1	1	0.5-4 h postdose
	2	6-10 h postdose
Cycle 1/Day 15[a]	3	Predose on Day 15 (Cycle 1)
	4	0.5-4 h postdose
	5	6-10 h postdose
Cycle 2 Day 1	6	Predose on Day 1 (Cycle 2)
	7	2-12 h postdose

h = hour(s).
a If dose interruption is necessary in these time points, only predose sample should be collected.

9.5.1.3.2 PHARMACODYNAMIC AND OTHER BIOMARKER ASSESSMENTS

Pharmacodynamic and Other Biomarker Assessments

Blood samples will be collected for peripheral blood mononuclear cell (PBMC) and plasma isolation from all study subjects at protocol specified time points, during the Randomization Phase of the study, as indicated in the Schedule of Procedures/Assessments (Table 6). There will be no further biomarker sample collection after the data cutoff for the primary analysis. Biomarker discovery or validation will be performed to identify blood biomarkers that may be useful to measure subject response to study drug, to understand the underlying disease biology, to provide further insight into the mechanism of action of the study drug as well as for potential use in diagnostic development.

These samples may undergo enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay and/or other appropriate analysis procedures to explore blood biomarkers (eg, VEGF, Ang-2). In addition, other pharmacodynamics target engagement and response biomarkers related to study drug may be assessed. See Appendix 12 for description of sample collection and handling, procedures for securing and retention of samples, and subject privacy information).

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual (see also Appendix 12).

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v4.03 grades (for both increasing and decreasing severity) and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and electrocardiograms (ECGs); and performance of physical examinations during the Randomization Phase. An echocardiogram or a MUGA scan including LVEF will be performed at screening, and as clinically indicated. After the data cutoff for the primary analysis, all AEs leading to study discontinuation, SAEs and concomitant medications will be monitored and recorded. Hematology and blood chemistry will be monitored prior to administration of study drug and as clinically indicated. Urine dipstick testing will be monitored at each visit and as clinically indicated. A serum or urine pregnancy test will be performed during the study for women of childbearing potential. A symptom-directed physical examination and vital signs (resting BP, HR, RR and body temperature) will be performed at each visit and as clinically indicated. A 12-lead ECG and Echocardiogram/MUCA scan will be performed as clinically indicated (Table 7).

Progression of RCC and signs and symptoms clearly related to the progression of RCC should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

9.5.1.4.1 Adverse Events and Events Associated with Special Situations

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are lenvatinib and everolimus.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease 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 (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. All AEs and SAEs will be collected for 28 days after the last dose.

After the data cutoff for the primary analysis, all AEs leading to study drug discontinuation and SAEs will be recorded until 28 days after the last dose of study drug. SAEs, irrespective of relationship to study drug, must be reported as soon as possible but not later than 24 hours from the date when the investigator becomes aware of the event.

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

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

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. Subjects with onset of an AE or deterioration of a preexisting AE will be followed until resolution to baseline, start of a new anticancer treatment, or death. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

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

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

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

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

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

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution. A blood sample to measure study drug plasma concentrations will no longer be needed after the data cutoff for the primary analysis.

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urine dipstick testing, and a serum or urine pregnancy test (for female subjects of childbearing potential), are summarized in Table 5. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 6) and the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7) shows the visits and time points at which blood for clinical laboratory tests and urine for dipstick testing (and possible 24-hour urine collection to quantify the 24-hour urine protein excretion) will be collected in the study.

Clinical laboratory tests during the Randomization Phase of the study will be performed by a central laboratory. All blood and urine samples (except urine sample for urine dipstick) will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern or to guide clinical dosing, a local laboratory may be used in addition to the central laboratory testing. If central laboratory results are not available within the necessary timeframe to allow the subject to be enrolled, local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study. After the data cutoff for the primary analysis, clinical laboratory tests can be performed by the local laboratory and samples will no longer be sent to the central laboratory.

Urine dipstick testing will be performed, preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site).

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with automated differential (including absolute neutrophil count and absolute lymphocyte count) INR[a]
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, magnesium, phosphorous, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function tests[b]	Thyroid stimulating hormone, free T4 level
Other	Albumin, cholesterol, glucose[c], lactate dehydrogenase, total protein, triglycerides, amylase, lipase, creatine kinase Serum or urine pregnancy test[d] (β-hCG or hCG)
Urine Dipstick Testing[e]	glucose, hemoglobin (or blood), ketones, pH, protein[f], specific gravity

Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 1 and Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 1 treatment cycle (ie, 56-day cycle). A diary will be provided to the subject to capture the BP evaluations between study visits. See subsection for management of hypertensive subjects (Section 9.4.2.2).

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 6) and in the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF. A symptom-directed physical examination will be performed as clinically indicated.

9.5.1.4.6 ELECTROCARDIOGRAMS

ECGs will be performed during screening and every 4 weeks on Day 1 of each cycle during the Randomization Phase beginning with Cycle 2 and at the Off-Treatment Visit (Table 6). After the data cutoff for the primary analysis, ECGs may be performed as clinically indicated (Table 7). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects are suggested to be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.4.7 ECHOCARDIOGRAM OR MULTIPLE GATED ACQUISITION SCAN

A MUGA scan (using technetium-^{99}m-pertechnetate) or an echocardiogram to assess LVEF will be performed at Screening and as clinically indicated (Table 6) and (Table 7). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at Baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

9.5.1.4.8 PREGNANCY TEST

A serum or urine pregnancy test (β-hCG or hCG with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than

Table 6 Schedule of Procedures/Assessments in E7080-G0000-218

Phase	**Prerandomization Phase**		**Randomization Phase All cycles are 28 days in duration**								
Period	**Screening[a]**	**Baseline[a]**	**Study Treatment Period[b]**							**Off-Tx**	**Follow- Up**
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7, 9, etc.**	**8, 10, 12, 14, etc.**		
			Cycle 1			**Cycle 2**		**Cycles 3 - Last**			
Day	**-28 to -3**	**-3 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**15**	**99**	
Procedures/Assessments											
Informed consent	X										
Medical/surgical history	X	X									
Demographic data	X										
KPS[c]	X	X				X		X			
NYHA[c]	X										
AJCC staging[d]	X										
Inclusion/exclusion	X	X									
Randomization		X									
Vital signs[e]	X	X	X		X	X	X	X	X	X	
Physical examination[f]	X	X[g]			X	X		X		X	
12-lead ECG[h]	X					X		X		X	
Echocardiogram/MUGA scan[i]	X		As clinically indicated								
Pregnancy test[j]	X	X				X		X		X	

forwarded to the sponsor and/or the designated CRO, depending on responsibility for regulatory documents, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 8 weeks of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 8 weeks 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 Reporting of Serious Adverse Events [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 24 hours from when the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from when the investigator becomes aware of the event of the outcome.

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

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

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

healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling/packaging/nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

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

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, 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 described above.

9.5.4.5 Breaking the Blind

As of 14 Jul 2018, the subjects' treatment assignment is no longer blinded.

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.

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

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 6) and Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary

measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

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

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

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 ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

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

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

- Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a subject discontinues study treatment due to TEAEs.
- Lenvatinib and everolimus exposure parameters and PK and PD drug-drug interactions.
- Overall survival (OS), measured from the date of randomization until date of death from any cause. In the absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or the date of data cutoff for the primary analysis, whichever comes earlier.
- Health-Related Quality of Life (HRQoL) will be assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L instruments.
- PFS2, defined as the time from randomization to the date of disease progression after next line of therapy or death from any cause or the date of data cutoff for the primary analysis, whichever occurs first. PFS2 censoring rules will be defined in the SAP.

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Tumor response endpoints ORR_{24W}, ORR, and PFS based on IIR assessment. These endpoints will be defined in the same way as those based on the investigator assessments.
- Associations between blood biomarker and efficacy related endpoints.
- Development of exposure/biomarker/clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data.

9.7.1.2 Definitions of Analysis Sets

Full Analysis Set will include all randomized subjects. This will be a secondary analysis set for efficacy endpoints, which will be analyzed according to the treatment randomized, regardless of the treatment actually received.

Per-Protocol Analysis Set 1 will include all randomized subjects minus the 32 subjects who had received ≥2 incorrect lenvatinib doses due to IxRS issues. This will be the primary analysis set for efficacy endpoints, which will be analyzed according to the treatment randomized.

Per-Protocol Analysis Set 2 will include all subjects who received at least 1 dose of study drug, had no major protocol deviations, and had both baseline and at least 1 post-baseline tumor assessment. Subjects for whom death occurred before the first post-baseline tumor assessment will also be included. The Per-Protocol Analysis Set 2 will be a secondary analysis set for efficacy endpoints. The 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues are considered as having experienced major protocol deviations and will be excluded from the Per-Protocol Analysis Set 2. (A 33rd subject received a single incorrect lenvatinib dose due to IxRS issues, but given the brief exposure of the incorrect [slightly higher] dose before detection and correction, and because there were no adverse

effects, this subject will be considered to have experienced a minor protocol deviation and will not be excluded from analysis sets.)

Safety Analysis Set will include all subjects who were randomized and received at least 1 dose of study drug. This will be the analysis set for all safety evaluations, which will be analyzed according to the treatment actually received.

Per-Protocol Safety Analysis Set will include all treated subjects in Per-Protocol Analysis Set 1. This will be the primary analysis set for the primary safety endpoint, which will be analyzed according to the treatment actually received.

Pharmacokinetic (PK) Analysis Set will include all subjects who received at least 1 dose of study drug with documented dosing history and have at least 1 evaluable lenvatinib plasma or everolimus whole blood concentration data.

Pharmacodynamic Analysis Set will include all subjects who received at least 1 dose of study drug with documented dosing history and have at least 1 evaluable pharmacodynamic data.

For the Pharmacokinetic, Pharmacodynamic and other Biomarker endpoints, their respective analysis plans will specify if the analysis set will or will not include the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues

Quality of Life (QoL) Analysis Set will consist of all subjects who have any QoL data.

The analysis sets are summarized in the following table.

Analyses for:	**Efficacy Parameters**	**Safety Parameters**
Analysis Set:	**Full Analysis Set**	**Safety Analysis Set**
Definition:	All subjects randomized	All randomized subjects who received at least 1 dose of study drug
Used as:	A secondary analysis set for efficacy endpoints	An analysis set for safety parameters
Analysis Set:	**Per-Protocol Analysis Set 1**	**Per-Protocol Safety Analysis Set**
Definition:	All randomized subjects minus the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues	All treated subjects minus the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues
Used as:	The primary analysis set for the primary efficacy endpoint	The primary analysis set for the primary safety endpoint
	An analysis set for the secondary efficacy endpoints	An analysis set for other safety parameters
For interim analyses:	The analysis set for the planned 2 interim analyses of the primary efficacy endpoint	The analysis set for the planned two interim analyses of the primary safety endpoint

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.

An overview table, including the incidence of and the number of subjects with TEAEs, SAEs, deaths, and those TEAEs that led to study drug discontinuation, dose modification, or dose interruption will be provided.

The incidence of TEAEs will be summarized by system organ class (SOC), preferred term (PT), CTCAE grade, and relatedness to study drug. All summaries will be performed by treatment group. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that MedDRA term with the highest CTCAE grade (in the summary by CTCAE grade) or with the closest relationship to study treatment (in the summary by relatedness to study treatment).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

In addition, the overall proportion of subjects with TEAEs of CTCAE Grade 3 or higher and the overall proportion of subjects with intolerable CTCAE Grade 2 TEAEs that result in dose modification will be summarized.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment arm using descriptive statistics. Laboratory parameters will be categorized according to CTCAE v4.03. Grades, and shifts from baseline CTCAE Grade to worst postbaseline Grade will be assessed using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and at least 1 postbaseline result.

Common Terminology Criteria for Adverse Events v4.03 (Appendix 3) will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). A more detailed definition of TEMAV will be specified in the SAP. A summary of TEMAVs will be presented by treatment arm.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, and weight) and changes from baseline will be presented by visit and treatment group. Subjects will be included in the summary if they had both a Baseline value and at least 1 postbaseline value.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and by treatment group. Shift tables will present changes from baseline in ECG

Phase	**Prerandomization Phase**		**Randomization Phase All cycles are 28 days in duration**								
Period	**Screening[a]**	**Baseline[a]**	**Study Treatment Period[b]**							**Off-Tx**	**Follow-Up**
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7, 9, etc.**	**8, 10, 12, 14, etc.**	**99**	
			Cycle 1			**Cycle 2**		**Cycles 3 - Last**			
Day	**-28 to -3**	**-3 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**15**		
Procedures/Assessments											
Clinical chemistry/hematology[k]	X	X			X	X	X	X		X	
Urine dipstick testing[l]	X	X			X	X	X	X[l]		X	
Study drug administration			Once daily								
PK blood samples[m]			X		X	X					
Tumor assessments (CT/MRI)[n]	X		Performed every 8 weeks (counting from date of randomization), or sooner if clinically indicated, until documentation of disease progression							X	X
Bone scan[o]	X		Every 24 weeks, and as clinically indicated, and to confirm CR								
Brain scan (CT/MRI)[p]	X		X								
HRQoL[q]		X				X		X		X	
Phone contact or visit[r]				X							
Prior /Concomitant meds[S]	Throughout										Only anticancer Tx recorded during Follow-up Period
AEs/SAEs[t]	Throughout										
PFS2 and Survival[u]											X

administration of study drug for all cycles. Assessments may be performed within 72 hours prior to the visit.

h. Urine dipstick testing for subjects should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site). For subjects with a dipstick proteinuria ≥2+, see section 9.4.2.3 for management of proteinuria.

i. After the data cutoff for the primary analysis: Tumor assessments using contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis and other areas of known disease at screening or newly suspected disease should be performed as per local standard of care but not less frequently than every 12 weeks or earlier if clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques that were used for the assessment during the Prerandomization and Randomization Phases should be used after the data cutoff for the primary analysis. Scans will no longer be sent to the imaging core lab after the data cutoff for the primary analysis.

j. A bone scan to assess bone metastases should be performed as clinically indicated.

k. Subjects with protocol-eligible treated brain metastases should also have brain CT/MRI performed as per local standard of care. For other subjects, brain scans should be performed as clinically indicated.

l. All AEs leading to study drug discontinuation and SAEs will be recorded until 28 days after the last dose of study drug. SAEs, irrespective of relationship to study drug, must be reported as soon as possible but not later than 24 hours from the date when the investigator becomes aware of the event.

m. Concomitant medications will be recorded until 28 days after last dose.

9.1.1 Prerandomization

The Prerandomization Phase will last no longer than 28 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment.

9.1.1.1 Screening Period

Screening will occur between Day -28 and Day -3. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility according to the inclusion and exclusion criteria listed in Sections 9.3.1 and 9.3.2, respectively. The screening assessment can serve as the baseline assessment if performed within 72 hours before randomization. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a histological or cytological confirmed diagnosis of predominant clear cell RCC (original tissue diagnosis is acceptable) and documented evidence of advanced RCC.

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

9.1.1.2 Baseline Period

The baseline assessment can be performed from Day -3 through Day -1 or prior to randomization on Cycle 1/Day1. The screening assessment can serve as the baseline assessment if performed within 72 hours before randomization. Laboratory tests and a pregnancy test (for female subjects of childbearing potential) may be performed up to 72 hours before randomization.

Subjects who complete the Baseline Period and meet the criteria for inclusion and exclusion (Sections 9.3.1 and 9.3.2, respectively) will begin the Randomization/Treatment Phase.

9.1.2 Randomization Phase

The Randomization Phase will begin at the time of randomization of the first subject and will include both a Treatment Period and a Follow-Up Period. The data cut off for the primary analysis will occur at the end of the Randomization Phase, which is defined as when the last subject enrolled completes the Week-24 tumor or discontinues study treatment prior to Week 24. Subjects will be randomized in a 1:1 ratio. After the data cut off for the primary analysis, subjects who are still on study treatment will continue to receive investigational product until they complete the Off-Treatment Visit. The last subject last visit will be the date of the Off-Treatment Visit for the last subject's last assessment after the data cutoff for the primary analysis.

Appendix 4 Karnofsky Performance Status

Karnofsky Performance Status Scale		
Definitions	**Rating (%)**	**Criteria**
Able to carry on normal activity and to work: No special care needed	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with efforts; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his/her personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self. Requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal process progressing rapidly
	0	Death

Source: Mor V, Laliberte L, Morris JN, et al. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer 1984;53:2002-2007.

Appendix 9 Health-Related Quality of Life Questionnaire FKSI-DRS

FKSI -DRS

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
BRM 3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
RCC2	I have had blood in my urine	0	1	2	3	4

16 November 2007
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Appendix 10 Health-Related Quality of Life Questionnaire EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): __ __ __ __ __ __
Today's date (Day, Month, Year): 31 __ __ __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

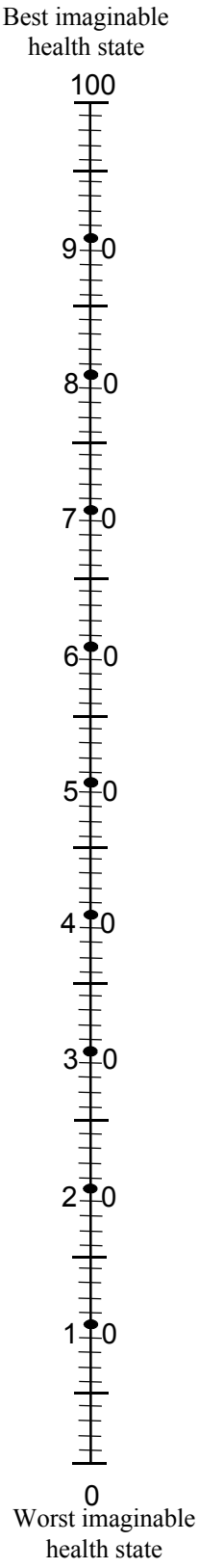
30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



1:1 ratio.

The **Treatment Period** for an individual subject will begin at the time of randomization and will end upon completion of the Off-Treatment Visit, which will occur within 28 days after the final administration of study drug. The Treatment Period consists of open-label treatment with study drug in 28-day treatment cycles that will be counted continuously regardless of dose interruptions. Serious adverse events (SAEs) and AEs must be captured for 28 days after the last dose of study drug. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments and will continue to receive study treatment until disease progression. The **Follow-up Period** will begin immediately after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent, or until the data cutoff for the primary analysis. Subjects who discontinue study drug treatment prior to disease progression will continue to have tumor assessments performed every 8 weeks until documentation of disease progression or initiation of another anticancer treatment. Following the Off-treatment Visit, subjects will continue to be followed every 12 weeks (±1 week) for survival and PFS2, and all anticancer treatments received will be recorded until the data cutoff for the primary analysis (ie, Follow-up ends at the end of the Randomization Phase). This information will be recorded unless this information is not allowed to be provided due to confidentiality.

If a subject discontinues study treatment and does not consent to continued follow-up, the investigator must not access confidential records that require the subject's consent. However, an investigator may consult public records to establish survival status.

While receiving investigational product, subjects should continue with the same assessments as noted in the Schedule of Assessments/Procedures.

All subjects who are still on study treatment after the data cutoff for the primary analysis (ie, at the end of the Randomization Phase) will continue to receive investigational product until they complete the Off-Treatment Visit.

After the data cutoff for the primary analysis, the **Treatment Period** will consist of **56-day treatment cycles** and an Off-Treatment Visit, where subjects still on study treatment following the data cutoff of the planned primary analysis (ie, at the end of the Randomization Phase) will continue to receive the same treatment they received during the Randomization Phase. Study treatment will continue until confirmed disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, lost to follow up or study termination by the sponsor. If the study is terminated by the sponsor, study drug (s) will be provided to subjects where commercial access is not available. Tumor assessments will be performed according to the local standard of care, and scans will no longer be required to be sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 28 days after the final dose of study treatment. After the data cutoff for the primary analysis, all AEs leading to study drug discontinuation and SAEs will be recorded until 28 days after the last dose of study drug.

The definition of the **End of the Study** is the last subject's last assessment (Off-Treatment Visit) after the data cutoff for the primary analysis.

The data obtained after the data cutoff for the primary analysis will be summarized and included in the CSR at the end of study as an addendum.

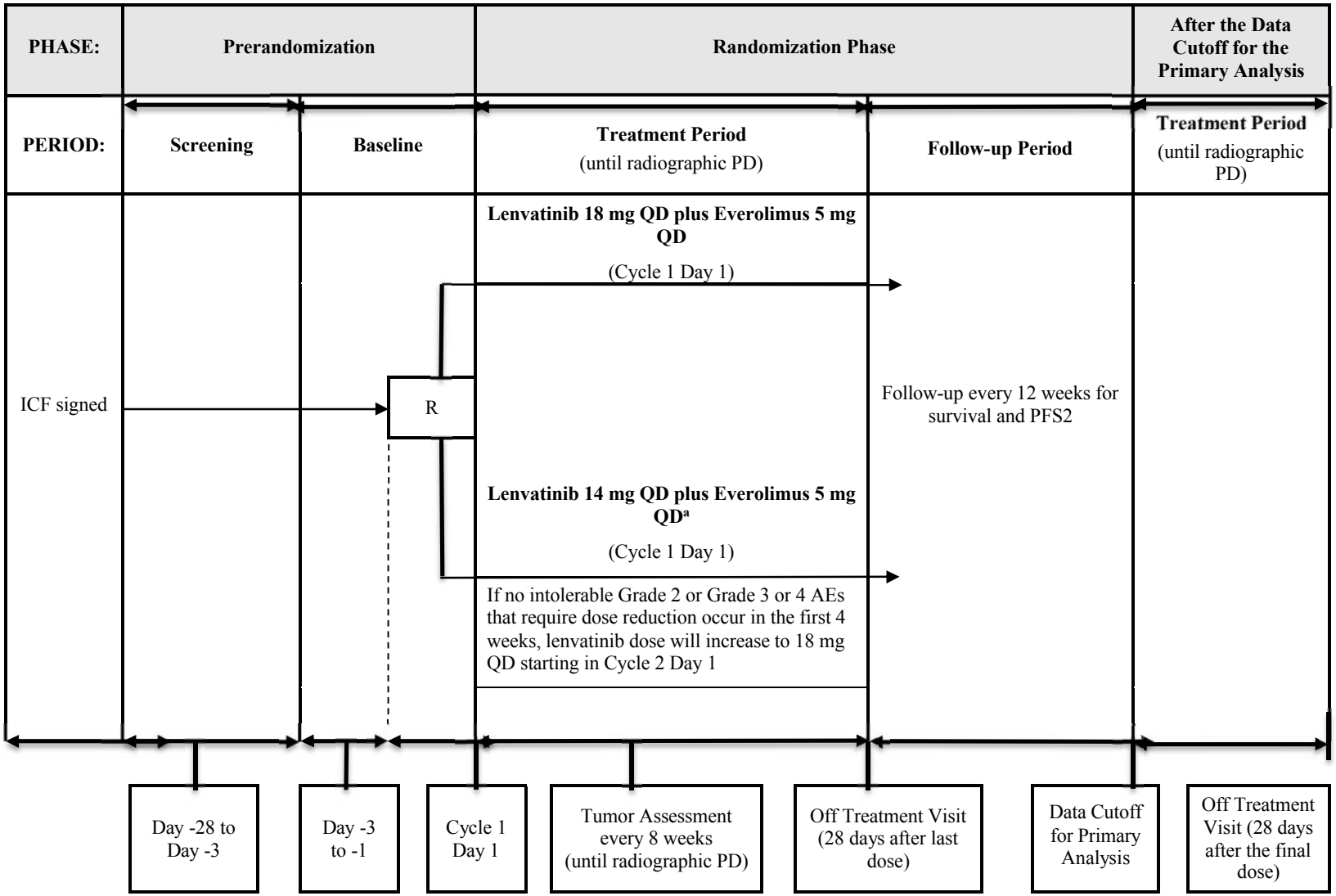
Number of Subjects

Approximately 338 subjects will be randomized (169 subjects in each treatment arm).

Inclusion Criteria

1. Histological or cytological confirmation of predominant clear cell RCC (original tissue diagnosis of RCC is acceptable).

Abbreviation	Term
PK	pharmacokinetics
PO	orally (per os)
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOPs	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TEAE(s)	treatment-emergent adverse event(s)
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WHO	World Health Organization


PHASE:
Prerandomization
Randomization Phase
After the Data Cutoff for the Primary Analysis
PERIOD:
Screening
Baseline
Treatment Period
(until radiographic PD)
Follow-up Period
Treatment Period
(until radiographic PD)
Lenvatinib 18 mg QD plus Everolimus 5 mg QD
(Cycle 1 Day 1)
ICF signed
R
Follow-up every 12 weeks for survival and PFS2
Lenvatinib 14 mg QD plus Everolimus 5 mg QD[a]
(Cycle 1 Day 1)
If no intolerable Grade 2 or Grade 3 or 4 AEs that require dose reduction occur in the first 4 weeks, lenvatinib dose will increase to 18 mg QD starting in Cycle 2 Day 1
Day -28 to Day -3
Day -3 to -1
Cycle 1 Day 1
Tumor Assessment every 8 weeks (until radiographic PD)
Off Treatment Visit (28 days after last dose)
Data Cutoff for Primary Analysis
Off Treatment Visit (28 days after the final dose)

9.3.2 Exclusion Criteria

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

1. More than 1 prior VEGF-targeted treatment for advanced RCC.
2. Subjects with Central Nervous System (CNS) metastases are not eligible, unless they have completed local therapy for at least 4 weeks and have discontinued the use of corticosteroids for this indication or are on a tapering regimen of corticosteroids (defined as ≤10 mg prednisolone equivalent) 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.
3. Active malignancy (except for RCC or definitively treated basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within the past 24 months.
4. Any anti-cancer treatment (except for radiation therapy, see exclusion #5) within 21 days or any investigational agent within 30 days prior to the first dose of study drug; subjects should have recovered from any toxicity related to previous anti-cancer treatment to Common Terminology Criteria (CTC) grade 0 or 1.
5. Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start.
6. Known intolerance to study drug (or any of the excipients) and/or known hypersensitivity to rapamycins (eg, sirolimus, everolimus, temsirolimus) or any of the excipients.
7. Subjects with proteinuria >1+ on urinalysis will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible.
8. Fasting total cholesterol >300 mg/dL (or >7.75 mmol/L) and/or fasting triglycerides level >2.5 x ULN. NOTE: these subjects can be included after initiation or adjustment of lipid-lowering medication.
9. Uncontrolled diabetes as defined by fasting glucose >1.5 times the ULN. NOTE: these subjects can be included after initiation or adjustment of glucose-lowering medication.
10. Prolongation of QTc interval to >480 ms.
11. Subjects who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.
12. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib or everolimus.
13. Bleeding or thrombotic disorders, or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
14. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

2. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added.
3. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted. It should be restarted at 1 dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at an additional dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at a third dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
   - Additional dose reduction should be discussed with the sponsor.

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

1. Institute appropriate medical management
2. Discontinue study treatment

9.4.2.3 Management of Proteinuria

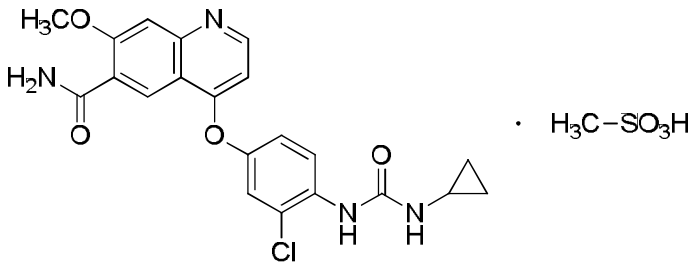
Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments (Table 6) and the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). Guidelines for assessment and management of proteinuria:

1. Grading will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained in Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity,"
2. A 24-hour urine collection (within 72 hours) to verify the grade of proteinuria for protein quantitation is required in the following situations:
   - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug

hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc. Everolimus will be supplied by the sponsor as 5-mg tablets, packaged in blisters.

9.4.3.1 Chemical Name, Structural Formula of Lenvatinib

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



9.4.3.2 Comparator Drug

Not applicable.

9.4.3.3 Labeling for Study Drug

Lenvatinib, identical placebo, and everolimus will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The following information will be provided (but not limited to):

- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Unique package number
- Storage conditions, expiration date if necessary

9.4.3.4 Storage Conditions

Study drugs 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 if regionally required, the head of the medical institution) or designee is responsible for ensuring that the temperature is

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

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 (Appendix 3). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity). For Grade 2 AEs that lead to changes in study drug administration (dose held, dose reduced, or dosing discontinuation), the investigator will be required to confirm in the CRF that the AE is considered intolerable.

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization

Category	Parameters

RBC = red blood cell, WBC = white blood cell, INR = International Normalized Ratio.

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

b. Free T4 and TSH levels will be performed at the Screening Visit, at the Baseline Visit (or within 72 hours prior to the first dose of study drug). TSH levels will be repeated at Day 1 of every other cycle (starting with Cycle 2) and at the Off-Treatment visit.

c. For subjects with blood glucose >ULN, a fasting (>6 h, water only) blood glucose sample will be obtained.

d. For women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months)

e. If urine dipstick testing suggests a urinary tract infection, a urinalysis with microscopy and/or urine culture with sensitivities should be considered, if clinically indicated, at the institution's laboratory.

f. If urine protein by dipstick is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection should be done to quantify the 24-hour urine protein excretion.

All hematology, clinical chemistry (including pregnancy test, as applicable), and urine samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of Cycle 1, and within 48 hours of Day 1 in each treatment cycle and within 72 hours of Day 1 after the data cutoff for the primary analysis. Refer to Table 2 for management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. After the data cutoff for the primary analysis, one BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart.

Vital sign measurements (resting BP [including date and time of measurement], HR, RR and body temperature) will be obtained, excluding weight at the visits designated in the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7).

For subjects with an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mmHg), confirmation should be obtained by performing 2 assessments a minimum of 30 minutes apart.

12 months). Samples of blood or urine will be taken at designated time points as specified in the Schedule of Procedures and Assessments (Table 6) and Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7).

9.5.1.5 Other Assessments

HRQoL will be assessed at Baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle, and at the Off-Treatment Visit in the Randomization Phase. HRQOL will not be assessed after the data cutoff for the primary analysis. Every effort should be made to administer HRQoL surveys prior to study drug administration and before other assessments and procedures. Subjects will complete the Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS; Appendix 9), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 (Appendix 10) and the European Quality of Life (EuroQol) EQ-5D-3L (Appendix 11) instruments.

The FKSI-DRS consists of 9 items that experts and patients have indicated are important targets for the treatment of advanced kidney cancer, and that clinical experts have indicated are primarily disease-related, as opposed to treatment-related. Symptoms assessed on the FKSI-DRS include pain, fatigue, shortness of breath, fevers, weight loss, coughing, and blood in urine. The total score can range from 0 (worst) to 36 (best).

The QLQ-C30 measure comprises 9 multiple-item scales and 6 single items. Multiple-item scales of QLQ-C30 consist of 6 functional scales (physical, role, emotional, cognitive, social and global QoL) and 3 symptom scales (fatigue, nausea and vomiting, pain). Six single-item scales of QLQ-C30 involve dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact. All of the derived scales range in score from 0 to 100. For the overall HRQoL and functioning scales, a higher score is correlated with better HRQoL, whereas a higher score represents worse HRQoL for symptom scales.

The EQ-5D-3L generic QoL questionnaire is comprised of 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 3 levels (1) no problem, (2) some problem, or (3) extreme problem. Thus, the final scoring consists of 243 possible combinations or health states. The utility value for each state is assigned on the basis of a set of preference weights (tariffs) elicited from the general population.

9.5.2 Schedule of Procedures/Assessments

Table 6 presents the schedule of procedures/assessments for the study. Table 7 presents the schedule of procedures/assessments after the data cutoff for the primary analysis.

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed (based on the data cut off for the primary analysis) and the database is locked and released. The interim analyses will be performed by an independent statistical reporting team. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

- Objective response rate at Week 24 (ORR_{24W}) as assessed by the investigator according to RECIST 1.1 (Appendix 8). ORR_{24W} is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) at the Week-24 (after randomization) time point or earlier. To be considered a BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.
- Proportion of subjects with intolerable Grade 2 or any ≥ Grade 3 TEAEs within 24 weeks after randomization (as of the Week-24 time point).

9.7.1.1.2 SECONDARY ENDPOINTS

- Progression-free survival (PFS), defined as the time from the date of randomization to the date of first documentation of disease progression or date of death or the date of data cutoff for the primary analysis, whichever occurs first. PFS censoring rules will be defined in the statistical analysis plan (SAP) and will follow FDA guidance.
- ORR as assessed by the investigator according to RECIST 1.1 at the end of treatment. ORR is defined as the proportion of subjects with BOR of CR or PR at the end of treatment. To be considered BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.
- Overall safety profile and tolerability of lenvatinib in combination with everolimus.
- Proportion of subjects who discontinue treatment due to toxicity, defined as the proportion of subjects who discontinue study treatment due to TEAEs.

Analysis Set	Per-Protocol Analysis Set 2	
Definition	All randomized subjects who received at least one dose, had no major protocol deviation, and had both baseline and at least 1 post-baseline tumor assessment. Subjects for whom death occurred prior to the first post-baseline tumor assessment will also be included.	
Used as	An analysis set for a sensitivity analysis of the primary efficacy endpoint	An analysis set for a sensitivity analysis of the primary safety endpoint
	An analysis set for the secondary efficacy endpoints	

9.7.1.3 Subject Disposition

Subject disposition will be summarized for the Per-Protocol Analysis Set 1, Per-Protocol Analysis Set 2, and Full Analysis Set. All subjects who were screened for the study will be accounted for and reported in the study results. The reasons for screen failures will be described and documented by subject and summarized by total number of subjects with screen failures. If deemed relevant, the reasons for excluding subjects will be evaluated to determine if these reasons could help clarify the appropriate subject population for eventual drug use.

The number (percentage) of randomized and treated subjects will be summarized as well as subjects who completed the study/discontinued from the study and reasons for discontinuation by treatment arm. The number (percentage) of subjects who completed the study treatment/discontinued from the study treatment and reasons for discontinuation will also be summarized by treatment arm.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the Per-Protocol Analysis Set 1, Per-Protocol Analysis Set 2, and Full Analysis Set. For continuous demographic/baseline variables including age, weight, and height, results will be summarized and presented as N, mean, standard deviation, median, Q1, Q3, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

9.7.1.5 Prior and Concomitant Therapy

Prior and concomitant therapy will be summarized for the Per-Protocol Analysis Set 1 and Full Analysis Set. All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications will be defined as medications that were started prior to the first dose of study drug and were stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (i) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (ii) started on or after the date of the first dose of study drug up to 28 days following the last dose in randomization phase. Medications that cannot be determined

interpretation (categorized as normal; abnormal, not clinically significant; and abnormal clinically significant).

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive summary statistics for LVEF assessed on echocardiogram or MUGA scans and changes from baseline will be calculated and summarized by treatment group.

9.7.2 Determination of Sample Size

The objective of the study is to assess whether a starting dose of lenvatinib 14 mg QD in combination with everolimus 5 mg will provide comparable efficacy with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg. Determination of whether 14 mg lenvatinib can be used as an alternative dosing strategy will be based on clinical judgment by the Sponsor in consultation with the independent DMC (as specified in the DMC charter) by assessing risks and benefits according to the totality of data at either of the interim or primary analyses. Nevertheless, the sample size is guided by the plan of testing non-inferiority on the primary efficacy endpoint and superiority on the primary safety endpoint. The details and assumptions are provided below.

Sample size is based on detecting both the non-inferiority of ORR_{24W} and superiority of the primary safety endpoint of the proportion of subjects with intolerable Grade 2 or any ≥ Grade 3 TEAEs within 24 weeks after randomization in comparison of the 14-mg arm to the 18-mg arm (Appendix 13).

Non-Inferiority of ORR_{24W} Comparing the 14-mg Arm to the 18-mg Arm

Based on the assumption from Study 205 that the confirmed ORR for the 18 mg lenvatinib + 5 mg everolimus arm is 37% (19 responders out of N=51) vs 6% for the everolimus arm (3 responders out of N=50), the 95% CI of the odds ratio comparing everolimus vs. lenvatinib 18 mg + everolimus arm is (0.029, 0.395). The non-inferiority margin is chosen to ensure that a reasonable fraction of the lenvatinib 18 mg + everolimus vs. everolimus treatment effect is preserved. A 70% retention of the treatment effect of lenvatinib 18 mg + everolimus vs. everolimus is used for this design. Following the approach in Rothmann, et al. (2003), using the 95% CI upper limit method based on logarithm of the odds ratio, the non-inferiority margin is estimated as

$\exp((1-\delta) * (upper\ limit\ of\ 95\%\ CI\ of \log odds\ ratio\ (eve\ /lenv\ 18\ mg +\ eve\ )))$, where $0 < \delta < 1$ is the retention rate.

To retain 70% of the lenvatinib 18 mg + everolimus vs. everolimus treatment effect, the non-inferiority margin of the odds ratio is estimated to be

$\exp\big((1-0.7) * log(0.395)\big) = 0.76$ (ie, Ha: OR (14 mg/18 mg)> M). Listed below are the non-inferiority margins on the scale of difference in ORR_{24W} between the lenvatinib 14-mg + everolimus arm and the lenvatinib 18-mg + everolimus arm corresponding to a 0.76 non-inferiority margin on the odds ratio scale for a different ORR_{24W} in the lenvatinib 18-mg + everolimus arm.

Phase	Prerandomization Phase		Randomization Phase All cycles are 28 days in duration								
Period	**Screening[a]**	**Baseline[a]**	**Study Treatment Period[b]**							**Off-Tx**	**Follow-Up**
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7, 9, etc.**	**8, 10, 12, 14, etc.**	**99**	
			Cycle 1			**Cycle 2**		**Cycles 3 - Last**			
Day	**-28 to -3**	**-3 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**15**		
Procedures/Assessments											
Blood sample for Biomarkers[v]		X			X	X		X		X	

AEs = adverse events, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D15 = Cycle 1/Day 15, CT = computed tomography, ECG = electrocardiogram, HR = heart rate, ICL = imaging core laboratory, meds = medications, KPS = Karnofsky Performance Status, MRI = magnetic resonance imaging, MUGA = multigated acquisition, NYHA = New York Heart Association, PET = positron emission tomography, PFS2 = progression-free survival after next line of therapy, PK = pharmacokinetic, RECIST = Response Evaluation Criteria in Solid Tumors, RR = respiratory rate, SAEs = serious adverse events, Tx = treatment.

a. Subjects must be screened within 28 days prior to randomization. The screening assessment can serve as the baseline assessment, if performed within 72 hours before randomization. Baseline assessments may be performed on Day -1 or on C1D1 prior to randomization. Patients randomized after the baseline assessment must have all baseline assessments reviewed prior to C1D1. Informed consent may be obtained up to 4 weeks prior to randomization.

b. Efforts should be made to conduct study visits on the day scheduled (±3 days). The study visit (and safety assessments) still needs to occur regardless of a study medication hold per the visit schedule.

c. KPS assessment will be performed at the Screening and Baseline Visits, on C2D1, and on Day 1 of every subsequent cycle. NYHA assessment will only be performed at the Screening visit. See protocol appendices for KPS assessments and NYHA Cardiac Disease Classification.

d. TNM staging, according to AJCC criteria (Edge, et al., 2010), should be reported based on the initial diagnosis of RCC.

e. Assessments will include vital signs (resting BP [including date and time of measurement], HR, RR and body temperature), weight, and height. Height will be measured at the Screening visit only. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. An elevated BP assessment (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg should be confirmed by a repeat assessment after a minimum of 1 hour. Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 1 and Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months. A diary will be provided to the subject to capture the blood pressure evaluations between study visits. See subsection for management of hypertensive subjects.
Note: During Cycle 3 and subsequent cycles, subjects may return to the clinic for the Day 15 visit if BP monitoring testing is required as specified above. The Day-15 visit is mandatory in Cycles 1 and 2.

f. A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visits, on Cycle 1/Day 15, on Day 1 of each subsequent cycle, and at the Off-Treatment assessment. A symptom-directed physical examination will be performed on C1D1

9.5.2.1 Description of Procedures/Assessments Schedule

Refer to Table 6 for a description and timing of each procedure and assessment in the Prerandomization and Randomization Phase and to Table 7 for procedures and assessments after the data cutoff for the primary analysis.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of metastatic RCC. The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urine dipstick testing, and assessment of AEs, are standard evaluations to ensure subject safety.

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

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

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

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

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

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

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

For sites in the US, the investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be

9.1.2.1 Treatment Period

The Treatment Period will begin with the first dose of study drug administration in Cycle 1 and continue in 28-day cycles until completion of the Off-Treatment Assessments (within 28 days after the last study drug administration). Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 6). Subjects will continue to receive study drug until confirmed disease progression, lost to follow-up, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor. Subjects who discontinue treatment before the data cutoff for the primary analysis will enter the Follow-up Period and will be followed every 12 weeks (±1 week) after the Off-Treatment Visit. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.

9.1.2.2 Follow-Up Period

The Follow-Up Period will begin immediately after the off-treatment assessments have been completed and will continue as long as the study subject is alive, until the study subject withdraws consent, or until the data cutoff for the primary analysis. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessments every 8 weeks and as of Amendment 06, send these to the imaging core laboratory (ICL) until documentation of disease progression or start of another anticancer therapy. Following the Off-Treatment Visit, subjects will continue to be followed every 12 weeks (±1 week) for survival and PFS2, and all anticancer treatments received will be recorded until the data cutoff for the primary analysis. This information will be recorded unless the information is not allowed to be provided due to confidentiality.

If a subject discontinues study treatment and does not consent to continued follow-up, the investigator must not access confidential records that require the subject's consent. However, an investigator may consult public records to establish survival status. Copies of tumor assessment scans will no longer be sent to the ICL and independent review will not be carried out during the Follow-Up Period.

All subjects who are still on study treatment following the data cutoff for the primary analysis (ie, at the end of the Randomization Phase) will continue to receive the same study treatment. Tumor assessments will be performed according to the local standard of care, but not less frequently than every 12 weeks or earlier if clinically indicated, and scans will no longer be required to be sent to the ICL. Subjects will continue to receive study treatment until confirmed disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, lost to follow up or study termination by the sponsor. If the study is terminated by the sponsor, study drug (s) will be provided to subjects where commercial access is not available.

The Off-Treatment Visit will occur within 28 days after the final dose of study treatment. All AEs and SAEs will be captured up to 28 days after last dose of study drug (Table 7).

Appendix 5 New York Heart Association Cardiac Disease Classification

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

Class	NYHA Status
Class I:	Patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
Class II:	Patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III:	Patients with cardiac disease resulting in marked limitation of activity; they are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV:	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA = New York Heart Association.
Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Note: NYHA Classification only applies to subjects with underlying cardiac disease.

Appendix 11 Health-Related Quality of Life Questionnaire EQ-5D-3L

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

Appendix 12 Pharmacodynamic and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

Sample collection for pharmacodynamic, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

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

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

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All pharmacodynamic and other biomarker samples will be single coded. Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID “key.”