TRIAL TO ASSESS THE EFFICACY OF LENVATINIB IN METASTATIC NEUROENDOCRINE TUMORS (TALENT STUDY)

Sponsor:	GETNE (Grupo Español de Tumores Neuroendrocrinos)
Coordinator:	Dr. Jaume Capdevila
Type of Document:	Clinical Trial Protocol
EudraCT number:	2015-001467-39
Phase:	II
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1. Synopsis

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Clinical trial title	"**TRIAL TO ASSESS THE EFFICACY OF LENVATINIB IN METASTATIC NEUROENDOCRINE TUMORS (TALENT STUDY)**."
Protocol number	GETNE1509 (TALENT)
Study Coordinator and Principal Investigator	Dr. Jaume Capdevila Medical Oncology Department. Gastrointestinal and Endocrine Tumor Unit Vall d'Hebron University Hospital Pg Vall d'Hebron, 119-129; 08035 Barcelona Tel. +34934894350; Fax. +34932746781 jacapdevila@vhebron.net; jcapdevila@onco.cat
Planned sites	Approximately 25 sites in several countries in Europe (planned sites in Spain, Italy, United Kingdom, and Austria)
Name and qualifications of the persons in charge of Monitoring	Experior, S.L. C/ Vicente Galmés, 1A; 46139 La Pobla de Farnals (Valencia) Tel: 902.105.255; Fax: 96.145.21.91
Experimental Drug	**Lenvatinib** Lenvatinib will be provided as #4-size hydroxypropyl methylcellulose (HPMC) capsules in 2 strengths differentiated by color: 4-mg capsule (yellowish-red cap and body) and 10-mg capsule (yellowish-red cap with yellow body). Dosing schedule of 24 mg once a day (two 10-mg capsules + one 4-mg capsule) has been selected for continued lenvatinib development
Trial Phase	II
Design	Prospective, international, multi-center, open label, stratified, exploratory phase II study evaluating the efficacy and safety of lenvatinib

Primary Endpoint	The primary endpoint of the study is overall response rate (ORR) by RECIST v 1.1 upon central radiologic assessment
Study population and total number of subjects	Patients with advanced/metastatic, histologically confirmed, grade 1/2 (G1/G2) of 2010 WHO classification neuroendocrine tumors of the pancreas after progression to a previous targeted agent (cohort A) or gastrointestinal tract after progression to somatostatin analogues (cohort B). **Number of patients:** 110 patients in total (55 per each cohort)
Objectives	Primary objective To assess the efficacy of lenvatinib on tumor objective response rate in two independent cohorts of patients with advanced neuroendocrine tumors: patients with advanced/metastatic G1/G2 pancreatic neuroendocrine tumors after progression to a previous targeted agent (cohort A), and patients with advanced/metastatic G1/G2 neuroendocrine tumors of gastrointestinal tract after failure to somatostatin analogues therapy (cohort B). Secondary objectives To determine the safety and tolerability of lenvatinib. To estimate the early tumor shrinkage rate and the deepness of response of lenvatinib in each cohort of patients. To estimate progression-free survival in both cohorts of patients. Exploratory objectives To evaluate biochemical response (changes in CgA and NSE levels) and its association with response rate and progression-free survival. To assess whether baseline tumor and blood biomarkers may be predictive of response to lenvatinib. To explore additional hypotheses related to biomarkers and relationship to lenvatinib, neuroendocrine tumors, other endocrine disorders and/or cancer which may arise from internal or external research activities.
Inclusion Criteria	Subjects must meet all of the following criteria to be included in this study: 1. Subjects must have histologically confirmed diagnosis of one of the following advanced/metastatic neuroendocrine tumor

	types: a) WHO Classification G1/G2 (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF) pancreatic neuroendocrine tumor b) WHO Classification G1/G2 (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF) gastrointestinal neuroendocrine tumor (including stomach, small intestine and colorectal origins). 2. Subjects must have evidence of measurable disease meeting the following criteria: a) At least 1 lesion of ≥ 1.0 cm in the longest diameter for a non-lymph node, or ≥ 1.5 cm in the short-axis diameter for a lymph node, which is serially measurable according to RECIST 1.1 (Appendix I) using computerized tomography/magnetic resonance imaging (CT/MRI). If there is only one target lesion and it is a non-lymph node, it should have a longest diameter of ≥ 1.5 cm. b) Lesions that have had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation or liver embolization must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion. 3. Subjects must show evidence of disease progression by radiologic image techniques within 12 months (an additional month will be allowed to accommodate actual dates of performance of scans, i.e., within ≤ 13 months) prior to signing informed consent, according to RECIST 1.1 (Appendix I). 4. Subjects must meet the following inclusion criterion regarding primary tumor site: a) Pancreatic origin: progression after a previous targeted agent (including mTOR inhibitors, such as everolimus or antiangiogenic therapies, such as sunitinib, sorafenib, axitinib, bevacizumab within others). Combination therapies in the same treatment line (such as sorafenib plus

	bevacizumab, chemotherapy plus antiangiogenic drugs) are considered one treatment line and are allowed to be included in the study. Patients must be treated with only one previous line of targeted agent(s)-based therapy. Previous therapy with somatostatin analogues and/or interferon is allowed and is not considered as a previous targeted agent therapy. b) Gastrointestinal origin: progression after therapy with antitumoral doses of somatostatin analogs (octreotide LAR 30 mg every 28 days or Lanreotide 120 mg every 28 days) and/or interferon treatment. 5. Only for patients with pancreatic origin neuroendocrine tumors, one previous line with chemotherapy is allowed. 6. Concomitant somatostatin analogues are allowed in both cohorts during the study. 7. Patients with known brain metastases who have completed whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection, will be eligible if they have remained clinically stable, asymptomatic and off of steroids for at least one month. 8. All prior chemotherapy or radiation-related toxicities must have resolved to < Grade 2 (following CTCAE V 4.03 grade levels), except alopecia and infertility. 9. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 − 1 (Appendix II). 10. Previous liver locoregional therapies, such as (chemo) embolization, radiofrequency or liver-directed radioembolization, or systemic peptide-receptor radionucleotide therapy are allowed if the procedure was performed at least 6 months previous the informed consent form signature. 11. Adequately controlled blood pressure with or without antihypertensive medications, defined as BP < 150/90 mmHg

	at screening and no change in antihypertensive medications within 1 week prior to the Screening Visit. 12. Adequate renal function defined as calculated creatinine clearance ≥ 30 mL/min per the Cockcroft and Gault formula (Appendix III). 13. Adequate bone marrow function, defined as: a) Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 × 103/µL). b) Platelets ≥ 100,000/mm3 (≥ 100 × 109/L). c) Hemoglobin ≥ 9.0 g/dL. 14. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤ 1.5. Prophylactic low molecular weight heparin therapy is allowed. 15. Adequate liver function: a) Bilirubin ≤ 1.5 × the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome. b) Alkalin phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × the ULN (≤ 5 × ULN if subject has liver metastases). 16. Males or females age ≥ 18 years at the time of informed consent. 17. All females must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadotropin (β-hCG) at the baseline visit (and/or within 72h prior to the first dose of study drug). Females of childbearing potential must agree to use a highly effective method of contraception (e.g., total sexual abstinence*, an intrauterine device, a double-barrier method such as condom + spermicide or condom + diaphragm with spermicide or have a vasectomized partner with confirmed azoospermia*) throughout the entire study period and for 30 days after study drug administration. The only subjects who

	will be exempt from this requirement are postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or subjects who have been sterilized surgically or who are otherwise proven sterile (i.e., bilateral tubal ligation with surgery at least 1 month prior to dosing, hysterectomy, or bilateral oophorectomy with surgery at least 1 month prior to dosing). The women using oral hormonal contraceptives should add an additional barrier method as there is unknown whether lenvatinib may reduce the effectiveness of the hormonal contraceptives. All women who are of reproductive potential and who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. ** Sexual abstinence will be acceptable only when this is in line with the preferred and usual lifestyle of the subject. 18. Male subjects who are partners of women of childbearing potential must use or their partners must use a highly effective method of contraception (e.g., condom + spermicide, condom + diaphragm with spermicide, IUD) beginning at least 1 menstrual cycle prior to starting study drug(s), throughout the entire study period, and for 30 days after the last dose of study drug, unless they are sexually abstinent or have undergone a successful vasectomy. Those with partners using hormonal contraceptives must also be using an additional approved method of contraception, as described previously. 19. Voluntary provision of written informed consent and the willingness and ability to comply with all aspects of the protocol.
Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from this study: 1. WHO Classification G3 neuroendocrine tumors of the

	pancreas and gastrointestinal tract. 2. Two or more prior lines of targeted agents-based therapy in pancreatic origin and any previous line of targeted therapy for gastrointestinal origin or any ongoing antiproliferative treatment for advanced/metastatic neuroendocrine tumors, with the exception of somatostatin analogues therapy. 3. More than one previous line of chemotherapy in pancreatic neuroendocrine tumors. 4. Previous chemotherapy in gastrointestinal neuroendocrine tumors. 5. Prior treatment with lenvatinib. 6. Subjects who have received any anti-cancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug and should have recovered from any toxicity related to previous anti-cancer treatment. This does not apply to the use of somatostatin analogues for symptomatic therapy. 7. Major surgery within 3 weeks prior to the first dose of study drug. 8. Subjects having > 1+ proteinuria on urine dipstick testing will undergo 24h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥ 1 g/24h will be ineligible. 9. Gastrointestinal malabsorption, or any other condition in the opinion of the investigator that might affect the absorption of lenvatinib. 10. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina; myocardial infarction or stroke within 6 months prior to the first dose of study drug, or cardiac arrhythmia requiring medical treatment. The left ventricular ejection fraction in the echocardiogram must be of at least 50%. 11. Prolongation of QTcF interval to > 480 msec. 12. Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic

	international normalized ration (INR) monitoring. Treatment with low molecular weight heparin (LMWH) is allowed. 13. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug. 14. Active infection (any infection requiring treatment). 15. Active malignancy within the past 5 years (except for definitely treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix). 16. Known intolerance or hypersensitivity to the active substance (or any of the excipients). 17. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial. 18. Females who are pregnant or breastfeeding. 19. Documented active alcohol or drug abuse. 20. Patients with a prior history of non-compliance with medical regimens.
Primary Analysis	Data cut-off for the study primary analysis will *take place* after the last patient *enrolled* in the study has performed the second tumor assessment (week 12 after first dose of study drug, given that first evaluation will be performed 6 weeks after the first dose. Starting on week 12 subsequent tumor assessments will be performed every 12 weeks until documentation of disease progression or start of another anticancer therapy
Estimated duration of subject participation	24 months
Calendar and expected termination dates	Recruitment Start: September 2015 End of Recruitment Period: March 2017 3rd Tumor assessment of LP (Primary Analysis): July 2017 Database Lock for Interim Analysis: October 2017 End of Follow up Period: March 2019 FPFV: September 2015 LPLV: September 2018 Clinical Study Report: September 2019

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3. Abbreviations

AE	Adverse Event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BP	Blood pressure
CR	Complete response
CRA	Clinical Research associate
CRO	Clinical research Organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting Toxicity
DNA	Deoxyribonucleic acid
DpR	Deepness of Response
EBRT	external beam radiotherapy
EC	Ethics committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOT	End of treatment visit
FVFP	First Visit first patient
g-CSF:	Granulocyte colony-stimulating factor
GEPNEN	Gastroenteropancreatic neuroendocrine neoplasms
GEPNETs	Gastroenteropancreatic neuroendocrine tumors
GETNE	Grupo Español de Tumores Neuroendrocrinos)
GPC	Good Clinical Practice
h	hours
HPMC	hydroxypropyl methylcellulose

HR	Hearth Rate
ICF	Informed Consent Form
ICH	International Conference Harmonization
IGF	insulin-like growth factor
INR	International Normalized Ratio
IU	International Units
IUD	Intrauterine Dispositive
IV	intravenous
L	liter
LMWH	low molecular weight heparin
LP	Last Patient
LPLV	Last Patient last visit
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MRI	magnetic resonance imaging
msec	milliseconds
MTD	Maximum tolerated dose
Mtor	mammalian target of rapamycin
NE	Non Evaluable
NSAIDs	nonsteroidal anti-inflammatory drugs
NSE	Neuron specific enolase
ORR	Overall response rate
PD	Progressive disease
PDGFR	PDGF receptors
PDGFR	Platelet-derived growth factor
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
PR	Partial response

PT	Preferred Term
pTNM	Classification of Malignant Tumors
qd	Once daily
RA	Regulatory authority
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
RF	Radiofrequency
RNA	Ribonucleic acid
RR	respiratory rate
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
SOP	standard operating practices
Surg	surgical
TEAE	Treatment-emergent adverse event
TEAV	treatment-emergent abnormal laboratory values
UK	United Kingdom
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor
vs.	versus
w/in	within
WHO	World Health Organization

4. General information

4.1 *Trial identification*

Protocol number: GETNE1509

Short study code: TALENT.

EudraCT: 2015-001467-39

Title: "TRIAL TO ASSESS THE EFFICACY OF LENVATINIB IN METASTATIC NEUROENDOCRINE TUMORS (TALENT STUDY)."

4.2 *Type of clinical trial*

Prospective, multi-center, open label, stratified, exploratory phase II study evaluating the efficacy and safety of lenvatinib.

4.3 *Description of study drugs*

Experimental drugs:

Lenvatinib will be provided as #4-size hydroxypropyl methylcellulose (HPMC) capsules in 2 strengths differentiated by color: 4-mg capsule (yellowish-red cap and body) and 10-mg capsule (yellowish-red cap with yellow body).

Dosing schedule of 24 mg once a day (two 10-mg capsules + one 4-mg capsule) has been selected for continued lenvatinib development

4.4 *Sponsor*

GETNE (Grupo Español de Tumores Neuroendrocrinos)

París 162, Pral. 1ª. 08036, Barcelona

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Contact: getne@getne.org

4.5 *Technician responsible for central radiology review*

Dr. Xavier Merino
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4.6 *CRO responsible for monitoring*

Experior, S.L.

C/ Vicente Galmés, 1A

46139 La Pobla de Farnals (Valencia)

Tel: 902.105.255; Fax: 96.145.21.91

4.7 *Participating Sites*

It is planned to include approximately 25 sites in several countries in Europe (planned sites in Spain, Italy, United Kingdom, and Austria).

4.8 *Trial planned duration*

Start of Recruitment September 2015

End of Recruitment Period March 2017

3rd tumor assessment of the LP (primary analysis): July 2017

Database Lock for Interim Analysis: October 2017

End of Follow up Period: March 2019

FPFV: September 2015

LPLV: September 2018

Clinical Study Report: September 2019

5. Rationale and objectives

5.1 *Overview of gastroenteropancreatic neuroendocrine tumors*

Gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) constitute a heterogenic group of tumors derived from the Kultchitzky cells of the diffuse neuroendocrine system located in the gastrointestinal tract (origin of classical carcinoid tumors) and pancreatic islet cells (origin of pancreatic endocrine tumors). Although GEPNENs represent less than 2% of all gastrointestinal cancers, they constitute the second most prevalent advanced tumor of the gastrointestinal tract after colorectal cancer[1]. The biological behavior of GEPNENs depends mainly on their histological characteristics, mainly differentiation grade and Ki67 expression. The most recent 2010 WHO classification divides GEPNENs in three groups regarding Ki67 value and mitotic count: gastroenteropancreatic neuroendocrine tumors (GEPNETs) that include grade 1(G1) and grade 2 (G2) with Ki67 value ≤20% and mitotic count ≤20 mitoses x

10 HPF, and neuroendocrine carcinomas that include grade 3 (G3) with Ki67>20% and/or mitotic count >20 mitoses x 10 HPF.

Table 1.-Groups of GEPNEN following the recent WHO classification GEPNEN

Grade	Mitotic count (10 HPF)	Ki-67 index (%)
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

The medical treatment of advanced GEPNETs has included somatostatin analogs, interferon and cytotoxic agents. The lack of effectiveness of conventional cytotoxic agents has prompted exploration of new targeted drugs exploiting phenotypical features of GEPNETs. GEPNETs are characterized by being remarkably vascular and expressing several growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF), and transforming growth factor (TGF)-α and -β. In addition, expression of several receptors of these growth factors and ligands has been described, including stem cell factor receptor (c-KIT), epidermal growth factor receptors (EGFR), VEGF receptors (VEGFR)-2 and 3, IGF receptors (IGF-R), and PDGF receptors (PDGFR). The (over)expression of some of these factors has been associated with poor prognosis and decreased progression-free survival (PFS), as well as with tumor growth, aggressiveness, and disease extent in patients with GEPNETs[2]. Several targeted agents have been studied in the treatment of GEPNETs including antiangiogenic compounds (such as bevacizumab), inhibitors of multiple receptors with kinase activity (such as sunitinib), and inhibitors of intracellular downstream effector proteins such as the mammalian target of rapamycin (mTOR), such as everolimus. Two phase III studies with everolimus and sunitinib have demonstrated efficacy in pancreatic neuroendocrine tumors becoming two new treatment options in the management of these patients. However, even there are several phase II clinical trials suggesting the efficacy of new targeted agents in gastrointestinal neuroendocrine tumors, currently, and with the exception of somatostatin analogues, no drug is approved for the antiproliferative therapy in non-pancreatic neuroendocrine tumors.

5.2 *Introduction of investigational treatment*

5.2.1 *Overview of lenvatinib*

Lenvatinib is an orally available potent inhibitor of the split-kinase family of transmembrane growth factor receptors including Flt-1/VEGFR-1 and KDR/VEGFR-2. Receptor tyrosine kinase cell free assays demonstrate IC50 values of 22 (Flt-1/VEGFR-1) and 4 nM (KDR/VEGFR-2). Additionally, lenvatinib potently inhibits vascular endothelial growth factor receptor 3 (VEGFR-3, IC50 5nM), fibroblast growth factor receptor (FGFR)-1 (IC50 46 nM), 2, 3, 4 and platelet-derived growth factor receptor (PDGFR, IC50 39 nM) beta tyrosine kinases. Lenvatinib also inhibits (IC50 5.2 nM) SCF-driven tube formation of HUVEC, which express SCF receptor, KIT[3,4].

5.2.2 *Clinical Experience with Lenvatinib*

A global Phase 1 program in patients with solid tumors has been conducted to determine the safety, tolerability and pharmacokinetics of three different regimens including continuous once-daily dosing (Study E7080-E044-101), intermittent (Schedule 1) and continuous (Schedule 2) twice-daily dosing (Study E7080-A001-102), and an intermittent schedule of twice daily dosing for 2 weeks of a 3 week cycle (Study E7080-J081-103).Pharmacokinetic analysis has demonstrated that lenvatinib is rapidly absorbed with maximum concentrations observed from 1 to 3 hours postdose. Lenvatinib elimination occurs with a bi-exponential decline composed of an initial rapid decline followed by a slower decline. The terminal half-life is approximately 30 hours and steady state is achieved within 5 days. A dose dependent increase in soluble VEGF, consistent with an anti-angiogenic effect was observed during 2 weeks of continuous dosing. Hypertension and proteinuria were the most common dose limiting toxicities (DLT). A dose of 25 mg once daily was found to be the maximum tolerated dose (MTD) for the once daily continuous dosing schedule. A cohort of 24 patients treated at this dose level established the safety and tolerability of the lenvatinib 25 mg dose for once daily continuous dosing. To simplify drug administration, a dose of 24 mg (two 10 mg capsules + one 4 mg capsule) once daily has been selected for ongoing lenvatinib development[5].

Several clinical trials are currently in development for different tumor types with lenvatinib. Recently, an international, randomized, placebo-controlled, phase III trial with lenvatinib in advanced, radioactive-refractory differentiated thyroid cancer has been reported demonstrating a significant benefit in median progression-free survival (18.3 vs. 3.6 months, HR: 0.21, $p<0.0001$) and in response rate (65% vs. 2%, $p<0.0001$)[6]. Lenvatinib demonstrated significant benefit regardless previous antiangiogenic therapy and in all subgroups of patients included in the study. Main side effects included hypertension, diarrhea, fatigue, decreased

appetite, nausea-vomiting, decreased weight, stomatitis, palmar-plantar erythrodysesthesia syndrome, proteinuria, headache and dysphonia.

5.3 *Trial Objectives*

This two arm phase II clinical trial has been designed to analyze the antitumoral efficacy of lenvatinib 24 mg daily in two different cohorts of patients with advanced/metastatic G1/G2 neuroendocrine tumors.

5.3.1 *Primary objective:*

- To assess the efficacy of lenvatinib on tumor objective response rate (ORR) (complete (CR) and partial responses (PR) in two independent cohorts of patients with advanced/metastatic G1/G2 neuroendocrine tumors: patients with pancreatic neuroendocrine tumors after progression to a previous targeted agent (cohort A), and patients with neuroendocrine tumors of the gastrointestinal tract after failure to somatostatin analogues therapy (cohort B)

5.3.2 *Secondary objective:*

- To determine the safety and tolerability of lenvatinib.
- To estimate the early tumor shrinkage rate and the deepness of response of lenvatinib in each cohort of patients.
- To estimate progression-free survival in both cohorts of patients.

5.3.3 *Exploratory objectives*

- To evaluate biochemical response (changes in CgA and NSE levels) and its association with response rate and progression-free survival.
- To assess whether baseline tumor and blood biomarkers may be predictive of response to lenvatinib.
- To explore additional hypotheses related to biomarkers and relationship to lenvatinib, neuroendocrine tumors, other endocrine disorders and/or cancer which may arise from internal or external research activities.

6. Randomization process

Not applicable, no randomization is done in this study; all patients will receive the same study treatment independently of the cohort of the study.

7. Type of trial and trial design

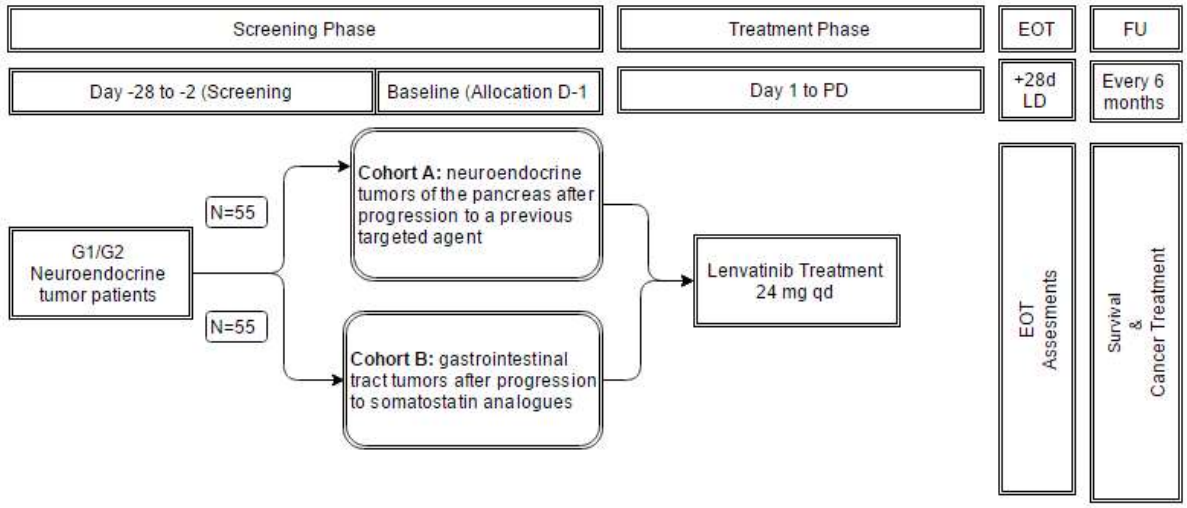
Prospective, international, multi-center, open label, stratified, exploratory phase II study evaluating the efficacy and safety of lenvatinib.

7.1 *Overall study design and plan*

The patient recruitment period of the study will last approximately 18 months. The maximum treatment period for each subject on study is anticipated to be approximately 36 months. However, subjects will continue on treatment as long as they demonstrate clinical benefit.

This study will be conducted in 3 phases: a screening phase, a treatment phase stratified by tumor origin and a follow up phase. An overview of the study design is presented in figure 1.

Figure 1Study Design



7.2 *Screening phase*

Screening will occur between Day -28 and Day -1. The purpose of the screening period is to establish protocol eligibility. Informed consent will be obtained up to 4 weeks prior to Cycle 1 Day 1 and after the study has been fully explained to each subject and prior to the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 17.3

Subjects must have a histological confirmed diagnosis of well-moderately differentiated G1/G2 neuroendocrine tumor meeting the criteria for being progressive to other targeted agent within the prior 12 months in pancreatic origin and progressive to somatostatin analogues within the prior 12 months in gastrointestinal origin.

The purpose of the baseline visit is to establish disease characteristics prior to treatment and allocation and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1/Day 1). Tumor assessments will be performed using CT/MRI of the abdomen and pelvis. A CT/MRI will only be performed in the other organs in case of lesions; otherwise, it will not be required (including neck and chest) (see Section 12.2). **Baseline assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests (Table 4) including pregnancy test (where applicable) can be performed within 72 hours prior to the first dose of study drug.** Subjects who complete the baseline visit and continue to meet the criteria for inclusion/exclusion (Section 8.1 and Section 8.2) will begin the treatment phase of this study.

7.3 *Treatment phase*

The treatment phase will begin at the time of allocation of the first subject and will consist of the study treatment cycles. The treatment phase will end when the last patient discontinues the study drug. Prior to the completion of the final primary study analysis, an individual subject will remain in the treatment phase until documentation of disease progression.

Subjects who discontinue study drug administration prior to disease progression will continue to be followed in the treatment phase according to the tumor assessment schedule listed in table 3 (performed at week 6 after the first dose of study drug and then, every 12 weeks or sooner if clinically indicated) until documentation of disease progression or start of another anticancer therapy.

Subjects will be allocated in each primary tumor cohort to receive lenvatinib 24 mg by continuous once daily oral administration. Subjects will undergo safety and efficacy assessment as defined in Table 3. Other reasons for discontinuation of study drug different from disease progression include development of unacceptable toxicity, withdrawal of consent or sponsor discontinuation of lenvatinib development.

7.3.1 *End of Treatment Visit (Off Treatment Assessment)*

Whenever possible, the off treatment assessments should be performed within 28 days after subjects have discontinued study treatment.

Subjects who discontinue study administration prior to disease progression will continue to undergo disease assessment every 12 weeks until documentation of disease progression or start of another anticancer therapy, at which time the subject will enter the follow-up period.

7.4 *Follow up Phase*

The follow-up period (see Section 14.1.6 and 14.1.7) for such subjects will begin immediately after the end of treatment visit and will continue as long as the study subject is alive or until discontinuation of survival follow-up by sponsor.

All subsequent anticancer therapies received will be recorded during the follow-up phase.

Data cut-off for the study primary analysis will take place after the last patient enrolled in the study has performed the second tumor assessment (week 12 after first dose of study drug, given that the first assessment will be performed 6 weeks after the first dose). Subsequent tumor assessments will be performed starting on week 12every 12 weeks until documentation of disease progression or start of another anticancer therapy. The sponsor may choose to discontinue survival follow-up at some point following the performance of the primary study analysis.

7.5 *Blinding techniques*

Not applicable, open label study.

8. Subject screening

Approximately 110 patients will be enrolled and allocated in a balanced manner into either the pancreatic or gastrointestinal cohorts at approximately 25 sites in Europe (Spain, UK, Italy, and Austria). Subjects who meet all of the inclusion criteria and none of the exclusion criteria and are willing to participate will be eligible to receive study drug.

8.1 *Inclusion criteria*

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

1. Subjects must have histologically confirmed diagnosis of one of the following advanced/metastatic neuroendocrine tumor types:
    a) WHO Classification G1/G2 (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF) pancreatic neuroendocrine tumor
    b) WHO Classification G1/G2 (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF) gastrointestinal neuroendocrine tumor (including stomach, small intestine and colorectal origins).
2. Subjects must have evidence of measurable disease meeting the following criteria:
    a) At least 1 lesion of ≥ 1.0 cm in the longest diameter for a non-lymph node, or ≥ 1.5 cm in the short-axis diameter for a lymph node, which is serially measurable according to RECIST 1.1 (Appendix I) using computerized tomography/magnetic resonance imaging (CT/MRI). If there is only one target lesion and it is a non-lymph node, it should have a longest diameter of ≥ 1.5 cm.
    b) Lesions that have had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation or liver embolization must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.
3. Subjects must show evidence of disease progression by radiologic image techniques within 12 months (an additional month will be allowed to accommodate actual dates of performance of scans, i.e., within ≤ 13 months) prior to signing informed consent, according to RECIST 1.1 (Appendix I).
4. Subjects must meet the following inclusion criterion regarding primary tumor site:

a) Pancreatic origin: progression after a previous targeted agent (including mTOR inhibitors, such as everolimus or antiangiogenic therapies, such as sunitinib, sorafenib, axitinib, bevacizumab within others). Combination therapies in the same treatment line (such as sorafenib plus bevacizumab, chemotherapy plus antiangiogenic drugs) are considered one treatment line and are allowed to be included in the study. Patients must be treated with only one previous line of targeted agent(s)-based therapy. Previous therapy with somatostatin analogues and/or interferon is allowed and is not considered as a previous targeted agent therapy.

b) Gastrointestinal origin: progression after therapy with antitumoral doses of somatostatin analogs (octreotide LAR 30 mg every 28 days or Lanreotide 120 mg every 28 days) and/or interferon treatment.

5. Only for patients with pancreatic origin neuroendocrine tumors, one previous line with chemotherapy is allowed.
6. Concomitant somatostatin analogues are allowed in both cohorts during the study.
7. Patients with known brain metastases who have completed whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection, will be eligible if they have remained clinically stable, asymptomatic and off of steroids for at least one month.
8. All prior chemotherapy or radiation-related toxicities must have resolved to < Grade 2 (following CTCAE V 4.03 grade levels), except alopecia and infertility.
9. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 − 1 (Appendix II).
10. Previous liver locoregional therapies, such as (chemo) embolization, radiofrequency or liver-directed radioembolization, or systemic peptide-receptor radionucleotide therapy are allowed if the procedure was performed at least 6 months previous the informed consent form signature.
11. Adequately controlled blood pressure with or without antihypertensive medications, defined as BP < 150/90 mmHg at screening and no change in antihypertensive medications within 1 week prior to the Screening Visit.
12. Adequate renal function defined as calculated creatinine clearance ≥ 30 mL/min per the Cockcroft and Gault formula (Appendix III).

13. Adequate bone marrow function, defined as:

    a) Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 × 10^3/µL).

    b) Platelets ≥ 100,000/mm3 (≥ 100 × 109/L).

    c) Hemoglobin ≥ 9.0 g/dL.

14. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤ 1.5. Prophylactic low molecular weight heparin therapy is allowed.

15. Adequate liver function:

    a) Bilirubin ≤ 1.5 × the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome.

    b) Alkalin phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × the ULN (≤ 5 × ULN if subject has liver metastases).

16. Males or females age ≥ 18 years at the time of informed consent.

17. All females must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadotropin (β-hCG) at the baseline visit (and/or within 72h prior to the first dose of study drug). Females of childbearing potential must agree to use a highly effective method of contraception (e.g., total sexual abstinence*, an intrauterine device, a double-barrier method such as condom + spermicide or condom + diaphragm with spermicide or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug administration. The only subjects who will be exempt from this requirement are postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or subjects who have been sterilized surgically or who are otherwise proven sterile (i.e., bilateral tubal ligation with surgery at least 1 month prior to dosing, hysterectomy, or bilateral oophorectomy with surgery at least 1 month prior to dosing). The women using oral hormonal contraceptives should add an additional barrier method as there is unknown whether lenvatinib may reduce the effectiveness of the hormonal contraceptives. All women who are of reproductive potential and who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to

dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

* Sexual abstinence will be acceptable only when this is in line with the preferred and usual lifestyle of the subject.

18. Male subjects who are partners of women of childbearing potential must use or their partners must use a highly effective method of contraception (e.g., condom + spermicide, condom + diaphragm with spermicide, IUD) beginning at least 1 menstrual cycle prior to starting study drug(s), throughout the entire study period, and for 30 days after the last dose of study drug, unless they are sexually abstinent or have undergone a successful vasectomy. Those with partners using hormonal contraceptives must also be using an additional approved method of contraception, as described previously.
19. Voluntary provision of written informed consent and the willingness and ability to comply with all aspects of the protocol.

8.2 *Exclusion criteria*

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

1. WHO Classification G3 neuroendocrine tumors of the pancreas and gastrointestinal tract.
2. Two or more prior lines of targeted agents-based therapy in pancreatic origin and any previous line of targeted therapy for gastrointestinal origin or any ongoing antiproliferative treatment for advanced/metastatic neuroendocrine tumors, with the exception of somatostatin analogues therapy.
3. More than one previous line of chemotherapy in pancreatic neuroendocrine tumors.
4. Previous chemotherapy in gastrointestinal neuroendocrine tumors.
5. Prior treatment with lenvatinib.
6. Subjects who have received any anti-cancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug and should have recovered from any toxicity related to previous anti-cancer treatment. This does not apply to the use of somatostatin analogues for symptomatic therapy.
7. Major surgery within 3 weeks prior to the first dose of study drug.
8. Subjects having > 1+ proteinuria on urine dipstick testing will undergo 24h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥ 1 g/24h will be ineligible.

9. Gastrointestinal malabsorption, or any other condition in the opinion of the investigator that might affect the absorption of lenvatinib.
10. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina; myocardial infarction or stroke within 6 months prior to the first dose of study drug, or cardiac arrhythmia requiring medical treatment. The left ventricular ejection fraction in the echocardiogram must be of at least 50%.
11. Prolongation of QTcF interval to > 480 msec.
12. Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic international normalized ration (INR) monitoring. Treatment with low molecular weight heparin (LMWH) is allowed.
13. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.
14. Active infection (any infection requiring treatment).
15. Active malignancy within the past 5 years (except for melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix).
16. Known intolerance or hypersensitivity to the active substance (or any of the excipients).
17. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial.
18. Females who are pregnant or breastfeeding.
19. Documented active alcohol or drug abuse.
20. Patients with a prior history of non-compliance with medical regimens.

9. Number of expected subjects

It is expected to include 110 patients in the study.

The study will enroll 55 patients in each cohort. Patients who meet study eligibility criteria will be stratified in cohort A or cohort B in function of primary tumor origin.

10. Recruitment period duration

The patient recruitment period of the study will begin on approximately September 2015 and will end on or before March 2017 (18 months approximately). The maximum treatment period for each subject on study is anticipated to be approximately 36 months. However, subjects will continue on treatment as long as they demonstrate clinical benefit.

11. Treatment description

11.1 *Description of dose, interval, route and dosing regiment*

The sponsor will package the study drug. Lenvatinib will be provided as #4-size hydroxypropyl methylcellulose (HPMC) capsules in 2 strengths differentiated by color: 4-mg capsule (yellowish-red cap and body) and 10-mg capsule (yellowish-red cap with yellow body). Dosage formulation and capsule strength of lenvatinib are presented in table 2.

Lenvatinib should be stored in accordance with the labeled storage conditions (room temperature).

Oral lenvatinib will be administered as follows: lenvatinib 24 mg (two 10-mg capsules + one 4-mg capsule).

Table 2: Dosage formulation and capsule strength of lenvatinib

Component	Function	Capsule Strength	
		4 mg	10 mg
E7080 drug substance[a]	Drug substance	4	10
D-mannitol[b]	Filler	17	11
Microcrystalline cellulose	Filler	15	15
Calcium carbonate	Disintegrant	33	33
Low-substituted HPC	Disintegrant	25	25
Hydroxypropyl cellulose	Binder	3	3
Talc	Lubricant	3	3
Purified water[c]	Solvent	qs	qs
Fill weight (mg)		100	100
HPMC capsule (size #4)		38	38
Total capsule weight (mg)		138	138

HPC = hydroxypropyl cellulose; HPMC = hydroxypropyl methylcellulose; qs = quantum sufficit.

a: Adjusted for the assay value (%) of anhydrous-free base.

b: Adjusted based on the quantity of E7080 compensated in order to maintain a constant fill weight.

c: Driven off during drying.

11.1.1 *Chemical name, structural formula of lenvatinib*

Study drug code: E7080

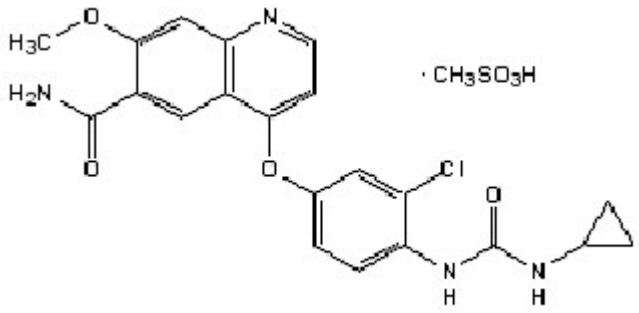
Generic name: lenvatinib

Chemical name: 4-[3-Chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate

Molecular formula: C21H19ClN4O4•CH3SO3H

Molecular weight: 522.96

Structural formula:



11.2 *Storage Conditions*

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

11.3 *Administration of study treatment*

This is an open-label study for study patients, investigator site personnel and sponsor. The patient will receive on Day 1 of each cycle enough treatment for a whole treatment cycle, i.e. 3 packages: 2 packages containing 30 capsules of 10-mg and 1 package containing 30 capsules of 4 mg.

Study subjects will be administered 3 capsules of the study drug (two 10-mg capsules and one 4-mg capsule) to be taken once daily each morning during 28 days from Cycle 1 onward. Study drug should be taken at approximately the same time each morning. Study drug may be taken in a fasting state or following a meal. Criteria for interruption of treatment, dose reduction, and resumption of treatment dose reduction and interruption instructions for subjects who experience treatment-related toxicity are presented in Table 3.

11.4 *Selection of Doses in the Study*

Three Phase 1 studies were conducted examining escalating doses of lenvatinib administered once or twice daily on continuous and interrupted dosing schedules. The 25-mg dose administered in the continuous once daily schedule was identified as the MTD. This dosing

schedule appeared to provide an optimal balance of safety and efficacy in a multivariate analysis of these studies. To simplify drug administration in this study, a dosing schedule of 24 mg once a day (two 10-mg capsules + one 4-mg capsule) has been selected for continued lenvatinib development.

11.5 *Selection and Timing of Dose for Each Subject*

Study drug capsules are to be taken orally once a day at approximately the same time in the morning without regard to food intake for 28 days from Cycle 1 onward. The starting dose will be 24 mg per day. If a subject misses a dose, it may be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours have elapsed from the time of the usual daily dose, study drug should be taken the next day at the usual time in the morning. In the event a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

11.6 *Prior and Concomitant Therapy*

All prior medications (including over-the-counter medications) administered 30 days prior to the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication which is considered necessary for the subject's health and which is not expected to interfere with the evaluation of or interact with study drug may be continued during the study.

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

Concomitant somatostatin analogues are allowed in both cohorts during the study

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

If concomitant medication/therapy is administered for an adverse event, investigators will record that adverse event on the Adverse Events eCRF.

11.7 *Dose reduction and interruption instructions*

In case of treatment related toxicity please follow the dose reduction and interruption instructions provided in Table 3.

For details about the instructions for dose reduction and interruption in case of hypertension and proteinuria, please see Sections 14.8.1 and 14.8.2 of the protocol. In case of doubts regarding other specific cases, see the study reference information (Investigator Brochure and/or Summary of Product Characteristics) provided by the study sponsor.

Table 3. - Dose reduction and interruption instructions

Treatment-Related Toxicity[a,b]	During Therapy	Adjusted Dose
Grade 1		
	Continue treatment	No change
Intolerable Grade 2[c]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	20 mg orally once a day
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once a day
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once a day
Fifth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 3		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg orally once a day
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once a day
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once a day
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[d]: Discontinue Study Treatment		

Note: For grading see CTCAE v.4.03 (Appendix IV). Collect all CTC grades of AE, decreasing and increasing grade.

a) A delay of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed
b) Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment interruption or dose reduction
c) Applicable only to Grade 2 toxicities judged by the subject and physician to be intolerable.
d) Excluding laboratory abnormalities judged to be non-life threatening, in which case manage as Grade 3.

11.8 *Unused drugs*

All used and unused study drugs, including empty containers are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and ultimately to the sponsor's designated contractor or depot by the conclusion of the study, unless approval is given by the sponsor for destruction of supplies and containers at the investigational site.

Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by the sponsor's personnel, study drug that is to be returned to the sponsor's approved contract vendor must be boxed and sealed and shipped back to the sponsor's approved contract vendor following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the sponsor's specified location by sponsor representatives. Drug accountability will be reviewed during investigational site visits and at the completion of the study.

11.9 *Drug-Drug Interactions*

There have been no completed human studies, at present, specifically evaluating drug-drug interactions with lenvatinib. The weak inhibitory effect on CYP P450 enzymes (in vitro) exhibited by lenvatinib suggests a low risk of lenvatinib interference with the pharmacokinetics of other drugs co-administered in usual clinic practice. However, preliminary preclinical studies identify CYP3A4 as an important enzyme responsible for human hepatic metabolism of lenvatinib. Caution should be exercised when administering drugs metabolized by CYP3A4 or drugs that are inhibitors or inducers of CYP3A4 (including herbal supplements or grapefruit), as administration of such drugs could affect the metabolism of lenvatinib. Please refer to Appendix V and http://medicine.iupui.edu/flockhart/table.htm for the most current information.

11.10 *Prohibited Concomitant Therapies and Drugs*

Subjects should not receive other anti-tumor therapies while on study. If subjects receive additional anti-tumor therapies such as chemotherapy, palliative radiotherapy, or immunotherapy, this will be judged to represent evidence of disease progression and study drug will be discontinued. These subjects should complete all off treatment assessments and continue to be followed for survival in the Follow-Up Period.

11.11 *Treatment Compliance*

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

11.12 *Drug Supplies and Accountability*

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement;
- A copy of the final protocol signature page signed and dated by both the sponsor and investigator;
- Written proof of approval of the protocol, the informed consent form(s) (ICFs), and any other information provided to the subjects by the Ethics Committee (EC) for the institution where the study is to be conducted;
- The EC membership list;
- A copy of the regulatory authority (RA) approval for the country in which the study is being conducted (if required), and the Import License (if required);
- A signed and dated curriculum vitae (CV) for the Principal Investigator (PI);
- Financial Disclosure Form(s);
- A signed and dated clinical trials agreement.
- An insurance policy contracted for the clinical trial.

The investigator and study staff (if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local and/or regional requirements. Under no circumstances will the investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study. An accurate and timely record of the receipt of all clinical supplies, dispensing of study drug to the subject, collection of unused supplies returned by the subject, and subsequent return of unused study drug to the sponsor must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study drug dispensing/return reconciliation log, (c) study drug accountability log, (d) all shipping service receipts, and (e) documentation of drug returned to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the investigational site wishes to use must be approved by the sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the sponsor, a representative of the Regulatory Authorities and/or Ethics Committee.

12. Study Methods

12.1 *Demography and baseline characteristics*

Demographic information and baseline characteristics will be collected at the screening visit. Standard demography parameters include age, sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG performance status, Medical and surgical histories will be obtained during the screening 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 visits and procedures (table 4). 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 eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF. Clinical laboratory tests and pregnancy test will be done according to Table 5

12.2 *Primary Efficacy assessments*

The primary efficacy endpoint is overall response rate (ORR) by RECIST v1.1

- ORR is the proportion of subjects who have best overall response of CR or PR.

Tumor assessments

- Tumor assessments will be performed using RECIST 1.1. (Appendix I) Investigator determined response assessments will be performed at each assessment time point and entered onto the eCRF. Copies of all tumor imaging studies will be sent to an imaging core laboratory (Central Review) for prospective on-study primary efficacy assessment. Tumor assessments will be carried out following the guidelines provided by the study sponsor. Tumor assessments (CT of abdomen, and pelvis, and of all other known sites of disease) will be performed during the screening phase and, the first assessment will be performed 6 weeks after the first dose, the second assessment will be performed 12 weeks after the first dose, then every 12 weeks during study treatment cycles in the treatment phase or sooner if clinically indicated until documentation of disease progression.
- A brain CT/MRI will be performed at screening, as clinically indicated. In addition, for subjects with history of treated brain metastases, brain scans must be performed at screening and every tumor assessment time point.

- Data from somatostatin receptor schintigraphy or PET-CT (octreoscan) with specific radiolabeled agents for neuroendocrine tumors (such as Ga68, 5-HTP or F-Dopa) will be collected if available and performed within the 6 months prior to the first dose of study drug but are not acceptable as tumor assessment techniques during treatment phase.
- Data from bone scan will be collected, if available and performed within 6 months prior to first dose of study drug and every 24 weeks after first dose of study drug, and at the final visit unless the last scan was performed less than 24 weeks before.
- Somatostatin schintigraphy, PET and bone scan are not compulsory. They will be collected, if performed.
- A chest x-ray or skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.
- Subjects who discontinue study drug prior to disease progression must continue to undergo tumor assessments every 12 weeks in the follow-up period, until disease progression is documented or another anti-cancer therapy is initiated.
- A dynamic study of multiphasic imaging, at least biphasic imaging, with arterial and venous/portal phases must be performed using CT and/or MG, since one or other technique may be recommended depending on different clinical characteristics. As a general rule, TCs will be performed. Although, for example, for patients allergic to iodinated contrast (in the CT), a MR with a dynamic study would be better.
- The preferred type of CT scan is a diagnostic quality spiral or multidetector CT with oral and iodinated IV contrast, and the preferred MRI scan is performed with IV gadolinium chelate, unless there is a medical contraindication to contrast. Scans of the neck, abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with non-contrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). It is recommended that spiral/multidetector CT be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.
- The same imaging modality and image-acquisition protocol (including use or nonuse of IV contrast) should be used consistently across all time points to allow consistent comparison of lesions. Low-dose non-contrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable.

Ultrasound should not be used for radiographic tumor assessment. A chest x-ray or skeletal x-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

- To be considered a target lesion at baseline, the minimum size of non-lymph nodes should be 1.0 cm in the longest diameter. If this is the only target lesion, the longest diameter should be ≥ 1.5 cm. (However, if a slice thickness > 5 mm is used, the minimum lesion size should be twice the slice thickness.) For a lymph node to be considered a target lesion at baseline, the minimum lesion size should be ≥ 1.5 cm in the short-axis.
- Brain scans should be performed with and without contrast-enhanced CT or MRI with 5-mm contiguous slices recommended (maximum inter-slice gap of 1 mm on MRI).
- The recommended bone scan technique is 99m-technetium-methylene diphosphonate (99m-Tc MDP) scintigraphy or whole body-bone MRI, although 18F-sodium fluoride PET (NaF PET) may be used if the 99m-Tc MDP tracer is not available. If an alternative scanning method is used, it should be continued throughout the rest of the study. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.
- If a bone lesion is to be followed as a non-target lesion, it is preferable that this be done using CT/MRI. For bone non-target lesions that can be followed only on bone scans, a time point response other than Not Evaluable (NE) will be allowed despite an individual lesion assessment of NE for weeks when bone scans are not required.
- If subcutaneous masses or nodes are palpable (e.g., bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions.
- Assessments are to be performed at the site by appropriately qualified personnel and results of the site interpretation are to be recorded on the appropriate eCRF page.

12.3 *Secondary efficacy assessments*

- Progression-free survival (PFS) is defined as the time from the date of treatment start (C1D1) to the date of first documentation of disease progression or death (whichever occurs first) using RECIST 1.1. PFS censoring rules will follow FDA guidance in 2007[7].
- Early tumor shrinkage (ETS) rate defined as 20% reduction in target lesions after the first 6 weeks of treatment (first tumor assessment)
- Deepness of response (DpR) defined as percentage of maximum tumor shrinkage observed at the nadir compared with baseline.

12.4 *Pharmacodynamic, and Pharmacogenomic Assessments for the substudy*

Blood samples for the development of exploratory predictive biomarkers will be collected from all subjects prior to the first dose of study drug, and on Cycle 2/Day 1 and after documented disease progression. Biomarker discovery and validation will be performed to identify blood or tumor biomarkers which may be useful to predict subject response, as determined by evaluation of primary or secondary efficacy endpoints. Plasma samples from study subjects will undergo global proteomic and/or enzyme-linked immunosorbent assay (ELISA)-based analyses or multiplex bead-based immunoassay in an effort to identify protein biomarkers. In addition, DNA and RNA analyses will be performed in search of predictive or prognostic biomarkers and also biomarkers identified in other lenvatinib clinical studies may also be assessed in samples collected from subjects enrolled in this study.

Archived, fixed tumor tissue from will be collected for all subjects for confirmation of histology and assessment of somatic mutations of genes which may be important in the development and progression of neuroendocrine tumors. Gene-expression profiling (GEP), proteomic, or immunohistochemical (IHC) analysis will be performed based on the amount of tumor tissue available for analysis. All analyses will be limited to correlations relevant to neuroendocrine tumors and clinical outcomes related to treatment with lenvatinib.

Blood and tumor samples collected during the study will be stored at the study sites until the initial primary efficacy and safety analyses of the study will be completed and results will be available. Then, the study sponsor will decide whether to perform all or part of the pharmacogenetic/pharmacogenomics assessments.

A specific and optional patient information sheet and Informed consent will be obtained for the collection of blood and tumor samples for the pharmacogenetic/pharmacogenomics assessments. Patient could participate in the study even if they do not sign this specific consent for the collection of blood and tumor samples, this will not be considered as protocol deviation.

Data obtained will only be used for research, to assist in developing safer and more effective treatments, and will not be used to change the diagnosis of the subject or alter the therapy of the subject. Any DNA derived from the sample may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib. Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual. For details about samples see Appendix VI Pharmacogenomics.

12.5 *Safety Assessments*

Safety will be assessed by monitoring and recording all AEs including all CTCAE grades (for both increasing and decreasing severity) and serious adverse events (SAEs); regular

monitoring of hematology, clinical chemistry, and urine values; physical examinations; and regular measurement of vital signs, and electrocardiograms (ECGs) and detailed in the schedule of visits and procedures (Table 4).

13. Trial development

13.1 *Schedule of Visits and Procedures*

Table 4 Schedule of Visits and Procedures

This table presents the schedule of visits and procedures for the screening, treatment and follow-up phases of this study.

Phase	**Screening Phase**		**Treatment Phase**									**FU Phase**
Period	**Screening[a, b]**	**Baseline[a, b]**	**Study Treatment**									**Follow up**
Visit	**v1 -28 TO -2**	**V2 DAY -1**	**V3 C1D1**	**V4 C1 D7**	**V5 C1D15**	**v6 C2D1**	**v7 C2D15 W6**	**v8 C3D1**	**v9 C3D15**	**V10 C4D1 CXD1**	**EOT +28D LD**	**Every 6 months**
Informed consent	X											
Inclusion/exclusion	X	X										
Allocation		X										
Demographic data	X											
ECOG PS[c]	X	X	X[a]	X	X	X	X	X	X	X	X	
pTNM staging	X											
Med/Surg history	X	X										
Vitals signs[d]	X	X	X[a]	X	X	X	X	X	X	X	X	
Physical exam[f]	X	X[e]	X[a]	X	X	X	X	X	X	X	X	
12-lead ECG[g]	X					X					X	
Echocardiogram[h]	X				Performed every 24 weeks following the first dose of study drug or sooner, if clinically indicated							
Biochemistry and hematology[h]	X	X[h]	X[b]	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X[b]	X	X	X	X	X	X	X	X	
Pregnancy test[i]	X	X	X[b]									

Phase	Screening Phase		Treatment Phase									FU Phase
Period	**Screening[a, b]**	**Baseline[a, b]**	**Study Treatment**									**Follow up**
Visit	**v1 -28 TO -2**	**V2 DAY -1**	**V3 C1D1**	**V4 C1 D7**	**V5 C1D15**	**v6 C2D1**	**v7 C2D15 W6**	**v8 C3D1**	**v9 C3D15**	**V10 C4D1 CXD1**	**EOT +28D LD**	**Every 6 months**
Dispense Study Treatment			x			x		x		x		
Accountability Study Treatment			x			x		x		x	x	
Tumor assessments (CT/MRI)[j]	X		CT/MRI of abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease should be performed at week 6 after the first dose of treatment, 12 weeks after the first treatment dose and then, every 12 weeks or sooner if clinically indicated until documentation of disease progression									
Survival[k]				x		x		x		x	x	x
Biomarkers[l]		x				x					x	
Archival tumor blocks or slides[m]		x										
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	
AEs/SAEs[p]	x	x	x	x	x	x	x	x	x	x	x	

AEs = adverse events, BP = blood pressure, CT = computerized tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, HR = heart rate, LD = last dose, MRI = magnetic resonance imaging, PET = positron-emission tomography, RECIST = Response Evaluation Criteria In Solid Tumors, RR = respiratory rate, SAEs = serious adverse events, surg = surgical, 99m-Tc MDP = 99m-technetium-methylene diphosphonate,

a. 72 hours before Cycle 1 Day 1 (C1D1). The **baseline assessment can be performed on C1D1, prior to treatment**. Informed consent may be taken up to 4 weeks prior to C1D1. A physical examination is not mandatory for C1D1, if performed at baseline (day -1); however, a symptom-directed physical examination will be performed on Cycle 1/Day 1 and at any time during the study, as clinically indicated.

b. Efforts should be made to conduct study visits on the day scheduled (± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit.

c. ECOG will be performed at the Screening and Baseline Visits and at every subsequent treatment visit thereafter. For ECOG see Appendix II.

d. Assessments will include vital signs (supine BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. Elevated BP (≥140/90 mmHg) should be confirmed by 3 measurements (at least 5 minutes apart). If systolic BP is ≤ 140 mmHg to <160 mmgHg or dyastolic BP ≤90 mmHg to 100 mmHg, BP should be confirmed by repeat measurements after an hour.

e. Required if screening physical examination was performed > 7 days prior C1D1.

f. A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visit, on each visit of the Treatment phase, and at the off-treatment assessment. A symptom-directed physical examination will be performed on Cycle 1/Day 1 and at any time during the study, as clinically indicated.

g. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

h. Baseline Assessments scheduled may be performed within 72 hours prior to the visit. Repeat complete full blood count with differential and AEs assessment will be performed as per the investigator judgment (until improvement to < Grade 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor and probably will be discontinued.

i. A serum or urine pregnancy test will be performed at the Screening Visit, at the Baseline Visit (or within 72 hours prior to the first dose of study medication)

j. Screening tumor assessments using CT of the abdomen/pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast. Treatment phase: tumor assessments of the abdomen/pelvis and other areas of known disease or newly suspected disease should be performed after 6 weeks of first dose of study treatment, the second assessment will be performed 12 weeks after the first dose, and then every 12 weeks (or sooner if there is evidence of progressive disease) and should utilize the same methodology (CT or MRI) and scan

acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments. Brain metastases assessment should be performed every 12 weeks and bone lesions every 24 weeks, only when clinically indicated.

Screening CT/MRI of the brain and bone scan should only be performed in patients with known or suspected brain or bone lesions. During treatment phase evaluation of brain metastases should be performed every 12 weeks and bone lesions every 24 weeks.

A dynamic study of multiphasic imaging, at least biphasic imaging, with arterial and venous/portal phases must be performed using CT and/or MG, since one or other technique may be recommended depending on specific clinical characteristics of the patient. As a general rule, TCs will be performed. Although, for example, a MR with a dynamic study would be indicated for patients allergic to iodinated contrast (in the CT).k. Survival data will be collected every 4 weeks until end of treatment is declared. All anticancer therapies will be collected. Survival data and other cancer treatments received will be collected every 6 months until close of the study database. The study sponsor may elect to discontinue survival follow-up.

l Collection of blood sample to obtain plasma, serum, or other components to be used for biomarker studies. Samples will be obtained at baseline, Cycle 2/Day 1, and at end-of-treatment visit.

m. All subjects will have collection of most recent archived, tumor-biopsy sections for identification of predictive biomarkers.

n. Throughout the study from the signature of Informed Consent. SAE irrespective of relationship to study treatment must be reported within 24 hours since awareness of the SAE. AEs and concomitant meds collected 28 days from last dose.

13.2 *Screening period procedures*

Day -28 to Day -1 (Visit 1)

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates and written informed consent will be obtained. Once informed consent has been obtained (within 4 weeks of first dose of study drug), the following procedures and evaluations will be performed:

- Verify inclusion/exclusion criteria, including:
    - Histological confirmed diagnosis of one of the following neuroendocrine tumor subtypes:
        - G1/G2 pancreatic neuroendocrine tumor (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF).
        - G1/G2 gastrointestinal neuroendocrine tumor including stomach, small intestine and colorectal origins (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF).
    - Patients must show evidence of disease progression within 12 months (an additional month will be allowed to accommodate actual dates of performance of scans, i.e., within ≤ 13 months) prior to signing informed consent, according to RECIST 1.1 criteria (Appendix I).
        - In case of patients with tumors of pancreatic origin, progression after previous treatment with targeted agent should be verified (including mTOR inhibitors, such as everolimus or antiangiogenic therapies, such as sunitinib, sorafenib, axitinib, bevacizumab within others). Combination therapies in the same treatment line (such as sorafenib plus bevacizumab, chemotherapy plus antiangiogenic drugs) are considered one treatment line and are allowed to be included in the study. Patients must be treated with only one previous line of targeted agent(s)-based therapy. Previous therapy with somatostatin analogues and/or interferon treatment is allowed and is not considered as a previous targeted agent therapy.
        - In case of patients with tumors of Gastrointestinal origin: progression after therapy with antitumoral doses of somatostatin analogs (octreotide LAR 30 mg every 28 days or Lanreotide 120 mg every 28 days) and/or interferon should be verified.
    - Measurable disease:
        - At least 1 lesion of ≥ 1.0 cm in the longest diameter for a non-lymph node or **≥ 1.5 cm in the short-axis diameter** for a **lymph node** (lymph node

enlargement) which is serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI).

- NON-lymph node measurable lesion/ non-lymph node > 10 mm in maximum axis.
  - In case of a SINGLE NON-lymph node measurable LESION, the size must be > 15 mm in the maximum axis.
-
- Lesions that have had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion;

- Record demographic data;
- Evaluate ECOG performance status (subjects must register 0 or 1 on the ECOG scale for study eligibility) (Appendix II);
- Establish pTNM staging and diagnosis;
- Record medical and surgical history;
- Obtain vital signs (systolic and diastolic BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. BP, HR, and RR will be obtained after subjects have been resting for 5 minutes. For subjects with an elevated BP (≥140/90 mmHg), confirmation should be obtained by performing 3 measurements (at least 5 minutes apart) to yield a mean value. Systolic BP ≥140 mmHg to <160 mmgHg or dyastolic BP ≥90 mmHg to 100 mmgHg should be confirmed by repeat measurements after an hour;
- Perform a comprehensive physical examination (including a neurological evaluation);
- Perform a single, 12-lead electrocardiogram (ECG);
- Perform an echocardiogram any time during the screening phase;
- Collect blood samples for biochemistry and hematology analysis including INR (see Table 5 for the tests to be performed);
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed); Samples for hematology, urinalysis and chemistry laboratory testing may be collected at any time within 72 hours prior to first dose of study drug;
- Collect urine sample for β-hCG pregnancy testing from all premenopausal and any postmenopausal women who have been amenorrheic for < 12 months;
- Perform CT/MRI tumor assessments; If CT/MRI of abdomen/pelvis are available within 28 days previous to the first dose of the study drug it is not need to repeat them and they will be used as a baseline tumor assessment;

Scans of the abdomen, pelvis and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast;

- Record somatostatin receptor schintigraphy (octreoscran/ PET-CT) if available within the last 6 months previous C1D1;
- CT or MRI of the brain and bone scan if indicated;
- Record all prior and concomitant medication use (prescription and non-prescription medications as well as transfusions);
- Record any AEs or SAEs;

The screening form must be completed for all subjects screened, providing reasons for screen failure when applicable.

13.2.1 *Baseline period procedures*

Day 0 (Visit 2)

The results of all screening assessments and evaluations must be completed and reviewed by the Principal Investigator prior to the Baseline Visit. Baseline assessments can be performed either on Day -1 or on Cycle 1/Day 1 prior to treatment, although the hematology, clinical chemistry, and pregnancy assessments may be performed within 72 hours prior to the first dose of study drug (Cycle 1/Day 1). Only those subjects who continue to meet all of the inclusion and none of the exclusion criteria are eligible to continue in the study.

Reasonable efforts should be made to conduct all baseline and subsequent evaluations in the same test order at each visit. This is intended to minimize variability in subject response. It is further recommended, whenever possible, that subjects be evaluated at approximately the same time of the day (e.g., morning or afternoon) at each subsequent visit.

At the Baseline Visit, the following evaluations will be conducted:

- Reconfirm inclusion/exclusion criteria;
- Allocation to cohort A or Cohort B, no randomization needed for this study as all patients included will receive the same study treatment;
- Evaluate ECOG performance status;
- Update medical and surgical history;
- Obtain vital signs and weight;
- Perform a comprehensive physical examination if the Screening Visit physical examination was performed more than 7 days prior to Cycle 1/Day 1 A symptom-directed physical examination will be performed on Cycle 1/Day 1 and at any time during the study, as clinically indicated;

- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed). Screening results may be used if collected within 72 hours pre-dose;
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed);
- Collect urine sample from all premenopausal and any postmenopausal women who have been amenorrheic for < 12 months for β-hCG pregnancy testing. Screening pregnancy test results may be used if obtained within 72 hours pre-dose;
- Collect blood samples for biomarker analysis;
- Collect most recently archival tumor-biopsy sections or blocks for identification of predictive biomarkers;
- Record all concomitant medication use;
- Record any AEs or SAEs;

In case of any altered parameter of the screening/baseline parameters, these assessments could be repeated during the screening period (-28 to day -1) to check their stability/recovering. Other cases should be confirmed by the Sponsor prior to be considered as screening failure.
Subjects who complete the Baseline Period and remain eligible for the study will continue into the treatment phase.

13.2.2 *Treatment phase assessments schedule*

13.3 *Treatment cycle procedures*

Efforts should be made to conduct study visits on the day scheduled (window ± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures. Whenever possible, subjects should be evaluated at approximately the same time of the day (e.g., morning or afternoon) at each visit, and reasonable efforts should be made to conduct all evaluations in the same test order at each visit.

Cycle 1/Day 1 (Visit 3)

Baseline assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests for hematology, biochemistry and urine tests (see Table 4) including pregnancy test (where applicable) can be performed within 72 hours prior to the first dose of study drug. No need to repeat them if previously obtained at basal visit.

- Obtain vital signs (resting BP, HR, RR, body temperature) and weight;
- Evaluate ECOG performance status. No need to repeat it if previously obtained at Baseline visit (72 hours before C1D1).;
- Physical examination is not mandatory if performed at baseline (day -1) however a symptom-directed physical examination will be performed on Cycle 1/Day 1 and at any time

during the study, as clinically indicated. No need to repeat it if previously obtained at Baseline visit;

- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed). Screening/baseline results can be used if they have been obtained 72 hours before the first dose of study drug;
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed) Clinical laboratory tests including pregnancy test (where applicable) can be performed within 72 hours prior to the first dose of study drug;
- Administer/dispense study drug:
  - Study drug (oral, QD). First dose to be taken at the site;
  - Instruct the subject not to take the Day 7 dose of study drug before coming to the site;
  - Record all concomitant medication use;
  - Record any AEs or SAEs;
  - Record the accountability of the study drug;

Cycle 1/Day 7 (Visit 4)

- Obtain vital signs (BP, HR, RR and body temperature at rest) and weight
- Evaluate ECOG performance status.
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated.
- Instruct the subject not to take the Day 15 dose of study drug before coming to the site.
- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed).
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed). Repeat complete full blood count with differential and perform AEs assessment as per the investigator judgment (until improvement to < Grade < 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor who will probably determine to discontinue the subject.
- Record concomitant medication use.
- Record any AEs or SAEs.

Cycle 1/Day 15 (Visit 5)

- Obtain vital signs (resting BP, HR, RR, body temperature) and weight;
- Evaluate ECOG performance status;
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated;

- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed).
- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed). Repeat complete full blood count with differential and AEs assessment will be performed as per the investigator judgment (until improvement to < Grade 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor and probably will be discontinued;
- Instruct the subject to bring back the unused study drug (blister, boxes) for the following study visit;
- Record all concomitant medication use;
- Record any AEs or SAEs;

Cycle 2/Day 1(Visit 6)

- Evaluate ECOG performance status;
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight;
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated;
- Perform a single, 12-lead electrocardiogram (ECG);
- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed). Repeat complete full blood count with differential and AEs assessment will be performed as per the investigator judgment (until improvement to < Grade 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor and probably will be discontinued;
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed)
- Administer/dispense study drug;
- Unused study drug return and review the accountability of the study drug;
- Collect blood samples for biomarker analysis;
- Record all concomitant medication use;
- Record any AEs or SAEs;
- Record survival data;

Cycle 2/Day 15 (Visit 7)

- Evaluate ECOG performance status;
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight;
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated;

- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed) Repeat complete full blood count with differential and AEs assessment will be performed as per the investigator judgment (until improvement to < Grade 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor and probably will be discontinued;
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed);
- Tumor assessment by CT/MRI of neck/chest/abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease should be performed at week 6 after the first dose of treatment;
- Instruct the subject to bring back the unused study drug (Blister/boxes) for the following study visit;
- Record all concomitant medication use;
- Record any AEs or SAEs;

Cycle 3/Day 1 (Visit 8)

- Evaluate ECOG performance status;
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight;
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated;
- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed). Repeat complete full blood count with differential and AEs assessment will be performed as per the investigator judgment (until improvement to < Grade 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor and probably will be discontinued;
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed);
- Administer/dispense study drug;
- Unused study drug return and review the accountability of the study drug;
- Record all concomitant medication use;
- Record any AEs or SAEs;
- Record survival data;

Cycle 3/Day 15 (Visit 9)

- Evaluate ECOG performance status;
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight;
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated;

- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed). Repeat complete full blood count with differential and AEs assessment will be performed as per the investigator judgment (until improvement to < Grade 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor and probably will be discontinued;
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed);
- Instruct the subject to bring back the unused study drug (Blister/boxes) for the following study visit;
- Record all concomitant medication use;
- Record any AEs or SAEs.

Cycle 4 Through Last Cycle/Day 1 (Visit 10 and subsequent until PD)

- Evaluate ECOG performance status;
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight;
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated;
- Perform an echocardiogram every 24 weeks following the first dose of study drug or sooner if clinically indicated;
- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed);
- Repeat complete full blood count with differential and AEs assessment will be performed as per the investigator judgment (until improvement to < Grade 3). A delay of study treatment for more than 28 days (due to AE) will require a discussion with the sponsor and probably will be discontinued;
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed);
- Administer/dispense study drug;
- Unused study drug return and review the accountability of the study drug. Instruct the subject to bring back the unused study drug (Blister/boxes) for the following study visit;
- Perform tumor assessments at time points indicated in the Schedule of Visits and Procedures (Table 4). Assessments should utilize the same methodology and acquisition techniques as were used for the screening assessments:
    - Perform follow-up tumor assessments every 12 weeks or sooner, if clinically indicated) until documentation of disease progression.
- Record all concomitant medication use;
- Record any AEs or SAEs;
- Record survival data.

13.3.1 *End Off-treatment assessments*

Whenever possible, the following assessments should be performed within 28 days after subjects have discontinued study treatment:

- Obtain vital signs (supine BP, HR, RR, body temperature) and weight;
- Evaluate ECOG performance status;
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated;
- Perform a single, 12-lead electrocardiogram (ECG);
- Collect blood samples for biochemistry and hematology analyses (see Table 5 for the tests to be performed);
- Collect urine sample and perform urinalysis (see Table 5 for the tests to be performed);
- Record survival
- Collect blood samples for biomarker analysis;
- Unused study drug return and review the accountability of the study drug Record all concomitant medication use. Concomitant medications should be collected for 28 days after the last dose of study medication;
- Record any AEs or SAEs. AEs should be collected for 28 days after the last dose of study medication. SAEs, regardless of causality assessment, must be collected through the off-treatment assessment and for 28 days following study drug discontinuation, whichever is longer. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

13.4 *Record survival data. Post study treatment follow-up period procedures*

After study drug discontinuation, subjects will be followed for survival during the Post Study Treatment Follow-Up Period. Survival data and other cancer treatments received will be collected every 6 months until close of the study database. The study sponsor may elect to discontinue survival follow-up at any time.

13.5 *Laboratory measurements*

Clinical laboratory tests and urinalysis will be performed at the investigational site. The schedules of visits and procedures (Table 4) show the visits at which blood and urine will be collected for clinical laboratory tests. A Laboratory Manual will be provided to detail handling, processing, and shipping procedures. Regarding sample handling, Law 14/2007 of Biomedical Research will be complied with. All hematology, clinical chemistry (including pregnancy test, where applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior

to administration/dispensing of study drug at the beginning of Cycle 1 and within 24 hours after Day 1 of all subsequent cycles. Please refer to Study Drug Dose Reduction and Interruption Instructions (Table 3) for the management of clinically significant laboratory abnormalities. A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol and the eCRF Completion Instructions. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF. Table 5 presents the clinical laboratory tests to be performed.

Table 5 Clinical laboratory tests

Category	Tests
Hematology	• Hematocrit, hemoglobin, RBC, platelet count, WBC with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), MCH, MCHC, MCV • INR[a]
Clinical Chemistry	
Screening visit	• Pregnancy test (serum or urine β-hCG)[b] • Bicarbonate, chloride, potassium, sodium, BUN or urea, creatinine, glucose, magnesium, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, total bilirubin • TSH • Chromagranin A (pancreatic origin patients) • Chromagranin A +5 HIAA (only for gastrointestinal origin patients) • Levels of NSE[e]
Treatment visits without tumor assessment	• Bicarbonate, chloride, potassium, sodium, BUN or urea, creatinine, glucose, magnesium, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, total bilirubin
Treatment visits with tumor assessment	• Bicarbonate, chloride, potassium, sodium, BUN or urea, creatinine, glucose, magnesium, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, conjugated (direct) bilirubin, total bilirubin • TSH • Chromagranin A (pancreatic origin patients) • Chromagranin A +5 HIAA (only for gastrointestinal origin patients) • Levels of NSE[e]
Urine analysis [c]	glucose, hemoglobin (or blood), ketones, pH, protein specific gravity[d]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta human chronionic gonadotropin; BUN = Blood urea nitrogen; CPK=creatine phosphokinase; INR=International Normalized Ratio; LDH= lactate deshidrogenase; MCH=mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NSE = neuron-specific enolase; RBC=red blood cells; T4=thyroxine; TSH=thyroid stimulating hormone; WBC=White blood cells

a) INR should only be performed as part of the screening (baseline) assessment and when clinically indicated.
b) Pregnancy test should be performed during 72 hours prior to the study drug administration.
c) If urinanalysis suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture and sensitivity should be performed at the

institution laboratory.

d) If the urine protein is ≥2+ on urinalysis, then a 24-hour urine collection should be done to quantify the 24-hour urine protein excretion.

e) Levels of NSE will be obtained based on local availability to perform the test at each site.

For laboratory abnormalities meeting criteria as SAEs (Section 15.3), the study site must send the SAE report including the laboratory report to the SAE fax number or email address provided in the Investigator File.

13.6 *Vital signs and weight measurements*

Vital sign measurements (systolic blood pressure, diastolic blood pressure, heart rate [HR], respiratory rate [RR], body temperature [°C]), and weight will be obtained at the visits designated in the schedule of visits and procedures (Table 4). Height will be measured at the screening visit only. Blood pressure, HR, and RR will be obtained after subjects have been resting for 5 minutes. For subjects with an elevated BP (≥ 140/90 mmHg), confirmation should be obtained by performing 3 measurements (at least 5 minutes apart) to yield a mean value. Systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg should be confirmed by repeat measurements after an hour.

13.7 *Electrocardiograms*

Electrocardiograms will be complete, standardized, 12-lead recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 x 4 lead format. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects should be in the recumbent position for a period of 5 minutes prior to the ECG. An ECG abnormality may meet the criteria as an AE as described in this protocol (Section 15) and the CRF instructions. In case of basal ECG abnormality but does not involve any risk to the patient by the judgment of the investigator, the patient may be included in the study and need not be repeated ECG otherwise indicated by the investigator.

In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF. For ECG abnormalities meeting criteria as SAEs (Section 14.3), the study site must fax the SAE report including the ECG report to the number indicated in the Investigator File using the SAE reporting form.

13.8 *Echocardiograms*

An echocardiogram to assess left ventricular ejection fraction (LVEF) will be performed during the screening phase and every 6 months following the first dose of study drug while the subject is on treatment or sooner, if clinically indicated. Echocardiograms should be performed following the local protocol to assess LVEF. LVEFs as assessed by the institution will be entered onto the eCRF. Investigator assessment will be based upon institutional reports.

14. Adverse events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease.
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Reporting Laboratory abnormalities

An abnormal laboratory test result may be considered as an adverse event if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an adverse event if it:

- Results in the withdrawal of study treatment.
- Results in withholding of study treatment pending some investigational outcome.
- Upon medical evaluation, results in the initiation of an intervention (e.g., potassium supplement for hypokalemia).
- Is an out-of-range laboratory value that, in the investigator's judgment, fulfills the definition of an AE with regard to the subject's medical profile.
- Increases in severity compared to baseline by ≥ 2 CTCAE grades (see Appendix IV for CTCAE v4.03), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, a change of ≥ 2 grades will be evaluated by the investigator to determine if they are of clinical significance and, if so, will be considered an adverse event.

Abnormal 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. Any laboratory abnormality considered to constitute an adverse event should be reported on the Adverse Event CRF.

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

Regarding the Laboratory abnormalities only should be notified as SAE those abnormalities that meet Grade 3 or above following the CTCAE criteria (v.4.03), taking into account the following situations:

- Laboratory abnormality is within normal limits at baseline and has increased in severity to meet CTCAE (v4.03) criteria of Grade 3 or above **and** it is considered by the investigator to meet serious criteria should be reported as SAE. i.e. laboratory abnormality is within normal limits at baseline and has increased in severity to meet CTCAE (v4.03) criteria of Grade 3 or above and it is not considered by the investigator to meet serious criteria should not be reported as SAE.
- Laboratory abnormality is outside normal limits at baseline and increases in severity to CTCAE (v4.03) Grade 4 or above. These abnormalities are automatically considered to be serious and should be reported as SAE.
- Significant laboratory abnormalities should not be listed as separate AEs or SAEs if they are considered to be part of the clinical syndrome that is being reported as an AE or SAE.

An abnormal ECG result, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if either there is worsening by ≥ 2 CTCAE v4.03 grade levels from baseline or a QTc increase of ≥60 msec from baseline. Any ECG abnormality that the investigator considers to be an adverse event should be reported as such. In case of basal ECG abnormality but does not involve any risk to the patient by the judgment of the investigator, the patient may be included in the study and need not be repeated ECG otherwise indicated by the investigator.

Adverse events in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes. All AEs encountered during the clinical study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study consent through the last visit and for 28 days following study drug discontinuation.

Progression of malignant disease should not be recorded as an adverse event in studies where it is included as an endpoint for underlying disease. If the progression leads to an untoward medical occurrence (increased pain, pleural effusion, etc.), then this medical occurrence should be the adverse event.

All AEs must be followed until resolution or for 28 days after the subject's last study visit, whichever comes first.

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

14.1 *Assessing severity of adverse events*

AEs will be graded on a 5-point scale according to CTCAE v4.03 (Appendix IV) as follows:

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

Investigators will collect all CTCAE grades (Appendix IV) for AEs (for both increasing and decreasing severity). All adverse events reported using CTCAE classification and graded as 4 or 5 are to be considered serious. The criteria for assessing severity are different from those used for seriousness (see Serious Adverse Events and Other Events of Interest).

14.2 *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, considering 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 which are known to be associated with the occurrence of the event.

Classification of causality

- **Not Related**: A causal relationship between the study treatment and the AE is not a reasonable possibility.
- **Related**: A causal relationship between the study treatment and the AE is a reasonable possibility. The investigator must further qualify the degree of certainty as “possible” or “probable.”

14.3 *Serious adverse events and other events of interest*

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

- Results in death;
- Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- 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 serious adverse events. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest which include pregnancy and overdose. All events of these types are to be reported on the eCRF whether or not they meet the criteria for an SAE.
The following hospitalizations are not considered to be SAEs because there is no “adverse event” (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care;
- Planned hospitalizations required by the protocol;
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration);
- Hospitalization for administration of study drug or insertion of access for administration of study drug.

14.4 *Reporting Laboratory abnormalities*

An abnormal laboratory test result may be considered as an adverse event if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an adverse event if it:

- Results in the withdrawal of study treatment.
- Results in withholding of study treatment pending some investigational outcome.
- Upon medical evaluation, results in the initiation of an intervention (e.g., potassium supplement for hypokalemia).
- Is an out-of-range laboratory value that, in the investigator’s judgment, fulfills the definition of an AE with regard to the subject’s medical profile.

- Increases in severity compared to baseline by ≥ 2 CTCAE grades (see Appendix IV for CTCAE v4.03), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, a change of ≥ 2 grades will be evaluated by the investigator to determine if they are of clinical significance and, if so, will be considered an adverse event.

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

14.4.1 *Laboratory abnormality to be considered as SAE*

Regarding the Laboratory abnormalities only should be notified as SAE those abnormalities that meet Grade 3 or above following the CTCAE criteria (v.4.03), taking into account the following situations:

- Laboratory abnormality is within normal limits at baseline and has increased in severity to meet CTCAE (v4.03) criteria of Grade 3 or above **and** it is considered by the investigator to meet serious criteria should be reported as SAE. i.e. laboratory abnormality is within normal limits at baseline and has increased in severity to meet CTCAE (v4.03) criteria of Grade 3 or above and it is not considered by the investigator to meet serious criteria should not be reported as SAE.
- Laboratory abnormality is outside normal limits at baseline and increases in severity to CTCAE (v4.03) Grade 4 or above. These abnormalities are automatically considered to be serious and should be reported as SAE.

Significant laboratory abnormalities should not be listed as separate AEs or SAEs if they are considered to be part of the clinical syndrome that is being reported as an AE or SAE.

14.5 *Reporting of SAEs, Pregnancy, and Other Events of Interest*

14.5.1 *Reporting of SAEs*

All serious adverse events (SAEs), irrespective of relationship to study treatment, must be reported on a completed SAE form by email (farmacovigilancia@experior.es) or fax (0034 96 145 21 91) as soon as possible within **24 hours since awareness of the SAE**. Serious adverse events, regardless of causality assessment, must be collected from the signature of the ICF by the patient through the termination visit and for 28 days following study drug discontinuation, whichever is longer. All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor

regardless of the length of time that has passed since study completion. Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed-up within 24 hours since awareness of such information by emailing or faxing the completed SAE form. The detailed contact information for reporting of SAEs is provided in the Investigator 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 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.

The investigator should notify his/her EC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to the CRO monitor and filed in the Trial Master File.

14.5.2 *Reporting of Pregnancy*

Any pregnancy where the estimated date of conception occurs either prior to the study termination visit or within 28 days of the 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.

An induced abortion or a spontaneous abortion is considered to be an SAE and should be reported in the same timeframe and in the same format as all other SAEs. Pregnancies must be reported within 24 hours since awareness of it by fax (0034 96 145 21 91) or email (farmacovigilancia@experior.es). The contact information for the reporting of pregnancies is provided in the Investigator 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 within 24 hours since awareness of it.

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

14.5.3 *Reporting of Overdose*

Study drug overdose is the accidental or intentional use of the drug in the amount higher than the dose being studied. Any study drug overdose during the study should be noted on the study medication CRF.

All AEs associated with an overdose should both be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of SAEs even if the events do not meet serious criteria. If the AE associated with an overdose does not meet serious criteria, it must still be

reported using the SAE form and in an expedited manner but should be noted as non-serious on the SAE form and the Adverse Event CRF.

14.6 *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 (i.e., within specific timeframes). For this reason, it is imperative that investigational sites provide complete SAE information in the manner described above.

14.7 *Regulatory reporting of adverse events*

Adverse events will be reported to regulatory authorities in compliance with local and regional law and established guidance by the sponsor, or a third party acting on behalf of the sponsor. The format of these reports will be dictated by the local and regional requirements and will comply with the European Clinical Trial Directive 2005/28/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported as required to the Competent Authorities of all involved European member states.

14.8 *Treatment Emergent Adverse Event*

TEAE is defined as any event not present prior to the initiation of the study drug or any event already present that worsens in either intensity or frequency following exposure to the study drug. TEAE provides more relevant and useful information than a general AE to the investigators. Therefore, most AE tables in statistical reports should be based on TEAE. In this sense, any unfavorable and unintended sign prior to dosing 3 but not worsening during the treatment will be automatically excluded from the analysis. The programming practice to code a TEAE is comparing AEs onset date/time and first study drug administration date/time. If the AE has the same intensity before and after the first drug administration, then it is not counted as TEAE. Note that a TEAE is not necessarily a drug related AE.

14.8.1 *Management of hypertension*

Hypertension is a recognized side-effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP < 150/90 mmHg at the time of study entry and, if known to be hypertensive, are on antihypertensive therapy before they start treatment with lenvatinib. The 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 the BP is confirmed to be ≥ 140/90 mmHg on 3 measurements performed every 5 minutes after the first measurement, and a last measurement performed in an hour. The choice of antihypertensive

treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of anti-hypertensives should be started when BP ≥ 140/90 mmHg is first observed. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred.

Study drug should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (e.g., BP ≥ 160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the blood pressure is controlled, study drug should be resumed as described below.

The following guidelines should be followed for the management of systolic BP ≥ 140 mmHg to <160 mmgHg or diastolic BP ≥ 90 mmHg to 100mmgHg confirmed on repeat measurements after an hour:

- Continue study drug and institute antihypertensive therapy for subjects not already receiving this.
- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.
- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persists despite maximal antihypertensive therapy, then study drug administration should be interrupted and restarted at a dose of 20 mg once daily when BP ≤ 150/95 mmHg and the patient has received a stable dose of antihypertensive drugs within at least 48 hours. (Refer to Table 3 for instruction regarding duration of the interruption of drug administration and decision of reintroduction)
    - If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the 20-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a dose of 14 mg once daily when BP ≤ 150/95 mmHg.
    - If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the 14-mg once daily dose despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a dose of 10 mg once daily when BP ≤ 150/95 mmHg.

- 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):

- Institute appropriate medical management.
- Discontinue of study drug

A summary table of treatment for hypertension is shown below.

Table 6.- Treatment for hypertension

Level of blood pressure (BP)	**Recommended action**
Systolic BP ≥140mmHg to <160 mmHg or Diastolic BP ≥90 mmHg to <100 mmHg	Continue with treatment with lenvatinib and start antihypertensive treatment, if it has not been administered yet OR Continue with treatment with lenvatinib and increase the dose of current antihypertensive drug or start and additional antihypertensive treatment
Systolic BP ≥160 mmHg or Diastolic BP ≥100 mmHg despite the administration of a treatment optimal antihypertensive	1. Discontinue the administration of lenvatinib 2. If systolic BP is ≤150 mmHg, diastolic BP is ≤95 mmHg and the patient has received a stable dose of antihypertensive medication during at least 48 hours, resume the administration of lenvatinib to a reduced dose.
Life-threatening consequences (malignant hypertension, neurological damage or hypertensive crisis)	An immediate action is required. Discontinue treatment with lenvatinib and start appropriate medical treatment

14.8.2 *Management of Proteinuria*

Regular assessment for proteinuria should be conducted as detailed in the schedule of visits and procedures (table 4). Guidelines for assessment and management of proteinuria are summarized as follows:

- Initial episode of proteinuria: if proteinuria ≥ 2+ is detected on urinalysis, study drug will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03, Appendix IV) will be based on the 24-hour urinary protein result. Management of study drug

administration will be based on the grade of proteinuria according to the dose reduction and interruption instructions provided in Table 3.

- Urinalysis should be performed every 4 weeks subsequent to cycle 2 during the treatment phase and any increases in the level of proteinuria on urinalysis up to 3+ needs to be confirmed with a 24-hour urinary protein test which will be assessed and graded according to the dose reduction and interruption instructions provided in Table 3.

15. Data quality assurance

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

15.1 *Data Collection*

Data required by the protocol are collected on an electronic Case Report Form (eCRF) and entered into a validated data management system which is compliant to all regulatory requirements. As defined by ICH Guidelines, 'the Case Report Form (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 trial subject'. In this study, CRF should refer to electronic data collection form. Data collected 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, safety and laboratory data entered on the CRF.

The primary objective of the study will be ORR by central radiology review. Images of tumor assessments will be anonymized correctly identified with trial number patient (code dissociated) and send to Vall d'Hebron University Hospital for revision by an independent experienced radiologist.

15.2 *Clinical Data Management*

All software applications used in the collection and validation of data must be properly validated following standard computer system validation and must be compliant to all regulatory requirements.

The Data Management Plan (DMP) defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure data are properly entered, validated, coded, integrated, reconciled and reviewed.

Data cut-off for the study primary analysis will take place after the last patient enrolled in the study has performed the second tumor assessment (week 12 after the first dose of study drug) given that the first assessment will be performed 6 weeks after the first dose). Subsequent tumor

assessments will be performed starting on week 12 every 12 weeks until documentation of disease progression or start of another anticancer therapy.

15.3 *Database Quality Assurance*

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

16. Ethical aspects

16.1 *Ethics Committee*

The protocol, ICF, and appropriate related documents must be reviewed and approved by an EC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations. Any protocol amendment and/or revision to the ICF will be resubmitted to the EC for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s] or change of telephone number[s]). Documentation of EC compliance with ICH and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the EC Chairman must be sent to the Principal Investigator (if regionally required, the heads of the medical institutions) with a copy to the sponsor prior to study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the EC decides to suspend or terminate the study, the investigator (if regionally required, the heads of the medical institutions) will immediately send the notice of study suspension or termination by the EC to the sponsor. Study progress is to be reported to the EC annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the EC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or sponsor will submit, depending on local regulations, periodic reports and inform the EC (if regionally required, the heads of the medical institutions) of any reportable adverse events per ICH guidelines and local EC standards of practice. Upon completion of the study, the investigator will provide the EC with a brief report of the outcome of the study, if required.

16.2 *Ethical Conduct of the Study*

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

- In accordance to the principle of World Medical Association Declaration of Helsinki, 2013;
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use;
- European Clinical Trial Directive 2005/28/EC, for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states;
- And other applicable regulatory authorities.

16.3 *Subject information and Consent*

As part of administering the informed consent document, the investigator must explain to each subject (or guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an informed consent at the Screening Visit prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. An unsigned copy of an EC and sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations and provided to the sponsor. Each subject must sign an approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file, according to local procedure, at the study center.

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

17. Administrative procedures

17.1 *Changes to the Protocol*

There are to be no changes to the protocol without written approval from the sponsor. Protocols will be followed as written. Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable EC of all investigational sites and, in some countries, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the investigator to be necessary for safety reasons, the sponsor's appropriate study team member must be notified promptly and the EC for the site must be informed immediately. A protocol change intended to eliminate an immediate hazard may be implemented immediately, provided that the Regulatory Authorities are subsequently notified by protocol amendment.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or EC approval, but the EC (if regionally required, the heads of the medical institutions) must be kept informed of such changes. In these cases, the sponsor will send a letter to the EC (if regionally required, the heads of the medical institutions) detailing such changes.

17.2 *Adherence to the Protocol*

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

17.3 *Monitoring Procedures*

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

In accordance with ICH E6, Section 6.10, source documents include but are not limited to the following:

- Clinic, office, hospital charts;
- Copies or transcribed healthcare provider notes which have been certified for accuracy after production;
- Recorded data from automated instruments such as x-rays, and other imaging reports: e.g., sonograms, CT scans, MRIs, nuclear medicine scans, ECGs, rhythm strips, electroencephalograms (EEGs), polysomnographs, and pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives);
- Records of telephone contacts;
- Drug distribution and accountability logs maintained in pharmacies or by research personnel;
- Laboratory results and other laboratory test outputs: e.g., urine pregnancy test result documentation;
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the EC;

17.4 *Recording of Data*

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document. Any corrections to entries made on the CRF must be documented in a valid audit trail where the corrections must be dated, initialed, the reason for change stated, and original data not obscured. Only data required by the protocol for the purposes of the study should be collected.

17.5 *Retention of Records*

The circumstances of completion or termination of the study notwithstanding, the investigator (if regionally required, the heads of the medical institutions) has the responsibility to retain all study documents, including but not limited to the protocol, the Investigator's Brochure, regulatory agency registration documents, ICFs, and EC correspondence. The investigational site should plan to retain study documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least until 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

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

17.6 *Auditing Procedures and Inspection*

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's Standard Operating Procedures (SOPs) to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

17.7 *Handling of Study Drug*

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

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator (a designated pharmacist) must not destroy any drug labels or any partly used or unused drug supply prior to approval to do so by the sponsor. At the conclusion of the study and as appropriate during the course of the study, the investigator (a designated pharmacist) will either return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's designated contractor or, where approval is given by the sponsor, will destroy supplies and containers at the investigational site.

17.8 *Publication of Results*

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the CRO or the sponsor, as appropriate.

17.9 *Disclosure and Confidentiality*

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

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the investigator and sponsor (provided by the sponsor).

17.10 *Subject Insurance and Indemnity*

The sponsor will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study.

18. *Completion/Discontinuation of Subjects*

18.1 *Removal of Subjects from Therapy or Assessment*

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

The investigator may discontinue treating a subject with the study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study drug or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the follow-up period and be required to complete protocol-specified end of treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject is withdrawing from study treatment but agreeing to continue protocol-specified, end of treatment study visits, procedures, and survival follow-up, or whether the subject is withdrawing consent. If a subject withdraws consent, the date will be documented in the source documents.

Subjects who have discontinued study treatment without progression should have disease assessments every 12 weeks from the date of the last assessment until disease progression is documented or another anti-cancer therapy is initiated.

All subjects will be followed for survival and all post disease progression cancer treatments administered will be recorded until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up following completion of the primary study analysis.

18.2 *Completion/Discontinuation of Subjects*

A subject may elect to discontinue study drug at any time for safety, medical, or personal reasons. Patients who choose to discontinue study drug prior to disease progression will be followed in the post study treatment follow up period and continue to undergo regularly scheduled disease assessment until documentation of disease progression or start of an alternative anticancer therapy. All subjects who discontinue study drug will be followed for overall survival and all post progression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn. All subjects who discontinue study drug are to complete the study discontinuation procedures indicated in the Schedule of Visits and Procedures (Table 4). The investigator will promptly explain to the subject involved that the study drug 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 as much as possible to gather information such as the reason for failure to return and the status of treatment compliance, presence or absence of adverse events, and clinical courses of signs and symptoms, and the information will be recorded in the CRF.

Subjects who discontinue early from the study or treatment will be discontinued for 1 of these primary reasons: adverse event(s), lost to follow-up, subject choice, progressive disease, or administrative/other. In addition to the primary reason, the subject may have indicated 1 or more of these reasons as secondary reasons for discontinuation. Study disposition information will be collected on the appropriate CRF. A subject removed from the study for any reason may not be replaced.

19. *Confirmation of Medical Care by Another Physician*

The investigator will instruct the subject to tell beforehand when the subject is going to receive medical care by another physician. At each visit, the investigator will ask the subject whether the subject has done so 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.

20. *Statistical methods*

Statistical programming and analyses will be performed using R statistical software and/or other statistical software.

20.1 *Statistical and Analytical Plans*

The statistical analyses described in this section will be performed as further outlined in the Statistical Analysis Plan, which will be included in the clinical study report for this protocol.

20.2 *Analysis Sets*

The analysis sets will be defined as follows:

- **Full Analysis Set** will include all allocated subjects. This will be primary analysis set for the efficacy endpoints.
- **Per Protocol Analysis Set** will include those subjects who were allocated and received at least one dose of the assigned study drug and had no major protocol deviations. The subjects will complete both baseline and at least one post-baseline tumor assessments (week 6).
- **Safety Analysis Set** will include all subjects who were allocated and received at least one dose of the study drug and had at least one post-baseline safety evaluation (week 6). This will be the analysis set for all safety evaluations.
- **Pharmacodynamic Analysis Set**: All the subjects who have received at least one dose of study drug and have evaluable pharmacodynamic data.

20.3 *Demographic and other baseline characteristics*

Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as n, number of not available data (NA), mean, standard deviation, median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

20.4 *Prior and concomitant medications*

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

20.5 *Efficacy Analyses*

All efficacy analyses will be based primarily on the Full Analysis Set and secondarily on the Per Protocol Analysis Set.

Data cut-off for the study primary analysis will take place after the last patient enrolled in the study has performed the second tumor assessment (week 12 after the first dose of study drug, given that first evaluation will be performed 6 weeks after the first dose. Subsequent tumor assessments will be performed every 12 weeks until documentation of disease progression or start of another anticancer therapy.

20.5.1 *Analysis of primary efficacy variable*

The analysis of ORR will be performed independently for each study cohort when the last patient included in the corresponding cohort of the study will have at least two tumor assessments (12 weeks after the last patient recruited). The primary objective of the study will be based on the independent central radiology review.

20.6 *Sample Size and Accrual*

Sample size has been calculated using single stage design. For considering Lenvatinib as an effective treatment, a success rate of ORR of at least 25% is expected. However, a success rate of 10% or less would be considered unacceptable. With 90% power and a 5% level of significance, a total of 55 patients for each cohort are required.

20.7 *Data Analyses Plans*

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (n, NA, mean, standard deviation, median and minimum and maximum values). Ninety-five (95) percent confidence intervals may also be presented, as appropriate. Frequency counts and percentage of subjects within each category will be provided for categorical data.

Missing data will be ignored.

Secondary endpoints will be summarized with descriptive statistics. Continuous variables will be summarized with n, NA, mean, standard deviation, median and range. Frequency counts and percentage of subjects within each category will be provided for categorical data. Multivariate regression models may be used to study relations between explanatory variables and primary endpoint. Survival analysis will be performed to analyze PFS, Kaplan & Meyer curves will be presented and possible comparisons will be tested using the log-rank test or the Cox proportional hazard model for multivariate analysis.

Patients with lost of follow-up or treatment discontinuation will be included in the final analysis of primary endpoint if they have at least one tumor assessment and considered as censored data for survival endpoints.

20.8 *Safety Analyses*

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized separately by cohort. Adverse events and serious adverse events, laboratory test results, physical examination findings, vital signs, and echocardiogram results (including LVEF), and their changes from baseline will be summarized using descriptive statistics. Abnormal values will be flagged.

20.9 *Extent of exposure*

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

20.10 *Adverse events*

Adverse events will be graded using CTCAE v4.3. Investigators will collect all adverse event CTCAE grades (for both increasing and decreasing severity). Adverse events will be classified into standardized medical terminology from the verbatim description (investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be presented by preferred term (PT) nested within system organ class (SOC). Verbatim descriptions and MedDRA SOC and PT for all adverse events will be contained in the data listings of the clinical study report for this protocol.

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 SOC, PT, CTCAE grade, and relatedness to study drug. All summaries will be performed by cohort. 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). TEAEs will be defined as adverse events that emerge during treatment, having been absent pretreatment (at baseline) or those that:

- Reemerge during treatment, having been present at baseline but stopped prior to treatment, or
- Worsen in severity during treatment relative to the pretreatment state, when the adverse event is continuous.

Separate summary tables will be provided for: all TEAEs, treatment-emergent SAEs, TEAEs reported as treatment-related, treatment-emergent SAEs reported as treatment-related, and TEAEs leading to treatment discontinuation.

20.11 *Laboratory values*

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this protocol. Descriptive summary statistics for laboratory parameters and their changes from baseline will be calculated. Laboratory parameters that are graded in CTCAE v4.03 will be summarized by CTCAE grade.

20.12 *Vital signs*

Vital sign values will be evaluated on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range. Reference ranges for vital sign parameters will be included in the clinical study report for this protocol. Descriptive summary statistics for vital sign parameters and their changes from baseline will be calculated.

20.13 *ECG results*

ECG results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside the reference range. ECG findings will be summarized.

An abnormal ECG result, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if either there is worsening by ≥ 2 CTCAE v4.03 grade levels from baseline or a QTc increase of ≥60 msec from baseline. Any ECG abnormality that the investigator considers to be an adverse event should be reported as such.

20.14 *Echocardiograms*

Echocardiograms (including LVEFs) will be assessed. Summary statistics (mean plus/minus standard deviation, median, and range) for echocardiograms and their changes from baseline will be calculated and summarized for each treatment arm.

21. References

1. Yao JC, Hassan M, Phan A, et al. One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J Clin Oncol 2008;26:3063-72.

2. Fjällskog ML, Lejonklou MH, Oberg KE, Eriksson BK, Janson ET. Expression of Molecular Targets for Tyrosine Kinase Receptor Antagonists in Malignant Endocrine Pancreatic Tumors. Clinical Cancer Research 2003;9:1469-73.

3. Matsui J, Yamamoto Y, Funahashi Y, et al. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int J Cancer 2008;122:664-71.

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5. Yamada K, Yamamoto N, Yamada Y, et al. Phase I dose-escalation study and biomarker analysis of E7080 in patients with advanced solid tumors. Clin Cancer Res 2011;17:2528-37.

6. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in Radioiodine refractory thyroid cancer. New England J Ned 23015;372:621-30.

Appendix I Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Tumor response assessments in this clinical trial will utilize Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the 2009 article by Eisenhauer et al entitled, New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1). The sole modification to RECIST 1.1 to be implemented in this trial is that chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease. As required by RECIST 1.1, the protocol states that the minimum duration of stable disease is 7 weeks following the date of first dose of study drug. The Eisenhauer article, published in the European Journal of Cancer, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

Appendix II: Eastern Cooperative Oncology Group Performance Status

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

ECOG = Eastern Cooperative Oncology Group.

Adapted from Oken MM et al. Am J Clin Oncol. 1982;5:649-55.

Appendix III Cockcroft and Gault Formula

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 0.85}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

Adapted from Cockcroft DW et al. Nephron. 1976;16(1):31-41.

For serum creatinine measured in µmol/L:

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23}{\text{Creatinine (µmol/L)}} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{Creatinine (µmol/L)}} = \text{XX mL/min}$$

Appendix IV: Common Terminology Criteria for Adverse Events (CTCAE v4.03)

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.03 published 14 June 2010) provides descriptive terminology to be used for adverse event reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE version 4.03 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA®) terms.

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

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

CTCAE = Common Terminology Criteria for Adverse Events.

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

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

Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.0. Available from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf.

Appendix V Drug-Drug Interactions

Preliminary preclinical studies identify CYP3A4 as an important enzyme responsible for human hepatic metabolism of E7080. Caution should be exercised when administering drugs metabolized by CYP3A4 or drugs that are inductors or inhibitors of CYP3A4 (including herbal supplements, or large amounts of grapefruit juice), as administration of such drugs could affect the metabolism of E7080 (see table below).

Table 6 Drugs That Affect the Activity of CYP3A4

Class of Drug	Drug Name	
Drugs that inhibit CYP3A4 strongly	azole antifungal agent	itraconazole ketoconazole
	macrolide antibiotic agent	clarithromycin
	ketolide antibiotic agent	telithromycin
	anti-HIV agent	atazanavir indinavir saquinavir nelfinavir ritonavir
	antidepressant agent	nefazodone
Drugs that induce CYP3A4 strongly	antitubercular agent	rifampicin
	antiepileptic agent	carbamazepin

Abbreviations: CYP3A4, cytochrome P450 3A4; HIV, human immunodeficiency virus.

This list of clinically relevant agents is from: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp. Accessed 15.Jun.2009.

Please refer to this website for the most up-to-date listing and to the product inserts for more information. Caution should be exercised for CYP3A4 substrates with a narrow therapeutic index. A representative, but not exhaustive, list of examples includes astemizole, cisapride, cyclosporine, diergotamine, ergotamine, erythromycin, opioid analgesics (alfentanyl, codeine, fentanyl, levomethadyl acetate (LAAM), methadone), pimozide, quinidine, sirolimus, tacrolimus, and terfenadine.

Appendix VI Pharmacogenomics

All research performed with the samples during this study is ruled by the provisions of Law 14/2007 of biomedical research and RD 1716/2011 of November 18 which sets the basic requirements for authorization and running of biobanks for purposes of biomedical research y handling of human biological samples.

Subjects enrolled in this clinical study will have samples collected for pharmacogenomic and biomarker analysis. The aim of the analysis is to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

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

The patients will sign a specific Informed Consent form for the sample pharmacogenomic collection.

SAMPLE COLLECTION AND HANDLING

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

The sponsor of the study may decide not to conduct any pharmacogenomics analysis of the samples collected during the study if its primary efficacy endpoint is not achieved and there are not clinically relevant safety issues that raise additional interest. This decision will be notified to all IEC and regulatory authorities.

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

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

The laboratory in charge of processing, storing and destroying the samples is Laboratory of Hospital Vall Hebrón; Paseo de la Vall Hebrón, nº 119-129, 08035 Barcelona.

Samples will only be used for the purposes described in this protocol by the study sponsor. Laboratories contracted to perform the analysis on behalf of the study 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 study sponsor will not sell the samples to a third party and will not

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

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

RIGHT TO WITHDRAW

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

SUBJECT PRIVACY AND RETURN OF DATA

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

Laboratory personnel performing genetic analysis will not have access to the “key.” Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID “key.”

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

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

• Clinical research organizations retained by the sponsor;

• Independent ethics committees or institutional review boards that have responsibility for this research study;

• National regulatory authorities or equivalent government agencies

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

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

Appendix VII: Adverse event report form

Please see attached form