PROTOCOL

A PHASE II/III RANDOMIZED DOUBLE-BLIND STUDY OF SANDOSTATIN LAR IN COMBINATION WITH AXITINIB VERSUS SANDOSTATIN LAR WITH PLACEBO IN PATIENTS WITH ADVANCED G1-G2 NEUROENDOCRINE TUMOURS (WHO 2010) OF NON-PANCREATIC ORIGIN

Compound:	**AG-013736**
Name of Compound (if applicable):	**Axitinib**
Phase:	**2/3**
Protocol Number:	**AXI-IIG-02**
EUDRACT Code:	**2011-001550-29**
Version and Date:	**V.9.0 – 10 September 2018**

Sponsor: GETNE (Grupo Español de Tumores Neuroendocrinos [Spanish Group of Neuroendocrine Tumors])

Sponsor Protocol Code: GETNE 1503

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1. ABBREVIATIONS

NET	Neuroendocrine tumor
ORR	Overall response rate
OS	Overall survival
VEGF	Vascular endothelial growth factor
PDGF	Platelet-derived growth factor
BID	Two times a day (Latin *bis in die*)
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
VEGFR2	VEGF receptor 2
PDGFR β	PDGF receptor β
5-FU	5-Fluorouracil
LV	Leucovorin
FOLFOX	LV + 5-FU + Oxiplatin
PFS	Progression-free survival
FOLFIRI	5-Fluoracil + Leucovorin + irinotecan
PFS	Progression-free survival
mCRC	Metastatic colorectal carcinoma
IV	Intravenous
BEV	Bevacizumab
XELOX	Capecitabine + Oxaliplatin
NCI CTC	National Cancer Institute Common Terminology Criteria for Adverse Events
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
CYP3A4	Cytochrome P 450 3A4
QT	QT interval on the ECG

QTc	Corrected QT interval
CRF	Case Report Form
ECG	Electrocardiogram
CR	Complete response
UPC	Urine protein: creatinine ratio
CECs	Circulating endothelial cells
RTK	Receptor of tyrosine kinase
CESC	Circulating endothelial stem cells
IUE	Intrauterine exposure
AE	Adverse Event
SAE	Serious adverse event
ITT	Intention to treat
OR	Overall response
DP	Disease progression
TTP	Time to progression
HR	Hazard ratio
ICH	International Conference on Harmonisation
GCP	BCP: Good Clinical Practice
CREC	Clinical Research Ethics Committee
CRF	Case Report Form
TTP	Time to progression
HIF	Hypoxia-induced factor
PO	Per os, orally
IM	Intramuscular
SAs	Somatostatin analogues

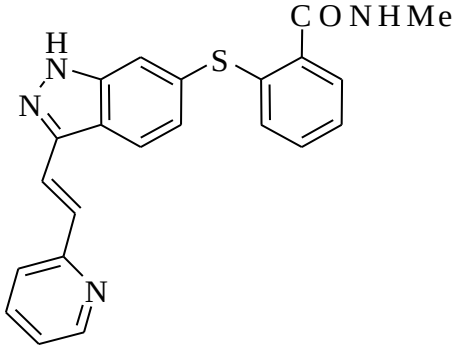
2. INTRODUCTION

2.1. Background

Neuroendocrine tumors (NETs) are part of a heterogeneous family of tumors with a broad and complex spectrum of clinical behavior. They originate in many tissues and are characterized by their ability to produce peptides that cause different hormonal syndromes. However, many remain clinically silent until the late stages of the disease. Although they are generally more indolent than carcinomas, they often have an unpredictable biological behavior and sometimes are associated with an aggressive clinical course. Recent international efforts are helping to improve the prognostic classifications of these tumors and to better individualize the therapeutic strategy for these patients.

2.2. AG-013736 Molecular Formula and Activity

Axitinib (AG-013736) is an orally administered drug that binds to the kinase domain of receptors 1, 2 and 3 of VEGF (VEGFR 1-3), inhibiting intracellular signaling mediated by these receptors and exerting an anti-angiogenic action accordingly. Its chemical name is N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl) -1H-indazol-6-yl-sulfanyl]-benzamide and has a molecular weight of 386.47. Its molecular formula is C22H18N4OS whose chemical structure is represented in the following figure:



Axitinib blocks VEGF-mediated endothelial cellular adhesion and its migration to the extracellular matrix, and it induces endothelial apoptosis. It also induces rapid and potent inhibition of endothelial nitric oxide (eNOS) and protein kinase B (AKT), and the phosphorylation of mitogen-activated protein kinases (ERK1/2) at concentrations that correlate with their inhibitory effect on VEGFRs.

Various preclinical studies have shown that axitinib is very potent and specific to subnanomolar concentrations for recombinant VEGFR, PDGFR -β, and c-Kit kinases. Axitinib also has shown antitumor activity additively or synergistically with docetaxel in murine models of human breast and lung cancer, with carboplatin in ovarian cancer models, and with gemcitabine in pancreatic cancer. The antiangiogenic activity of axitinib has also been documented *in vivo* using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), showing that axitinib decreases tumor blood flow and patency early, and this effect was correlated with lower microvessel density, cell viability,

and tumor growth. The antiangiogenic activity of axitinib has also been assessed by quantifying microvascular density using CD-31 staining after acute or prolonged exposure in xenograft animal models. Based on these observations, daily administration of axitinib was considered the optimal management scheme for achieving an antiangiogenic effect.

Phase I trials conducted in patients with refractory solid tumors have established the recommended dose of 5 mg twice daily for clinical development. Pharmacokinetic data indicate that axitinib is rapidly absorbed after fasting, reaching peak plasma concentrations 2 to 6 hours after administration of the medicinal product. Plasma half-life ranges between 2 and 5 hours. Several phase II trials have been completed or are currently underway in a wide range of tumors, including metastatic breast cancer, non-small-cell lung cancer, renal-cell carcinoma, thyroid cancer, melanoma, and pancreatic or colorectal cancer.

In all these studies, the starting dose of axitinib was 5 mg twice daily. Most of the studies allowed dose escalation, first to 7 mg twice daily and then to 10 mg twice daily in a second stage in patients who did not experience significant toxicities for 2 consecutive weeks (CTCAE Grade >2), unless BP was >150/90 mm Hg or the subject was receiving antihypertensive medication. Other than an increase in the frequency of hand-foot syndrome and a slight increase in hypertension, the patients who received the dose increase to 7-10 mg twice daily did not appear to experience greater toxicity if the dose of 5 mg twice daily had been well tolerated.

2.3. Study Rationale

The incidence of NETs is 2.5 and 5 per 100,000 in the Caucasian population. The incidence has increased substantially in recent decades, in part due to improved diagnostic techniques and possibly also to increased awareness among clinicians. In addition, the prevalence of these tumors is relatively high due to long survival, which can be 35% to 60% at 5 years for patients with advanced disease.[1,2] Moreover, gastroenteropancreatic NETs are the second most prevalent tumors derived from the digestive tract, after colorectal carcinoma.

NETs are characterized by extensive vascularization, and vascular endothelial growth factor (VEGF) and its receptor (VEGF-R) are over-expressed in 60%-84% of pancreatic and enteric NETs.[3] Other pro-angiogenic factors, such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), are also involved in the development and progression of NETs.[4] Some authors[3] have correlated VEGF expression with increased angiogenesis and metastasis and diminished duration of progression-free survival in patients with low-grade tumors. Furthermore, activation of the HIF pathway has been correlated with reduced disease-free survival in pancreatic endocrine tumors.[5]

The nature of these tumors dependent on extensive vascularization has led to a large number of trials to assess the activity of various agents with antiangiogenic properties,

such as sunitinib,[6] sorafenib,[7] everolimus,[8] bevacizumab,[9] and pazopanib,[10] among others. Two new targeted agents have been approved in recent years, sunitinib[6,11] and everolimus,[8,14] for the treatment of advanced neuroendocrine tumors of pancreatic origin, and they have proven capable of improving progression-free survival (PFS) (sunitinib and everolimus) and overall survival (OS) (sunibinib) in these patients. Everolimus has been approved by the FDA for this indication. In June 2009, Raymond et al reported the first positive results from a randomized Phase III trial, which showed substantial improvement in progression-free survival and overall survival with sunitinib versus placebo in patients with advanced NETs of pancreatic origin in progression,[11] but the randomized Radiant-2 study with everolimus in functioning NETs of nonpancreatic origin did not confirm this.[14] The results of the Radiant-3 randomized study also showed a significant impact on progression-free survival for everolimus versus placebo in the same disease context: advanced or metastatic neuroendocrine tumors of pancreatic origin. This trial revealed no benefit in favor of everolimus on overall survival, although its design with crossover of treatment arms on progression does not allow definitive conclusions in this regard.[12]

More recently, at ECC 2015 the results of the randomized Radiant-4 study of nonfunctioning NETs of pulmonary or gastrointestinal origin have been reported. This study showed that treatment with everolimus improved PFS by 7.1 months compared to placebo. An interim analysis showed an improvement of 36% in OS in favor of the group treated with everolimus. The FDA has recently approved everolimus for this indication (February 2016).

The purpose of this trial is to assess whether therapy with axitinib, a potent angiogenic inhibitor of the tyrosine kinase receptors of VEGF bioavailable by oral administration, can improve PFS in patients with advanced G1-G2 NETs of nonpancreatic origin with progressive disease documented in the 12 months prior to entering the study.

Moreover, the neuroendocrine tumors do not show FDG PET uptake and yet have demonstrated increased L-dopa decarboxylase activity, so they have increased uptake of 18FDOPA, a specific marker of cellular metabolic activity, as Dopa is a precursor in the synthesis of dopamine and serotonin. Although this radiotracer has shown greater sensitivity than octreoscan in detection of neuroendocrine tumors, there is not much information in the literature regarding its role in the evaluation of therapeutic response in patients with advanced disease. That is why we deemed it interesting to assess at least one group of patients by means of this imaging method, although all the patients will be monitored by conventional imaging methods. It is therefore an experimental procedure consisting of an exploratory study in this clinical trial to assess its potential as an early predictive tool of therapeutic efficacy. Since it is not a diagnostic test available at all sites or in every region, it will be performed as an optional exploratory study for patients with access to it.

Given the important role of angiogenesis in the pathogenesis of NETs, the demonstrated activity of other antiangiogenic agents in NETs (e.g., sunitinib, pazopanib, and others),

and, finally, axitinib activity in other VEGF-dependent tumors (e.g., renal cancer), it is very possible that axitinib will be active in NETs of nonpancreatic origin.

In the first phase of the study, 106 patients were randomized and 105 of them received treatment. In March 2015 (6 months after enrollment of the last patient), the median follow-up of the patients was 18 months, longer than the expected median in the control arm (8.6 months) and longer than the median reported in the everolimus arm in both the Radiant-2 study (12 months), as assessed by the investigator, and Radiant-4 study (11 months), in which a centralized review was made. Thus, although the follow-up was fairly long, the data were still not ripe for a final analysis, although the prognosis of the patients was expected to be substantially better than expected. Of the 106 patients randomized, the drop-out rate was 7% (10 patients), 45 patients had disease progression and 13 died. An interim safety study documented a safety profile like that known for this drug in the context of other human cancers (e.g., kidney cancer) for which it is marketed, without any particular flag for this patient population.

Based on the above, the final efficacy analysis still has not been made, the study is still blinded and the decision has been made to redesign it as a Phase II-III study to obtain more robust results that may yield a positive benefit-risk ratio for axitinib in G1-G2 NETs of nonpancreatic origin. In addition, patients who were enrolled in Phase II of the trial during 2.5 years will be part of the overall sample required for the current phase II-III study. This is particularly relevant in this study since NETs are uncommon tumors

3. STUDY OBJECTIVES

3.1. Primary Objective

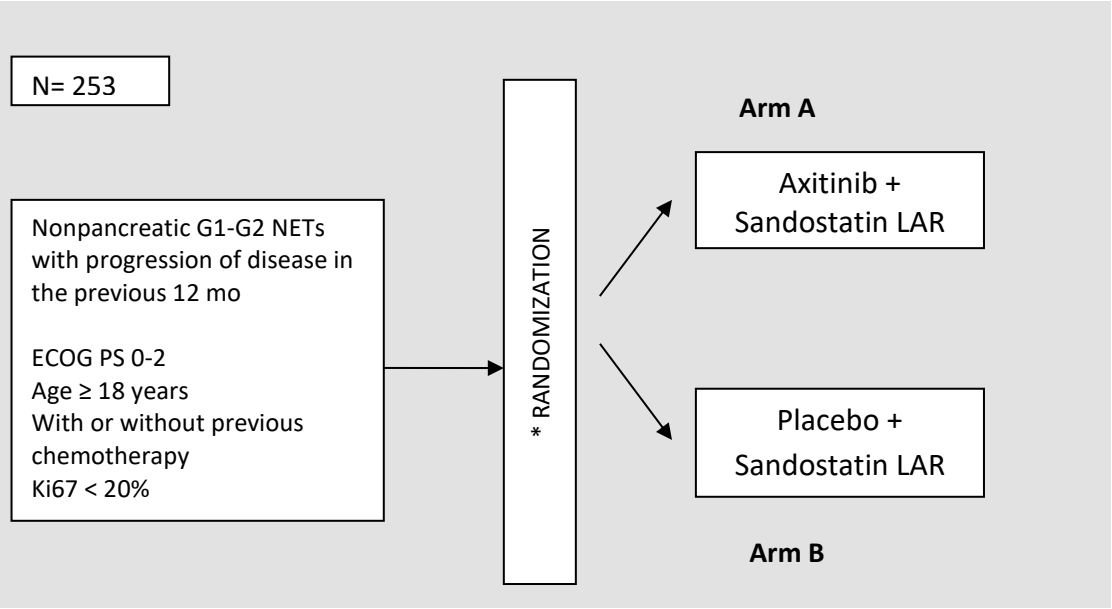
- ✓ Evaluate the effectiveness of axitinib in terms of PFS in patients with advanced G1-G2 neuroendocrine tumors of nonpancreatic origin and documented progression in the 12 months prior to entering the study.

3.2. Secondary Objectives

- ✓ Evaluate the objective response rate (ORR) (measured according to RECIST 1.1 criteria) and the duration of response.
- ✓ Evaluate the functional response rate using F-DOPA-PET (optional, depending on availability)
- ✓ Evaluate the biochemical response (5-OH-indoleacetic acid and chromogranin A)
- ✓
- ✓ Evaluate overall survival.
- ✓ Evaluate the safety and tolerability of axitinib (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.0)
- ✓ Explore potential biomarkers (, hypertension, and other serum, urinary or tumoral biomarkers).

4. OVERALL STUDY DESIGN AND PLAN

Phase II/III, prospective, multicenter, randomized (1:1), double-blind study to evaluate the efficacy and tolerability of axitinib in patients diagnosed with advanced G1-G2 neuroendocrine tumors (WHO 2010) of nonpancreatic origin that have presented documented disease progression in the 12 months prior to entering the study. In the first part of the study (Phase II), 105 patients were enrolled. The second part of the study is the expansion to Phase III, which is expected to include 148 additional patients. Patients will be randomized to receive Sandostatin LAR with axitinib or Sandostatin LAR with placebo until disease progression or unacceptable toxicity occurs. Randomization will be stratified by the time from diagnosis to enrollment in the study (more vs less than or equal to 12 months), the origin of the primary tumor (gastrointestinal tract vs non-gastrointestinal tract [lung or other sites]) and ki-67 (< 5% vs > 5%).



5. PATIENT SCREENING CRITERIA

The following eligibility criteria are designed to screen subjects for which the treatment protocol is considered appropriate. All medical and non-medical conditions should be taken into account when deciding whether this protocol is suitable for a particular subject.

5.1. Inclusion Criteria

Subjects must satisfy all the following inclusion criteria:

1. G1-G2 neuroendocrine tumor (WHO 2010) of histologically confirmed non-pancreatic origin, functioning and nonfunctioning
2. Metastatic or locally advanced disease not amenable to treatment with curative intent

3. Clinical and/or radiological disease progression documented in the 12 months prior to study entry.
4. Patients should have at least one measurable lesion as defined by RECIST 1.1 criteria. Patients should not have undergone local or regional ablative procedures (embolization, cryoablation, radiofrequency ablation, or others) in the 6 months prior to entering the study, unless there are other locations of measurable disease or clear radiological progression after carrying out these procedures (in these cases, local and regional ablation procedures shall be permitted if they have been performed at least 1 month prior to enrollment in the study).
5. Ki-67 $\leq$ 20%
6. Prior treatment with somatostatin analogues is allowed
7. Prior treatment with interferon is allowed
8. Prior treatment is allowed with up to 2 antineoplastic systemic treatment lines different from SAs or IFN (systemic treatment is understood as conventional cytotoxic chemotherapy or new drugs for therapeutic targets as mTOR or other, as long as it is not directed against VEGF/VEGFR). Treatment with SAs or IFN does not count as prior lines of antineoplastic treatment.
9. Prior treatment with targeted therapy against VEGF or VEGFR is not allowed.
10. Adequate organ function as defined by the following criteria:

    - Absolute neutrophil count $\geq$ 1500 cells/mm3,
    - Platelet count $\geq$ 75,000 cells/mm3,
    - Hemoglobin $\geq$ 9.0 g/dL,
    - AST y ALT $\leq$ 2.5 x upper limit of normal (ULN), except if liver metastases exist, in which case AST and ALT $\leq$ 5.0 x ULN is allowed,
    - Total bilirubin $\leq$ 1.5 x ULN,
    - Serum creatinine $\leq$ 1.5 x ULN or calculated creatinine clearance $\geq$ 60 mL/min,
    - Proteinuria < 2+ by reactive strip. If the reactive strip is $\geq$ 2+, a 24-hour urine sample should be collected and the patient may be eligible if urinary protein excretion is < 2 g every 24 hours.

11. Men or women aged $\geq$ 18 years.
12. ECOG performance status 0-2
13. Life expectancy $\geq$ 12 weeks
14. At least 4 weeks should pass from the end of the previous systemic treatment with resolution of all treatment-related toxicities to grade $\leq$ 1 according to NCI CTCAE Version 4.0 or to baseline, except for alopecia or properly treated hypothyroidism.
15. No prior evidence of uncontrolled hypertension should exist, as documented by 2 baseline blood pressure readings taken at least 1 hour apart. Baseline readings of

systolic blood pressure should be ≤ 150 mm Hg and baseline readings of diastolic pressure should be ≤ 90 mm Hg. Patients whose hypertension is being controlled with antihypertensive therapy are eligible.

16. Women (or their partners) should be surgically sterilized or postmenopausal, or must agree to use an effective contraceptive method during and for at least 6 months after receiving study treatment. All women of childbearing age should have a negative pregnancy test (serum/urine) within 7 days prior to starting treatment. Men (or their partners) should be surgically sterilized or must agree to use an effective contraceptive method during and for at least 6 months after receiving study treatment. The definition of an effective contraceptive method must comply with local regulations and will be based on the criterion of the principal investigator or a designated associate.

17. Breastfeeding women may not participate in this study.

18. Signed and dated informed consent document stating that the patient has been informed of all the pertinent aspects of the trial prior to recruitment.

19. Willingness and ability to comply with scheduled visits, treatment plans (including willingness to take axitinib or placebo according to randomization), laboratory tests, and other study procedures.

5.2. Exclusion Criteria

Subjects must be evaluated according to the following exclusion criteria:

1. The following types of endocrine tumors will not be included: paraganglioma, adrenal endocrine tumor, thyroid, parathyroid, or pituitary.
2. Major surgery within previous 4 weeks, or radiation therapy within 2 weeks prior to the start of treatment. Prior palliative radiotherapy for metastatic lesions is permitted if there is at least one measurable lesion that has not been irradiated (i.e., if there are other non-irradiated target lesions).

3. Gastrointestinal abnormalities, including:

    - Inability to swallow oral medication;
    - Need for intravenous feeding;
    - Prior surgical procedures that affect absorption, including total gastric resection;
    - Treatment for active peptic ulcer in the last 6 months;
    - Uncontrolled active gastrointestinal bleeding unrelated to cancer, as evidenced by hematemesis, hematochezia or clinically significant melena in the last 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    - Malabsorption syndromes;

4. Current or anticipated need for treatment with drugs that are potent inhibitors of CYP3A4 (grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir,

nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and delavirdine) unless they can be replaced by another medication with minimal potential for CYP3A4/5 inhibition. The use of low-dose oral steroids (< 5 mg/day prednisone or equivalent) is allowed. Co-administration of steroids may increase plasma concentrations of axitinib.

5. Current use or anticipated need for treatment with drugs that are known potent CYP3A4/5 inducers (carbamazepine, dexamethasone, felbamate, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampicin, and St. John's wort) unless they can be replaced by another medication with minimal potential for CYP3A4 induction. Co-administration of CYP3A4/5 inducers may decrease plasma concentrations of axitinib.
6. Need for anticoagulant therapy with oral vitamin K antagonists. Low doses of anticoagulants to maintain the patency of a central venous access device or to prevent deep vein thrombosis are permitted. Use with therapeutic doses of low molecular weight heparin is allowed.
7. Clinically relevant history of bleeding in the last 6 months, including severe hemoptysis or hematuria, unless it has been due to a treated cause (e.g., completely resected bleeding intestinal tumor).
8. Active epilepsy or evidence of brain metastases, spinal cord compression, or carcinomatous meningitis.
9. Serious uncontrolled illness or active infections that may interfere with the patient’s ability to receive the study treatment.
10. Any of the following events in the 12 months prior to administration of the study drug: myocardial infarction, uncontrolled angina, implantation of a coronary or peripheral bypass, symptomatic congestive heart failure, stroke or transient ischemic attack. Deep vein thrombosis or pulmonary embolism in the prior 6 months.
11. Ongoing grade ≥ 2 cardiac arrhythmias according to NCI CTCAE: atrial fibrillation of any grade or QTc interval > 450 ms for men or > 470 ms for women.
12. Patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome-related disease.
13. Prior history of cancer except those treated with curative intent for non-melanoma skin cancer in situ, breast or cervical cancer in situ, or those treated for any cancer with curative intent and no evidence of disease in the last 5 years prior to enrollment in the study.
14. Dementia or significantly altered mental status that could prevent compression, or submission of informed consent and compliance with the requirements of this protocol.
15. Any severe, acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with participation in the study

or with study drug administration, or that may interfere with the interpretation of results, and that could interfere with the patient's ability to take part in this study in the investigator's opinion.

16. The patient's participation or intention to participate (in the 4 weeks prior to starting drug administration) in a study in which the patient will receive an investigational medicinal product.

17. Subjects who are institutionalized by governmental or by judicial decision, or subjects who are dependent of the sponsor, the investigator or the trial site will be excluded from participation.

18. Breastfeeding women

19. Patients with known hypersensitivity to axitinib, sandostatin or one of the recipients should be excluded from the study.

5.3. Subject Withdrawal Criteria

Subjects are free to withdraw consent and discontinue participation in the study at any time and without prejudice to future treatment. A subject's participation in the study may be discontinued at any time at Investigator's discretion. Study treatments must be withdrawn for any of the following reasons:

- Intolerable AEs related to study treatment
- Pregnancy
- Termination of the study by the Sponsor
- Withdrawal of informed consent for any reason
- Any clinical AE or abnormal laboratory test result indicating, in the Investigator's opinion, that continue with thestudy drug dosing is not in the subject's best interest.
- Progression disease

6. DESCRIPTION OF THE CONTRACEPTIVE METHOD

During the study, women at risk of becoming pregnant should take precautions to avoid pregnancy because the effects on the fetus are unknown. Men with a partner at risk of becoming pregnant should take precautions to avoid pregnancy because the effects of these drugs on sperm are unknown. These restrictions should be maintained for 6 months after the last dose of the investigational product.

Women of childbearing potential (WOCBP) must be willing to use an highly effective contraception (failure < 1%) according to the Clinical Trial Facilitation Group (CTFG) recommendations:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Males should refrain from sperm donation for the duration of the study and for 6 months after the study termination.

7. ADMINISTRATION AND ALLOCATION SCHEME

7.1. Drug Administration Scheme

A total of 253 patients with G1-G2 (WHO 2010) neuroendocrine tumors of nonpancreatic origin and documented disease progression in the 12 months prior to entering the study will be enrolled. Patients will be randomized according to a double-blind design in a 1: 1 ratio to receive:

A) Sandostatin LAR 30 mg IM every 28 days + axitinib 5 mg PO 2 times daily (BID)

B) Sandostatin LAR 30 mg IM every 28 days + placebo PO 2 times daily (BID)

The designated treatment (Sandostatin LAR + axitinib or Sandostatin LAR + placebo) will continue until disease progression or unacceptable toxicity. Randomization will be stratified by the time from diagnosis to enrollment in the study (more vs less than or equal to 12 months), the origin of the primary tumor (gastrointestinal tract vs non-gastrointestinal tract) and Ki-67 ($\leq$ 5% vs > 5%).

7.2. Treatment Allocation

Once the subject has signed the informed consent, after all the screening procedures have been performed and the eligibility criteria have been checked, the site will contact a centralized Pivotal e-mail address for the allocation of study treatment, as detailed in the study procedures. The case report form (CRF) will be completed for all randomized patients, regardless of whether or not the patient finally receives medication. The system

will provide an ID number for each subject once the ICF is signed and the number of the vial of the medicinal product assigned if the subject is finally randomized. Study treatment will begin within one week of randomization.

7.3. Unmasking

For this trial, study subjects, investigators, staff, and the sponsor's clinical and medical representatives will all be blinded to the treatment assignments. Both study medication and placebo capsules are identical in appearance. The site will be instructed in the unmasking process.

The blind may be broken only in emergency situations. Investigators should be aware that the occurrence of a serious adverse event should not precipitate the decision about immediate unblinding. The blinding will be unmasked only in the case of a medical emergency for the safety of the patient. If the investigator feels that urgent unblinding is necessary, they may do it without previous authorization of the Sponsor. Nevertheless, every effort should be made to contact and discuss the case with the Sponsor.

Unblinding will be accomplished by the Principal Investigator and authorized site staff that will obtain the subjects treatment arm information, by opening the randomization blinded envelopes, which are provided with the axitinib/placebo bottles, according to the unblinding plan. The reason for breaking the blind must be documented in the subject's case report form (CRF) and in the subject's medical records. Documentation of contact or attempted contact with the Study Principal Investigator Coordinator of GETNE prior to breaking the blind must also be documented in the subject's medical records.

Once the final analysis of the study concludes, if positive results are obtained, patients who have not experienced disease progression may be unmasked and offered the opportunity to continue axitinib in an open-label type extension study for patients who previously received axitinib and experienced clinical benefit without progression, and for those initially allocated to the placebo arm.

In compliance with current regulations, if SUSARs (suspected unexpected serious adverse reactions) occur, the blind will be usually open prior notification to Health Authorities, Ethics Committees and Researchers if the SUSAR was considered related to blind treatment.

The plan for reporting SUSARs to the concerned Health Competent Authorities, Ethics Committees and Investigators is detailed in the study Safety Management Plan (SMP).

PIVOTAL's Safety Unit will remain blinded during the study, except for the purpose of expedited reporting of SUSARs to the concerned Health Competent Authorities and Ethics Committees.

Unblinding will only be accomplished by the Safety Unit personnel or other designee unblinded study staff. Unblinding of SUSARs will occur prior notification to the concerned Health Competent Authorities and Ethics Committees.

The Safety Unit will forward unblinded safety communications, as specified in the SMP, to the concerned Health Competent Authorities, Ethics Committees. Other blinded study staff, Sponsor and Investigators will not be aware of the treatment for the purpose of SUSARs reporting and, as a rule, will only receive blinded SUSAR reports.

8. DRUG SUPPLY

Pfizer will supply axitinib/placebo to the sponsor to conduct the clinical trial. The sponsor is responsible for the storage, preservation, labeling and distribution of the investigational product to the study sites. The investigational product will be sent to the study sites with instructions on how to confirm the correct reception of the product and the rest of the study material.

Sandostatin will be provided by the hospital according to the routine clinical practice at each site.

8.1. Formula and Packaging

Axitinib/ placebo will be supplied as film coated tablets of 1 mg and 5 mg for oral administration in containers that provide protection from light.

8.2. Preparation and Dispensing

Axitinib is considered a dangerous drug (due to its reproductive toxicity), and must be handled in accordance with the procedures described in the ASHP's current Technical Assistance Bulletin on the management of hazardous drugs and cytotoxic agents, AHFS drug information, and references. The procedures should be described in the pharmacy at each site or the hospital manual of standard operating procedures for handling hazardous drugs should be followed. Only qualified personnel familiar with the procedures for minimizing undue exposure of themselves and the environment should undertake the preparation, handling and safe disposal of axitinib.

8.3. Administration

Axitinib/placebo (blind treatment) will be self-administered BID orally with/or without food. Doses should be taken approximately 12 hours apart and at about the same time each day. Patients should be instructed that if they vomit after taking the dose, they should not compensate by taking an extra dose but should continue treatment as previously scheduled. Any missed dose may be taken up to 3 hours before the next scheduled dose; otherwise please omit that dose and continue with the next dose as scheduled. Doses that are vomited or forgotten should be recorded in the patient diary.

Sandostatin LAR 30 mg is administered intramuscularly every 28 days.

8.4. Compliance

Patients will keep a diary where they will record the information on missed or modified doses. A tablet count will be made when the containers are returned.

8.5. Storage and Responsibility

Axitinib/placebo will be supplied for the study by Pfizer and distributed to the sites by ALCURA HEALTH. The material for the clinical trial will be sent to the study sites with a form for acknowledging receipt of the investigational product. The investigator or an authorized representative (e.g., pharmacist) will ensure that all the axitinib/placebo is stored in a safe place in the recommended storage conditions and in accordance with applicable regulatory requirements. The drug should be stored at room temperature (i.e., 15°C-30°C), avoiding exposure to light.
Sandostatin will be provided at each site according to routine clinical practice.

9. STUDY PROCEDURES

9.1. Administration of Medicinal Products

The recommended dose of axitinib for starting is 5 mg twice daily (BID), taken orally with or without food on a continuous basis. A cycle is 28 days. Dose adjustments, including increases or decreases in dose, should be based on the adverse events experienced by the patient. Axitinib should be taken at the start of Day 1 of the study and then every 12 hours continuously. The study treatment will be administered in cycles of 4 weeks' duration.

Patients who tolerate axitinib/placebo without presenting any drug-related adverse events of grade 2 or higher according to CTCAE over a period of 2 consecutive weeks may receive a dose increased by one dose level, up to a maximum of 7 mg BID (unless the patient's blood pressure is > 150/90 mm Hg or the patient is receiving antihypertensive medication, in which case the dose should not be increased).

Patients who experience a reaction to the drug above grade 2 according to CTCAE should receive a dose modified according to protocol guidelines. Concomitant medications that are known to substantially inhibit the CYP3A4 enzyme should be avoided. Dose interruptions for toxicity or other adverse events should not exceed 4 weeks. Continuation of the study treatment after interrupting the dose for more than 4 weeks should be consulted with and authorized in writing by the medical coordinator of the study.

Available Axinitib/Placebo Dose Levels

Dose Level	**Dose**	**Mode of Administration**
+1	7 mg BID	5-mg Tablet × 1 + 1-mg Tablet × 2 BID
0 (Initial Dose)	**5 mg BID**	**5-mg Tablet × 1 BID**
-1	3 mg BID	1-mg Tablet × 3 BID
-2	2 mg BID	1-mg Tablet × 2 BID

The placebo will be administered orally according to the same schedule as axitinib until the documentation of disease progression, unacceptable toxicity or the withdrawal of the patient. Patients will continue treatment outside the trial at the discretion of and according to the judgment of the investigator.

Schedule of Activities

Activity	Screening Day -28 to Day 0	Day 1 (pre-dose) of Each Cycle*	Every 12 weeks (± 7 days), regardless of the duration of the cycle (from C1D1)	Post-treatment			
				End of Treatment visit**	Follow-up Visit 28 Days after Administration of the Last Dose	Long term follow-up visits, every 3 months (± 7 days)	End-of-Study/Withdrawal Visit
Informed consent [a]	X						
Medical history [b]	X						
Pregnancy test [c] (Serum/urine)	Day -7 to Day 0	X					
HIV serology	X						
Physical examination [d]	X	X		X			
Weight, temperature, BP , pulse [e]	X	X		X			

ECOG performance status	X	X		X			
Electrocardiogram (12-lead ECG) [f]	X		X	X			
Hematology [g]	Day -7 to Day 0	X		X			
Coagulation [h]	Day -7 to Day 0						
Biochemistry [i]	Day -7 to Day 0	X		X			
TSH, T3, T4 [j]	X		X	X			
Urinalysis [k]	Day -7 to Day 0		X	X			
Safety evaluation (adverse events) [l]	Monitoring throughout the study						
Concomitant treatment [m]	X	Monitoring throughout the study					
NET markers (chromogranin A,	X		X	X			

enolase and 5-HIAA -all tumors with carcinoid syndrome or small bowel tumors- and specific markers if indicated by tumor type)[n]							
Measurement of tumor size [o]	X		X			X (if applicable)	
Somatostatin Receptor Images Techniques	Day -90 to Day 0	Repeat only if clinically indicated in the opinion of the investigator					
[18F]-DOPA-PET [p] (optional)	X	Repeat at 1 month, at 6 months, and at end-of-study/progression					
Randomization	X						
Axitinib/Placebo [q]		Twice daily on a continuous basis					
Sandostatin		30 mg IM every 28 days					
Survival		Every 3 months until at least 24 months after the last patient randomization					

Biomarkers [r]	X		At the end of the first cycle, at 6 months, and at disease progression or at the end of treatment visit				
End of study reason							X

*The duration of one cycle is 4 weeks. The tests and procedures should be performed as scheduled, although occasional variations of +/- 2 days are allowed for holidays and other administrative reasons.

[a] Informed consent should be obtained before any study-specific procedure may be carried out.

[b]Including the history of previous treatments for cancer.

[c]Patients of childbearing potential should have a negative serum or urine pregnancy test within 7 days prior to treatment and every four weeks and should use appropriate methods.

[d]Including height and weight at the initial examination. After the initial full examination, subsequent examinations will be conducted based on the signs and symptoms presented by patients.

[e] Blood pressure is measured with the patient seated, after the patient has been in this position for 5 minutes. Patients should have their blood pressure measured at the baseline. After, patients should have their blood pressure measured once a week (before the dose), the same day of the week. Investigator will be able to decide an increased frequency if it is needed. The results should be recorded in the patient's diary, which will be collected by the investigator. Patient diaries will be source documents and part of the medical record.

[f]Additional ECG, only if clinically indicated.

[g]Hemoglobin, leukocytes, neutrophil and platelet counts. If the baseline values were obtained in the 7 days prior to Day 1 of Cycle 1, hematology does not have to be repeated on Day 1 of Cycle 1.

[h]INR, PT and PTT will be measured during the screening visit and when clinically indicated.

[i]Sodium, potassium, AST, ALT, alkaline phosphatase, LDH, total bilirubin, total protein, albumin, BUN, creatinine, and glucose. If the baseline values were obtained in the 7 days prior to Day 1 of Cycle 1, biochemistry laboratory tests do not have to be repeated on Day 1 of Cycle 1. LDH and albumin are measured only at baseline, end-of-treatment, and when clinically indicated.

[j]The thyroid function test (TSH) should be performed at baseline, after every 12 weeks, from C1D1 (coinciding with tumor assessments) and as clinically indicated. TSH will be determined every 12 weeks; if altered, T3 and T4 will be determined.

[k]Protein, glucose, and blood at the baseline visit. If proteinuria is ≥ 2+ using a semi-quantitative method (e.g., test strip) during treatment, it will then be quantitatively determined in 24-hour urine. Dose adjustments may be required. If the baseline values were obtained in the 7 days prior to Day 1 of Cycle 1, urinalysis does not have to be repeated on Day 1 of Cycle 1. Protein determination in urine is performed every 12 weeks (coinciding with tumor assessments).

[l] Adverse events must be collected throughout the study period, which will begin at the time the informed consent is signedup to at least 28 days after administration of the last dose of investigationalproduct. Serious adverse events suspected to be related to the investigational product or considered significant by the investigator or monitor will be followed up after discontinuing treatment until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator, monitor, or designated representative.

[m]SAEs will be collected from screening until the follow-up visit.

[n] Chromogranin A, enolase and urine 5-HIAA will be assessed baseline in all patients. Chromogranin will be assessed every 12 weeks until disease progression or end of treatment in all patients. Enolase and urine 5-HIAA will be assessed every 12 weeks only in patients with baseline elevated levels (above the ULN) or if clinically indicated per clinical judgement.

[o]The baseline evaluation of the disease should be made within 28 days prior to randomization. Tumor assessments (triphase thoracic, abdominal and pelvic CT) should be made every 12 weeks (±7 days), regardless of cycle duration, from C1D1. Response (CR/PR) requires confirmation 4 weeks after detection. For patients who have not progressed after discontinuing the investigational product, additional tumor assessment should be made approximately every 12 weeks until the patient meets the criteria for progression or a new cancer therapy is started. In patients in which the use of intravenous iodinated contrast is advised against by an allergy specialist, the tumor may be assessed using MRI with gadolinium. Tumor assessment should be performed using the same diagnostic technique throughout the whole trial.

[p][18F]-DOPA-PET is optional and will be performed at the sites that have this test available.

[q]For patients randomized to arm A or B. Patients who tolerate axitinib 5 mg/12 h without any axitinib-related adverse events grade 2 or more (according to CTCAE) for 2 consecutive weeks should receive a dose increased by one dose level unless they have BP > 150/90 mm Hg or are receiving antihypertensive treatment.

[r]The following samples will be collected for biomarker analysis:

- Tumor tissue sample: before starting the study treatment. A stored tumor sample will be provided, which will be a surplus sample from a diagnostic biopsy or a previous surgery before starting the trial treatment.
- 9 mL of peripheral blood and of urine:
    - Before starting the study treatment
    - At the end of cycle 1 (1 month after starting the study treatment)
    - At 6 months after starting the study treatment
    - At tumor progression and/or the end-of- treatment visit

9.2. Management of Axitinib-related Toxicities

This section contains recommendations for the management of adverse events other than hypertension and proteinuria, which will be discussed in the following sections. Patients who develop grade 1 or 2 adverse events according to CTCAE related to axitinib may continue with their dose at the same dose level.

Patients withdrawn from treatment for intolerable toxicity will be regularly monitored, with tumor assessments until disease progression or the start of a new treatment. From then on, they will have follow-up visits every 3 months to assess survival.

The criteria for dose modification for adverse events related to the investigational product (from previous active trials conducted over the course of the axitinib development program) are summarized in the table below:

CRITERIA FOR AXITINIB/PLACEBO DOSE MODIFICATION ACCORDING TO RELATED ADVERSE EVENTS OTHER THAN HYPERTENSION, OR PROTEINURIA	
Toxicity Grade	**INTERVENTION**
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level
Grade 3*	Interrupt the dose until recovery to grade < 2 or baseline, and then restart the study treatment at the same dose level. If grade 3 toxicity recurs, reduce to a lower dose level.
Grade 4**	Interrupt the dose until recovery to grade < 2 or baseline, then restart the study treatment at a lower dose level or definitively stop treatment if the investigator deems it necessary. If treatment is restarted at a lower dose and severe toxicity recurs, treatment discontinuation at the discretion of the investigator should be considered.

* Patients who develop symptomatic non-hematologic grade 3 toxicities that are controlled with drugs or asymptomatic grade 3 biochemical abnormalities may continue at the same dose level if the investigator deems it acceptable.

* Patients who develop grade 4 lymphopenia or asymptomatic grade 4 biochemical abnormalities may continue at the same dose level if the investigator deems it acceptable.

The dose reduction guidelines for specific adverse events are listed in the following sections.

Patients requiring dose reductions to less than 2 mg BID or dose interruptions for more than 4 weeks will be withdrawn from the study unless the medical coordinator of the study authorizes it in writing after discussion.

The dose reduction guidelines for specific adverse events are listed in the following sections.

9.3. Axitinib Dose Reduction for Hypertension

Patients should have their baseline blood pressure measured and subsequently, once a week (the same day of the week) before taking the drug.The investigator will be able to decide if blood pressure has to be measured more frequently if needed.

All blood pressure measurements will be recorded in the patient diary, which the patient should show to the nurse, coordinator, or investigator at each visit. Patients will be instructed by the study staff that if their systolic blood pressure rises above 150 mm Hg, diastolic blood pressure rises above 100 mm Hg, or if they develop symptoms related to an increase in blood pressure (e.g., headache and vision problems), they should see the doctor immediately.

Dose modifications for hypertension are described in the following paragraphs.

A new or additional antihypertensive therapy should be started (see Table 1. Hypertension Management Plan for Axitinib) if two blood pressure readings, preferably taken at the medical center and separated by at least one hour, show the following: two systolic blood pressure readings above 150 mm Hg or 2 diastolic blood pressure readings above 100 mm Hg. Alternatively, the dose of the existing antihypertensive medication(s) may be increased. If the patient is already receiving the maximum antihypertensive treatment, the dose of axitinib should be reduced by one dose level.

Patients who have two systolic blood pressure readings above 160 mm Hg, separated by at least 1 hour, or two diastolic blood pressure readings above 105 mm Hg, separated by at least 1 hour, must stop treatment with axitinib. (Note. If axitinib is interrupted, patients receiving antihypertensive medication should be monitored for hypotension and resume axitinib at one dose level lower as soon as blood pressure is lowered to < 150/100 mm Hg. The half-life of axitinib in plasma is 2 to 4 hours and blood pressure is usually reduced within 1 to 2 days after stopping the dose).

Patients withdrawn from treatment for intolerable toxicity should be followed up regularly with tumor assessments until disease progression or the start of a new treatment, and for survival from that moment on. Guidelines for treatment interruption and dose reduction for hypertension are summarized in the following table.

Table 1. HYPERTENSION MANAGEMENT PLAN FOR AXITINIB

Increased Blood Pressure Grade			**Management**
Systolic Blood Pressure		**Systolic Blood Pressure**	If not receiving maximum antihypertensive treatment, start with a new or additional antihypertensive agent and maintain the axitinib dose. If receiving maximum antihypertensive treatment, reduce axitinib to one dose level lower.
2 systolic blood pressure readings > 150 mm Hg separated by at least 1 hour	O R	2 diastolic blood pressure readings > 100 mm Hg separated by at least 1 hour	
2 systolic blood pressure readings > 160 mm Hg separated by at least 1 hour	O R	2 diastolic blood pressure readings > 105 mm Hg separated by at least 1 hour	Interrupt dose*; adjust the hypertensive medication; resume axitinib at a lower dose level as soon as blood pressure is <150/100 mm Hg.
Recurrent hypertension after a previous dose reduction (2 systolic blood pressure readings > 150 mm Hg separated by at least 1 hour)	O R	Recurrent diastolic blood pressure > 100 mm Hg (2 blood pressure readings separated by at least 1 hour) after a previous dose reduction	Reduce again the axitinib dose to one dose level lower. If a patient requires reduction to below 2 mg BID, contact the investigator.

* If axitinib is interrupted, patients receiving antihypertensive medication should be monitored for hypotension. The half-life of axitinib in plasma is 2 to 4 hours and blood pressure is usually reduced within 1 to 2 days after stopping the dose).

9.4. Axitinib Dose Reduction for Proteinuria

Proteins in urine should be regularly evaluated by test strip as described in the schedule of activities.

• If the test strip shows proteinuria > 1+, collect 24-h urine. The dose may continue while awaiting results.

• If proteinuria < 2 g/24 h, maintain the dose at the same level.

• If proteinuria > 2 g/24 h, interrupt the dose and repeat determination of proteinuria and creatinine clearance in a 24-h urine sample (at the interval chosen by the investigator) until proteinuria is < 2 g/24 h. Resume axitinib at the same dose level or at a lower level at the discretion of the investigator.

Patients withdrawn from treatment for intolerable toxicity should be followed up regularly with tumor assessments until disease progression or the start of a new treatment, and for follow-up of survival from that moment on.

9.5. Axitinib Dose Interruption for Surgery or Surgical Procedures

If a major surgical procedure or medical intervention (e.g., endoscopy) is required, treatment with axitinib should be discontinued at least 24 hours before the procedure and the patient's blood pressure should be monitored carefully for hypotension. Patients may resume treatment with axitinib seven days after minor surgery and 2-3 weeks after major surgery, assuming that the wound has healed and there have been no complications in the healing process (e.g., delayed wound healing, infection, or fistula).

9.6. Concomitant Medication

Palliative and support treatments are allowed for disease-related symptoms, including analgesics. Patients may receive loperamide or other drugs for the treatment or prophylaxis of potential diarrhea. Narcotic analgesic or anti-inflammatory agents may be offered as needed.

Patients with fever or infection may undergo diagnostic tests and antibiotic treatment if needed and may receive colony-stimulating factor therapy as appropriate. Erythropoietic agents may be used at the discretion of the physician. Packed red blood cell or platelet transfusions should be administered as clinically indicated. Low-dose oral (< 5 mg a day of prednisone or equivalent), short cycle (< 7 consecutive days), or topical or inhaled steroids may be used at any dose throughout the study.

Patients who require anticoagulant therapy during axitinib treatment should be treated with low-molecular-weight heparin as the therapy of choice. Low doses of coumarinic agents may be administered with proper monitoring of PT/INR.

9.6.1. Drug Interactions

Studies in vitro with human liver microenzymes and recombinant CYP enzymes indicate that axitinib metabolism is mediated primarily by the drug metabolizing enzyme CYP3A and, to a lesser extent, CYP1A2. The drug also undergoes N-glucuronidation in the microsomes of some species. Clinically, it is likely that plasma AXITINIB concentrations may be increased in the presence of co-administration of potent CYP3A inhibitors and glucuronosyl transferase enzymes. In a study of healthy volunteers, ketoconazole, a potent CYP3A inhibitor, produced a two-fold increase in plasma exposure and a 1.5-fold increase in the maximum plasma concentration of axitinib. There is thus a potential drug-drug interaction with CYP3A inhibitors such as grapefruit juice, ketoconazole, miconazole, itraconazole, erythromycin, clarithromycin, telithromycin, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and delavirdine. Caution should be exercised in patients receiving axitinib in combination with these and other potent CYP3A inhibitors until appropriate drug interaction studies are conducted.

The metabolism of axitinib can be induced in patients taking CYP3A4/5 inducers (carbamazepine, dexamethasone, felbamate, phenobarbital, amobarbital, phenytoin, primidone, rifabutin, rifampin, nevirapine and St. John's wort), which may reduce the plasma concentration of axitinib. Patients who require concomitant treatment with potent CYP3A4 inducers will not be eligible for the study unless another treatment with minimal CYP3A4/5 induction potential is substituted. As CYP1A2 is induced in chronic smokers, it is likely that plasma axitinib concentration may be reduced in these patients. (Note: these patients will not be excluded from the study but patient's smoking status must be recorded in the CRF).

The capacity of axitinib to increase the concentrations of co-administered drugs was also investigated in studies of human liver microsomes. At the expected therapeutic plasma concentrations (0.01 to 1.0 μg/mL), axitinib appears to inhibit the drug metabolizing enzymes CYP1A2 and CYP2C8, two enzymes that are not frequently observed as metabolizing enzymes. Theophylline and tacrine are among the few drugs whose plasma concentrations appear to be increased by axitinib administration.

Axitinib binds to human plasma proteins (99.5% is bound at concentrations between 0.2 and 20 μg/mL). Drug interactions with other agents that bind strongly to plasma proteins are thus possible.

It is unlikely that axitinib has drug-drug interactions with commonly used antihypertensive agents of the ACE inhibitor class, including angiotensin II receptor antagonists (enalapril, captopril, losartan, vasartan), beta blockers (atenolol, metoprolol, labetalol), or diuretics (hydrochlorothiazide, furosemide). Within the class of the calcium channel blockers, verapamil and, to some extent, nifedipine, nicardipine and diltiazem have some potential to increase the plasma concentration of axitinib by means of CYP3A inhibition and should not be used as first choice in antihypertensive treatment. Other calcium channel blockers (amlodipine, bepridil, felodipine) are less likely to increase plasma axitinib levels.

The above information is based on data from preclinical studies of animal and human metabolizing enzyme systems. All the concomitant medications and blood products, as well as interventions (e.g., analgesic use for paracentesis) that patients receive from their first dose of axitinib until completion of the study visits should be recorded in the CRF.

10. STUDY PROCEDURES

10.1. Blood Pressure Measurement

Blood pressure readings should be made with the patient in a sitting position and after resting quietly in that position for 5 minutes before administering the drug. Patients should have their baseline blood pressure measured and once a week (the same day of the week) before taking the drug. The investigator will be able to decide if it is needed that blood pressure has to be measured more frequently .. Patients will be instructed by the

study staff that if their systolic blood pressure rises above 150 mm Hg, diastolic blood pressure rises above 100 mm Hg, or if they develop symptoms related to an increase in blood pressure (e.g., headache and vision problems), they should see the doctor immediately.

10.2. Hematological Parameters

The following tests should be performed at the specified in the calendar of activities and table of procedures (on Day 1 of each cycle): hemoglobin (Hb), white blood cell count, absolute neutrophil count, and platelet count. The international normalized ratio (INR), prothrombin time (PT) and partial thromboplastin time (PTT) are required at screening, and thereafter only as clinically indicated.

10.3. Blood Biochemistry Parameters

The following tests should be performed at the intervals specified by the calendar of activities and table of procedures (on Day 1 of each cycle): blood urea nitrogen (BUN), creatinine, sodium (Na+), potassium (K+), alkaline phosphatase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), total protein, albumin, total bilirubin, and glucose.

The lactate dehydrogenase (LDH) and albumin determinations are required at screening and end of treatment. These determinations will only be made at other visits when the doctor considers it is clinically indicated.

10.4. Thyroid Function Tests

Preliminary results from a small study suggest that there may be a potential correlation between fatigue and abnormal levels of thyroid stimulating hormone in patients receiving axitinib. Serum or plasma thyroid function tests with TSH determination should be performed at baseline and then every 12 weeks (coinciding with tumor assessments), or more frequently if there is clinical indication. If the TSH value is abnormal, free or total T3 and free T4 should be determined.

Patients receiving axitinib should be monitored for signs or symptoms of hypothyroidism, such as fatigue, constipation, deepening of the voice, cold intolerance, anorexia, periorbital edema, myxedema, and changes in the skin and hair. Hypothyroidism should be treated according to standard clinical practice to maintain a euthyroid state.

10.5. Urinalysis

Urinary protein analysis will be performed semi-quantitatively (test strip) or by routine laboratory methods at the intervals specified in the schedule of activities. Patients with proteinuria > 2+ should undergo protein quantitation in 24-hour urine.

10.6. Efficacy Assessment

All patients receiving at least 1 dose of investigational product will be considered evaluable for safety. All randomized patients will be evaluable for efficacy according to the assigned treatment, whether or not they receive it (intention-to-treat analysis). An

efficacy analysis will also be made in the per protocol population (patients that receive at least 1 dose of the investigational product and have a baseline radiological assessment and at least one additional tumor size evaluation). Efficacy parameters (objective response rate and progression-free survival) will be evaluated by CT according to RECIST 1.1.

CT will be performed every 12 weeks, from C1D1, until disease progression. CT is performed with intravenous contrast (if not contraindicated) and image acquisition in, at least, the arterial and portal phases. The radiation exposure from one CT-scan will be 13 millisievert (mSv), which is equivalent to the amount of radiation exposure one experiences from our natural surroundings in 3 years. The radiation exposure from one somatostatin receptor scintigraphy or octreoscan (25 mSv) is the equivalent to 8 years natural exposition.

The primary endpoint, progression-free survival, and the first secondary endpoint, objective response rate, are based mainly on CT imaging studies. In order to verify the results and reduce the potential inter-site variability in image interpretation, a centralized retrospective and independent evaluation will be made of all the CT images obtained in patients over the course of the study. The review will be made in the first part of the study (phase II) as well as in the phase III, by two expert radiologists in CT, which will remain blind to treatment assignment and to any other clinical data of the patients.

[18F]-DOPA-PET will be performed optionally at baseline, 1 month, and 6 months after starting treatment, and at disease progression and/ or end-of-treatment visit, in the hospitals that have the technology. Exploratory analyses will be made to evaluate their potential predictive and/or prognostic role. The radiation exposure from one 14FDOPA scan will be 25 mSv which is the equivalent to 8 years natural exposition.

10.7. Biomarker Assessment

Biomarkers in Plasma and Urine

The aim is to identify prognostic and predictive markers of the response to axitinib. Circulating blood and urine will be used as the surrogate tissues. A 9-mL peripheral blood sample and a urine sample will be collected prior to treatment, 1 month and 6 months after starting treatment, and at tumor progression and/or the end-of-treatment visit. The blood and urine samples will be used for molecular studies of DNA, RNA and proteins, hypoxia-related genes, angiogenesis regulation, the mechanism of action of axitinib, or the tumor biology of neuroendocrine tumors. Their correlation with different clinical-pathologic characteristics of interest, as well as the evolution of the disease, was evaluated. The dynamic profile of these genes in response to axitinib will be analyzed to evaluate their value in predicting response.

The blood and urine samples will be processed at the participating sites based on a specific manual that will be provided to the investigator at the baseline visit. The processed samples will be frozen at -80°C until shipment for analysis to the i+12 Institute of the Doce de Octubre Hospital in Madrid.

Biomarkers in Tumor Tissue

Tumor tissue will be collected from all patients and embedded in paraffin to investigate the prognostic and predictive potential of different intracellular pathways related to VEGFR, PDGFR and other RTK-related signaling and angiogenesis.

The tumor samples will be stored in the pathology department at each site to be sent to the i+12 Institute at the end of the study, where the determinations will be made. The samples will be returned to hospital of origin when the investigations have been completed.

10.8. Urine Pregnancy Test

Urine pregnancy test will be performed every 4 weeks in case of WOCBP.

10.9. Electrocardiogram

ECG will be performed every 12 weeks.

11. INFORMATION ON ADVERSE EVENTS

11.1. Adverse Events

Any adverse event observed or reported voluntarily by the patient, regardless of the treatment group or suspected causal relationship with the investigational product, will be notified as described in the following sections.

For all adverse events, the investigator must seek and obtain all the possible information to determine whether the adverse effect satisfies the criteria for a serious adverse effect, and to properly follow it up. If it satisfies the criteria for a serious adverse event, the investigator must report it by completing a SAE fromto include all information required by the Regulatory Authorities of the participating Member States to the Sponsor or designee. To make this possible, the investigator has to communicate the SAE to the Sponsor or designee within 24 hours of awareness. In addition, the investigator must report such SAEs to the study monitor within the same period.

The information compiled by the investigator on all adverse events should be sufficient to determine its cause. The investigator should be the person who evaluates the causality of the adverse event. In those adverse events in which a causal relation with the investigational product is suspected, the investigator should closely monitor it until the adverse event or its sequelae have resolved or stabilized at an acceptable level for the investigator.

11.2. Reporting Period

Serious adverse events should be reported to the Sponsor or designee and the competent authorities, if applicable, from the time the patient signs the informed consent, which must be obtained before the patient enters the study and before any study-related

procedure is performed, until at least 28 days have passed since the last administration of the investigational product. Any serious adverse event occurring at any time during the treatment period shall be promptly notified if the investigator suspects a direct causal relationship with the investigational product. Outside this period, if a SAE related to the investigational product occurs, it must always be reported.

Adverse events (serious and non-serious) must be recorded in the CRF from the time the patient signs the informed consent and until the last visit or 28 days after the last dose, whichever comes later.

If a patient starts a new anti-cancer treatment, any possible non-serious adverse events that occur should not be reported once the first dose of the new medication has been taken. Deaths will be reported if they occur during the notification period for serious adverse events, after the last dose of the investigational product, regardless of the intercurrent treatments.

11.3. Definition of Adverse Event

An adverse effect is defined as any untoward medical event that occurs in a patient participating in a clinical trial in which an investigational medicinal product has been administered. The event need not necessarily be related to the treatment administered. Examples of adverse events may be:

- Abnormal laboratory results;
- Clinically significant symptoms and signs;
- Changes in the results of physical examination;
- Hypersensitivity.

In addition, adverse events include symptoms and signs due to:

- Overdose of the medicinal product;
- Withdrawal from the medicinal product;
- Abuse of the medicinal product;
- Noncompliance with the medicinal product;
- Drug interactions;
- Dependence on the medicinal product;
- Intrauterine exposure

The worsening of the signs and symptoms of malignant neoplasm in the study will be reported as an adverse event in the relevant section of the CRF. Disease progression, evaluated by measuring malignant lesions by radiological or other methods, should not be reported as an adverse event.

11.4. Abnormal Laboratory Results

The criteria for determining whether an objectively abnormal laboratory result should be reported as an adverse event are the following:

- The test result is associated with accompanying symptoms and/or
- The test result requires additional diagnostic tests or a medical or surgical intervention and/or
- The test result requires modification of the dose of the investigational product, withdrawal of the patient from the study, or concomitant administration or a pharmacological or other treatment and/or
- The test result is deemed an adverse event in itself by the investigator.

An abnormal laboratory result that recurs but does not meet any of the above criteria does not constitute an adverse event. An abnormal laboratory result that proves to be an error does not have to be reported as an adverse event.

11.5. Serious Adverse Events

A serious adverse event or serious adverse reaction to an investigational product consists of any event occurring during the clinical trial resulting in:

- Death;
- Life-threatening;
- Hospitalization of the patient or prolongation of an existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly or birth defect.

Progression of the malignant neoplasm under study (including the signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is death during the study or during the safety notification period. Hospitalization for signs and symptoms of disease progression should not be reported as a serious adverse event. However, hospitalization due to disease progression will be recorded in the CRF. If the malignant tumor causes death during the study or in the safety notification period, the event that caused the death should be recorded as a serious adverse event NCI-CTCAE grade 5 (see intensity assessment section).

Medical and scientific judgment should be used to determine whether a particular episode is a major medical event. A major medical event may not be life-threatening or cause the death or hospitalization of the subject. However, if it is determined that the adverse event could endanger the patient's life and/or require intervention to prevent any of the above mentioned outcomes, it must be reported as a serious adverse event.

These events include, by way of example, intensive treatment for allergic bronchospasm in the emergency department or the patient's home, blood dyscrasias, or convulsions despite not resulting in hospitalization, or the development of drug dependency or abuse.

Although there may not be an associated SAE, exposure to a Pfizer product during pregnancy, exposure to a Pfizer product duringbreastfeeding, and the lack of efficacy of a Pfizer product are also notifiable, as indicated in the training materials provided by Pfizer. The definition of SAE includes exposure during pregnancy, exposure during breastfeeding, and the lack of efficacy.

11.6. Hospitalization

Adverse events reported in clinical trials and associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (including one of less than 24 hours) is considered an adverse event. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., transfer from the psychiatry area to a medical ward, from a medical ward to the coronary care unit, or from the neurology ward to a tuberculosis unit).

Hospitalization does not include the following locations:

- Rehabilitation centers;
- Palliative care centers;
- Specialized nursing homes or support care center (e.g., for caregiver rest);
- Qualified nursing care;
- Geriatric centers;
- Routine emergency room admissions;
- Same-day surgery (e.g., outpatient surgery).

Hospitalization or prolongation of hospitalization in the absence of a precipitant clinical adverse event will not be considered a serious adverse event itself. For example:

- Admission for the treatment of a preexisting condition not associated with the emergence of a new adverse event or with worsening of the preexisting disease (e.g., for the study of persistent abnormal laboratory values prior to treatment);
- Admission for social reasons (e.g., of a person who has no place to sleep);
- Admission for administrative reasons (e.g., for an annual physical examination);
- Admission stipulated by the protocol during a clinical trial (e.g., for a procedure required by the trial protocol);
- Optional admission not associated with an adverse clinical event (e.g., for scheduled cosmetic surgery);

- Previously scheduled treatments or surgical procedures should be recorded in the documentation from baseline and throughout the protocol and/or for the individual subject.
- Admission exclusively for the administration of blood products.

Diagnostic and invasive and noninvasive therapeutic procedures, such as surgery, should not be reported as adverse events. However, the condition for which the procedure was performed should be reported if it satisfies the definition of an adverse event. For example, acute appendicitis that begins during the adverse event reporting period should be reported as an adverse event, and the resulting appendectomy should be reported as the treatment of this adverse event.

11.7. Assessment of Intensity

The investigator will use the following definitions of intensity according to version 4.0 of NCI-CTCAE to describe the maximum intensity of the adverse event. If the adverse event is serious, the NCI-CTCAE grade reported in the adverse events section of the CRF must coincide with the description of the NCI-CTCAE grade included in the narrative section of the serious adverse event report.

GRADE	**Clinical Description of Intensity**
0	No variation from the normal or reference range (this grade is not in version 4.0, but may be used under certain circumstances).
1	MILD adverse event
2	MODERATE adverse event
3	INTENSE adverse event
4	LIFE-THREATENING OR DISABLING adverse event
5	DEATH RELATED WITH an adverse event

Note the distinction between the intensity and seriousness of an adverse event. An intense event is not necessarily a serious adverse event. For example, a headache may be intense (significantly interfering with the normal function of the subject), but cannot be classified as serious unless it meets one of the criteria for serious adverse events mentioned above.

11.8. Causality Assessment

The investigator shall assess the causality of all adverse events regardless of seriousness. This causality assessment by the investigator is what determines whether there is a reasonable possibility that the investigational product causes or contributes to an adverse event. If the final determination of causality provided by the investigator is unknown and the investigator does not know whether the investigational product caused the event, it will be classified as “product-related" for purposes of notification. If the causality assessment is "unknown but unrelated to the investigational product", it should be clearly documented in the trial records.

Moreover, if the investigator concludes that a serious adverse event is associated with the trial procedures, this causal relationship must be properly explained in the source

documents and CRF, and communicate this assessment in accordance with the reporting requirements for serious adverse events, if applicable.

11.9. Exposure during Pregnancy

In the case of investigational products and marketed products, intrauterine exposure (IUE) occurs if:

- a woman becomes pregnant or is found to be pregnant while receiving or being directly exposed (e.g., by environmental exposure) to the investigational product, or a woman who becomes pregnant or discovers she is pregnant after interrupting or being directly exposed to the investigational product (maternal exposure);
- a man has been exposed through treatment or the environment to the investigational product before or around the time of conception, or is exposed during the pregnancy of his partner (paternal exposure).

If a woman participating in the study or the partner of a male participant becomes pregnant or discovers she is pregnant during treatment with the investigational product, the investigator shall send this information to the Sponsor or designee using an intrauterine exposure form. In addition, the investigator will provide information on any environmental exposure of any pregnant woman to a Pfizer product (e.g., a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or leakage) using the intrauterine exposure form. This procedure is obligatory regardless of whether an adverse event has occurred and should be done within 24 hours of becoming aware of the pregnancy. The information submitted should include the expected date of delivery (see below information regarding induced abortion).

Follow-up will be conducted to obtain information about the outcome of pregnancy in all IUE notifications with an unknown outcome. The investigator will follow-up the woman until delivery or interruption (induced abortion) of the pregnancy and then will report the outcome to the Sponsor or designee. The investigator will provide this information as follow-up to the initial intrauterine exposure form sent. If an abortion is performed, the reasons must be indicated. It will not be necessary to prepare an IUE form if an ectopic pregnancy is reported, as this type of pregnancy is usually not viable. In its place, an SAE case will be opened with the occurrence of an ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death or congenital anomaly [including the existing outcomes of fetal death, stillbirth or neonatal death]), the investigator should follow the procedures for the notification of serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of delivery (i.e., no mandatory minimum follow-up period is set in the case of a presumably normal newborn for the completion of the intrauterine exposure form). The “normality" of a non-live fetus can be assessed by visual inspection, unless there were prior laboratory results indicating a congenital anomaly.

Additional information is provided below about pregnancy outcomes that are considered serious adverse events:

- The term "miscarriage" covers the concepts of natural miscarriage and missed abortion.

- All neonatal deaths occurring in the month after birth must be reported, regardless of causality, as serious adverse events. In addition, every death of a child that occurs after a month and that the investigator considers possibly related to IUE to the investigational product.

The investigator may request additional information regarding the IUE. Subsequent follow-up of the outcome of delivery will be on a case-by-case basis (e.g., follow-up of premature infants to identify developmental delays). In the case of paternal exposure, the investigator should obtain permission from the partner of the participating subject before conducting any follow-up or collecting any information.

11.10. Recording and Reporting AEs and SAEs

Adverse events will be recorded in the respective section of the CRF. The grade of the adverse event will be coded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE scoring system). The worst toxicity score will be recorded.

SAE Report to PIVOTALPharmacovigilance Department

If a SAE occurs, the investigator should immediately complete the SAE form and fax it to the Pharmacovigilance Department of Pivotal within 24 hours of awareness:

Pivotal fax number for reporting SAEs: +34 91 307 60 47

Pivotal Safety E-mail: drugsafety@pivotal.es

Serious Adverse Event Reporting to Health Authorities

If the adverse event meets the criteria for serious adverse events, related and unexpected, the study sponsor will make an expedited report to the appropriate authorities in compliance with current legislation.

12. STATISTICAL ANALYSIS AND METHODS

12.1 Statistical Methods and Sample Size Determination

The sample size of the first part of the study was calculated according to the Simon screening procedures for phase II randomized clinical trials,[13] where the goal is not only to show that one treatment arm is significantly better than another (which requires a larger sample size), but to select the most promising treatment regimen for future phase III trials.

For the extension of study AXI-IIG-02, to be conducted to obtain more robust results that could result in a positive conclusion regarding the treatment of NETs G1-G2 with axitinib, the following considerations were taken into account to ensure data integrity and the acceptability of the study results:

- The extension study contemplates the enrollment of **148 additional patients, for a total of 253 patients.**
- Patients will follow the same protocol as in the first part of the study.
- No additional analysis (with more mature data) will be made of the patients enrolled in the first part until the end of the study. Only one blind analysis will be made, based on a centralized retrospective assessment of all the CT studies, in order to confirm that the result obtained after the blind interim assessment performed 6 months after the enrollment of the last patient in the first part of the study can be replicated by a centralized blind review (this process is currently under way). This review will be made with the same cutoff date as that used in the analysis conducted in March 2015 and will also be considered as an interim analysis. The analysis of the results of the centralized blind assessment will be evaluated by the IDMC. The investigative team will not be informed of the preliminary results to minimize observational bias and ensure full independence.

- **Primary assessment of PFS will be made in the total population (253 patients)** and will take place after 95 events have been observed in the second subgroup of patients, recruited after the interim analysis.

Study Design, Statistical Assumptions and Power of the Final Analysis

The basis for the study sample size is to test the null hypothesis that there is no difference in PFS between the two treatment arms (hazard ratio = 1) versus the alternative hypothesis of a hazard ratio = 0.6. This hazard ratio is based on the following assumptions:

- Primary study objective: PFS
- Estimated follow-up: 24 months
- Median PFS for the control group (placebo/sandostatin): 13 months (equivalent to PFS at 24 months of 28%).
- Hazard ratio for the comparison between treatment groups: 0.6; equivalent to an increase in the rate of PFS at 24 months of 18% (SLP for axitinib 46% at 24 months).
- 89% power (β error < 0.11)
- Single-sided α error = 0.025 (adjusted for multiplicity)
- Sample size: 253 patients (first phase: 105; second phase: 148).

First stage

The first 105 patients enrolled continue in follow-up and the data collected through March 2015 will be reviewed by a blind centralized review committee; these data will be analyzed and considered as an interim analysis.

Second stage

It is planned to recruit 148 additional patients after the interim analysis. The final analysis will be carried once 95 PFS events have been observed in the last 148 patients enrolled. Since follow-up of the first 105 patients enrolled will continue, a minimum of 151 events in total (in 253 patients) is expected at the time of the final analysis, which will provide power of 88% or more to test the primary hypothesis with a single-sided alpha level of 0.025.

Interim Analysis

An interim analysis is planned of the data collected through March 2015 (approximately 51 SLP events are expected, or 33% of the expected number of events). The O'Brien-Fleming completion limits, based on the Lan-DeMets function, will be applied in order to control for an overall Type I error. Futility criteria will not be used. These limits are flexible and the limits at the time of the final analysis can be adjusted based on the actual number of observed events.

Final Analysis

If the final PFS objective in the overall population is statistically significant, an analysis with a hierarchical approach will be applied and PFS will be reviewed separately in the first subgroup cohort of 105 patients recruited and the second subgroup of 148 patients recruited. The results of the two subgroups should be consistent.

12.2. Population Analyzed

All the primary analyses of the efficacy data will be made using the intention-to-treat population (ITT), defined as the subjects who were randomized to the study treatment.
All the primary analyses of the safety data will be made using the safety population, defined as the subjects who were randomized to the study treatment and received some study treatment.

12.3. Disposition of Subjects, Demographics and Disease Characteristics

The disposition of the subjects will be summarized overall and by treatment group. The number of subjects who did not continue in the study or with the study treatment will be summarized together with the reason for leaving.

12.4. Study Objectives

12.4.1. Primary Efficacy Endpoint - Progression-free Survival

The primary endpoint is PFS, which will be measured from the date of randomization to the date of the first documented progression by RECIST 1.1 criteria or the date of death from any cause (if the patient died before progression). For patients without documented progression or death at the time of analysis, PFS will be censored at the last tumor assessment date. If a patient does not have tumor assessments after baseline, the patient will be censored on Day 1.

12.4.2. Secondary Efficacy Endpoints – Overall Survival, Time to Progression, Overall Response Rate, Duration of Disease Response

Overall Survival
Overall survival is measured from the date of randomization to the date of death from any cause. For patients who have not died at the time of the analysis, OS will be censored at the last contact date.

Time to Progression
Time to progression is measured from the date of randomization to the date of first observed progression (radiological or clinical, whichever occurs sooner). For patients without documented progression or death at the time of analysis, TTP will be censored to the last tumor assessment date. If a patient does not have tumor assessments after baseline, the patient will be censored on Day 1.

Overall Response Rate (RECIST)
The overall response rate will be calculated as the incidence of the best overall response (OR), partial response (PR) or complete response (CR). The best overall response is the best response from randomization to disease progression (DP). RECIST 1.1 criteria will be used.

Duration of Disease Response
The duration of the overall response is measured from the date of the first documented PR or CR (whichever is recorded first) until the date of the first documented DP or death from any cause. Only subjects who achieve CR or PR will be included in this analysis.

Biochemical Response (5-OH-Indoleacetic Acid and Chromogranin A)
In patients with elevated baseline NET tumor markers, biochemical response will be defined as a decrease of > 50% in the levels of Chromogranin A or 5-hydroxyindoleacetic acid (5-HIAA) compared to baseline in patients with elevated baseline levels.

Safety Objectives
The safety objectives include AEs caused by treatment, laboratory parameters and vital signs. An AE may be caused by treatment if it begins or worsens after the first dose of

study treatment. A baseline AE is any AE recorded after signing the informed consent and before administration of the study drug. All recorded AEs will be collected according to the Anatomical Therapeutic Chemical Classification System (ATC) and will be expressed using the terms of the NCI-CTCAE v4.0 and MedDRA dictionaries. The primary analyses are made using NCI-CTCAE v4.0. The severity of AEs will be classified by grades according to the NCI-CTCAE v4.0 dictionary. As for the relationship with the medicinal product, AEs are classified as related or unrelated to the investigational product.

Other Objectives

Different exploratory analyses, such as evaluating the correlation between relevant biomarkers and clinical objectives, will be performed.

12.5. Statistical Analyses

12.5.1. Efficacy Analysis

The distribution of each target time to event (PFS, OS, TTP, and duration of overall response) were estimated using the Kaplan-Meier method for each treatment group. Median times are estimated from Kaplan-Meier estimates with confidence intervals of 95%.

The rate of PFS at 6 months is calculated with a confidence interval of 95%.

The best overall response will be summarized for each treatment group. The ORR for each treatment group is calculated as the proportion of subjects who achieve CR or PR as best overall response.

Following the Simon design, a formal statistical test of the treatments is performed.

12.5.2. Safety Analysis

The overall incidence of AEs associated with treatment will be presented according to the ATC system organ class and preferred term. Subjects will count at least once for each category. The overall incidence of AEs associated with treatment will be presented in two ways, by severity and relation with the medicinal product. For these presentations, AEs are counted at least once in each patient, and the most severe grade, relation to the study drug, ATC system organ class and preferred term are used.

The primary safety analyses are made using NCI-CTCAE v4.0 codes. Summaries of the number (%) of subjects in each treatment group with at least 1 AE in each of the ATC system organ class categories and preferred term will be provided for:

- Baseline AEs
- AEs related to the investigational product
- AEs grade 3 or 4
- AEs grade 3 or 4 related to the investigational product

The incidence of AEs leading to discontinuation of the investigational product and/or withdrawal from the study will also be summarized and listed.
The incidence of death and SAEs associated with treatment will be summarized. SAEs associated with treatment and SAEs associated with the investigational product will be summarized by ATC system organ class and preferred term.
The incidence of the worst grade of toxicity will be summarized by NCI-CTCAE at baseline and at any time after the start of administration of the investigational product (including unscheduled visits, follow-up visits and any data collected after the last dose of study drug).
A descriptive analysis of the laboratory parameters and vital signs in each cycle will be provided. Shift tables for changes from the baseline toxicity grade to the worst post-baseline toxicity grade will also be provided. The toxicity grade of selected laboratory values will be determined using the CTCAE v4.0.
The descriptive statistics will be calculated based on the extent of exposure to the study drug in subjects.

12.5.3. Other Analyses

Different exploratory analyses, such as evaluating the correlation between relevant biomarkers and clinical objectives, will be performed.

12.5.4. Interim Analyses

A blind descriptive interim analysis was made at 6 months of recruiting 50% of the patients in the sample (40 patients) to evaluate the progress of the study, especially regarding the safety of both treatment arms.
The final efficacy analysis of the first part of the study was planned for 6 months after the enrollment of the last patient (March 2015). However, on the planned date for this analysis, the data were immature and the study was not unblinded. Before deciding to expand and redesign the study as a phase II-III study, as described in section 11.1, another interim analysis was made with the centralized and independent reading of the CT scans obtained as of March 2015. No other interim analysis will be made until completion of the study.

12.6. Handling of Missing Data

In order to achieve the objective of a well-organized clinical study according to ICH GCP, everything possible will be done to collect all the data. Still, despite the best efforts, incomplete or missing data are inevitably reported. All partial or missing data will be presented in the list of the subject's data as described in the CRF.

12.7. Missing or Incomplete Data Relating to Efficacy Objectives

For patients without documented progression or death at the time of analysis, PFS will be censored on the last tumor assessment date. If a patient does not have tumor assessments after baseline, the patient will be censored on Day 1. About the efficacy variables summarized at the end of the study, if the end-of-treatment visit is not made, the last available value of the variable after randomization will be used.

12.8. Missing or Incomplete Data Relating to Safety Objectives

With regard to the safety variables summarized at the end of the study, if the end-of-treatment visit is not made, the last available value of the variable after randomization will be used. No other substitution of missing values will be made.

13. QUALITY CONTROL AND QUALITY ASSURANCE

- During the conduct of the trial, the investigators are responsible for ensuring that the trial complies with the protocol and Good Clinical Practice (GCP).
- The trial sites may be subject to review by the Clinical Research Ethics Committee (CREC) and/or quality assurance audits by the appropriate regulatory authorities.An independent external committee will be constituted to make relevant decisions about the study conduct and interpretation of the data analysis. The external committee will consist in no more than 4-5 members, integrated by oncologists, radiologists and pharmacologists.

14. DATA HANDLING AND RECORD STORAGE

Case Report Form/Electronic Case Report Form

- The CRF is necessary and must be completed for each patient enrolled.
- The investigator is responsible for reviewing and approving the CRFs and for ensuring that CRFs are filled out. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained in the CRFs is true. The investigator will at all times bear full responsibility for the accuracy and authenticity of the laboratory and clinical data included in the CRFs. The source documents for patients will be the medical records kept by the physician at the site where the study is conducted. In most cases, the source documents are hospital or medical records and the information recorded in the CRFs should match those records.

Record Maintenance

- In order to allow evaluations or audits by regulatory authorities, the investigator agrees to keep records, including the identity of all the participating patients (sufficient information to relate the records, e.g., CRFs and hospital records), all original signed informed consents, copies of all CRFs, serious adverse event forms, source documents, and detailed records of the allocation of treatment. The records will be kept by the investigator according to ICH guidelines, local regulations, or as specified in the contract, whichever is longer.
- If the investigator moves, retires, or for any reason decides to leave the trial, the trial records shall be transferred to an acceptable substitute, such as an investigator or another institution.
- Patient diaries are considered source document and will be treated as such.

Confidentiality

The doctors, nurses and other personnel of the centre involved in this trial will need to access the patient medical history, including medical records or previous results for the purposes of this trial.

Members of the investigative team, the sponsor or representatives acting on behalf of the sponsor, the responsible country specific Ethics Committees and Authorities (competent authorities and federal state authorities) as well as the European Medicines Agency (EMA), members of the Clinical Research Ethics Committee will have access to your personal data and clinical records, in order to guarantee the reliability of the data collected in this clinical trial and complying with clinical trial regulations. These people are committed to strict confidentiality.

Within the data collected for the purpose of the study, no patient will be identified in any report or publication. The personal information will not be traced to identify them, unless required due to a legal or clinical emergency. The sponsor, or representatives acting on behalf of the sponsor, are committed to using this information exclusively for clinical trial objectives purpose.
Access to this personal data will be restricted to sponsor or other authorized personnel; who will be required to keep all data confidential.

15. ETHICAL PARTICULARS

15.1. Clinical Research Ethics Committee (CREC)

- The investigator is responsible for the prospective approval of the study protocol, amendments to the protocol, informed consent forms and other relevant documents,

e.g., advertisements (where applicable), before the CREC. All correspondence with the CREC must be kept in the Investigator File.

- The only circumstance under which an amendment may be made may be initiated prior to CREC approval is when the change is necessary to eliminate apparently immediate hazards for patients.

15.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, *Good Clinical Practice* guidelines of the International Conference on Harmonization, and the applicable local regulations and laws.

15.3. Patient Information and Informed Consent

- The informed consent form should comply with ICH GCP, local administrative rules and legal requirements.

- The investigator should ensure that all the study subjects are fully informed about the nature and objectives of the study and the possible risks associated with participation. The investigator or designee shall obtain written informed consent from each subject prior to performing any study-specific activity. The informed consent used in the study and all its amendments must be approved by the clinical research ethics committee prior to use. The investigator shall keep the original consent forms signed by the subjects.

16. DEFINITION OF THE END OF STUDY

The end of the trial at all the participating sites is defined as obtaining data from the last time point of the study. Given that one of the endpoints of this trial is survival, it is anticipated that the last data collection point is the last follow-up for survival (i.e., the most recent date on which it is known that the patient is still alive or the date of death) before the cutoff date for database closure before the final clinical study report.

17. SPONSOR TRIAL INTERRUPTION CRITERIA

This study may be interrupted prematurely by a decision of the health authorities, change in the opinion of the CREC, drug safety problems, or at the discretion of the sponsor.

If a study is terminated or interrupted prematurely, the sponsor shall immediately notify the investigators and Pfizer. Upon notification, the investigator should contact all the participating subjects and the hospital pharmacy (if applicable) within one month. All study materials should be collected and all CRFs completed as much as possible, following the instructions of the sponsor.

18. PUBLICATION OF RESULTS

The final results of the study will be disseminated by publication in journals of recognized scientific interest. In any publication, the name of the study coordinator should be listed first, followed by the names of the participants ordered by the number of patients recruited. In any case, written authorization will be obtained from the investigators to use their names in any publication, except in the case of references to published works.

Presentation by the members of the investigative team of partial results in conference papers and scientific meetings will be allowed after prior consultation with the study coordinator.

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Appendix 1. SAE Notification Form

Supplied separately.

Appendix 2. Required Laboratory Tests

	Conventional Units	Conversion Factor	SI Units
Hematology			
Hemoglobin (Hb)	g/dL	× 10	g/L
Platelet count (Plt)	$103/mm^3$	$\times 10^9$	10^{12}/L
White blood cell count (WBC)	$103/mm^3$	$\times 10^6$	10^9/L
Neutrophils	%	× 0.01	fraction
Lymphocytes	%	× 0.01	fraction
Biochemistry			
Total bilirubin	mg/dL	× 17.1	μmol/L
Alanine transaminase (ALT)	U/L	N/A	U/L
Aspartate transaminase (AST)	U/L	N/A	U/L
Alkaline phosphatase	U/L	N/A	U/L
Total proteins	g/dL	× 10	g/L
Albumin	g/dL	× 10	g/L
Sodium	MEq/L	× 1.0	mmol/L
Potassium	MEq/L	× 1.0	mmol/L
Bicarbonate (HCO_3) or venous (CO_2)	mmol/L	N/A	mmol/L
Blood urea nitrogen (BUN)	mg/dL	× 0,357	mmol/L
Creatinine	mg/dL	× 88.4	μmol/L
Lactate dehydrogenase (LDH)	U/L	× 0.016667	μkat/L
Glucose	mg/dL	× 0,055	mmol/L
Thyroid Function Tests			
Serum thyrotropin (TSH)	μU/mL		
Serum triiodothyronine (T3)	ng/dL		
Serum thyroxine (T4)	μg/dL		
Urinalysis			
Urinary protein (24-hour urine)	N/A	N/A	N/A

Appendix 3. ECOG Performance Status Scale

Grade	ECOG
0	Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (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	Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5	Death

Appendix 4. RECIST Response Evaluation Criteria in Solid Tumors Version 1.1.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows [35]:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with P10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Lymph nodes with a short axis < 10 mm are considered non-pathological and are not recorded or monitored.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

If the measurable disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology/histology.

Baseline documentation of ‘target’ and ‘non-target’ lesions

Target lesions are identified as measurable lesions representative of all measurable lesions of all the organs involved, up to 2 lesions per organ and a total of 5 lesions, and are measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions are selected based on their size (lesions with the largest diameters) and suitability for repeated measurement (by imaging techniques or clinically).

The longest diameter of each target lesion will be documented. The sum of the largest diameters of all the target lesions is calculated as the sum of the largest diameters and serves as reference during treatment to characterize the objective tumor response of the measurable dimension of the disease.

Pathological lymph nodes an exception to the above proposal. Pathological lymph nodes are defined as measurable lesions and can be identified as non-target lesions if the criterion of ≥ 15 mm short axis on CT is met. Only the short axis of these lymph nodes will contribute to the baseline sum. Node size is typically communicated in two dimensions of the plane on which the image has been obtained (for CT it is almost always the axial plane, for MRI the acquisition plane may be axial, sagittal or coronal). The short axis is the smallest of these measures.

A sum of the diameters will be calculated (the longest diameter for non-nodal lesions, the short axis for nodal lesions) for all target lesions and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or disease areas) will be identified as **non-target lesions** and also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response criteria

Target lesions

In target lesions, response is defined as follows:

- **Complete response (CR):** Disappearance of all target lesions.

- **Partial response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of the target lesions and lymph nodes are reduced to "normal" size (< 10 mm), their measurement on scanners may continue to be communicated. This measurement is recorded although the lymph nodes are normal to not overstate progression if it was based on the increase in the size of lymph nodes. As noted, this means that patients with CR may not have a sum total of "zero" in the CRF.

Non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

In non-target lesions, response is defined as:

- **Complete response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Cytology, histology

If required by the protocol (for example, residual lesions in germ cell tumors), in rare cases, these techniques can be used to differentiate PR from CR. When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

In patients with effusion or ascites, only cases with cytological evidence of malignancy will be recorded in the CRF. Effusions that have not been evaluated by cytology or have not proven to be malignant are not recorded in the CRF.

New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: (i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor). If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable as a complement to assessment of PD by CT (particularly for possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- FDG-PET negative at baseline, with FDG-PET positive during follow-up.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Confirmation of tumor response

In nonrandomized trials with a primary endpoint of response, confirmation of response is required. It is not required in randomized trials as the control group is already a suitable medium for data interpretation.

Overall determination of response by RECIST 1.1

In the presence of both types of lesion, target and non-target, individual assessments are recorded separately. Overall assessment of the response will involve all the parameters indicated in Table 3.

Table 3. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	No CR/no PD	No	PR
CR	Not evaluated	No	PR
PR	No PD or not all evaluated	No	PR
SD	No PD or not all evaluated	No	SD
Not all evaluated	No PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease			
PD = progressive disease and NE = not evaluable.			

Best overall response

The best overall response is determined when all patient data are known. In trials in which the confirmation of partial or complete response is not required (i.e., randomized trials),best overall response is defined as the best response recorded at any assessment point (e.g., the best overall response of a patient with SD in the first assessment, PR in the second assessment and PD at the last assessment will be the PR). When the best response is considered to be SD, it also must meet the minimum time specified in the protocol. If SD is the best response in an assessment point in which the minimum time is not met, the best response of the patient depends on the following assessments. For example, in the case of a patient with SD in the first assessment and PD in the second assessment who does not meet the minimum duration of SD, the best response of PD will be assigned. If after the first assessment of SD the patient is lost to follow-up, the patient will be considered non-evaluable.

When confirmation of CR or PR is required (i.e., non-randomized trials with a primary endpoint of response), the best overall response is defined according to the tumor response throughout the study. Complete or partial response can only be claimed if the criteria for each as specified in the protocol (usually 4 weeks later) are met in the next assessment point.

Patients with global deterioration of health status requiring suspension of treatment without objective evidence of disease progression at the time will be considered as 'symptomatic deterioration'. Everything possible will be done to document objective progression, even after discontinuing treatment. Symptomatic deterioration is not an objective response descriptor: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity

Appendix 5. Toxicity Criteria of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0 dated 28 May 2009 of the NCI-CTCAE can be reviewed online at the following website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.html

Appendix 6. Patient Diary

APPENDIX 7. Patient Information and Informed Consent

(Supplied separately)

SPONSOR AND STUDY PRINCIPAL INVESTIGATOR COORDINATOR'S

SIGNATURE PAGE

AXI-II-02

TITLE: A PHASE II/III RANDOMIZED DOUBLE-BLIND STUDY OF SANDOSTATIN LAR IN COMBINATION WITH AXITINIB VERSUS SANDOSTATIN LAR WITH PLACEBO IN PATIENTS WITH ADVANCED G1-G2 NEUROENDOCRINE TUMOURS (WHO 2010) OF NON-PANCREATIC ORIGIN

Version**: 9.0 10 September 2018**

Protocol Number: AXI-IIG-02 **EudraCT Code:** 2011-001550-29

Sponsor: GETNE (Grupo Español de Tumores Neuroendocrinos [Spanish Group of Neuroendocrine Tumors])

Sponsor Protocol Code: GETNE 1503

I confirm that I have read and understood the above clinical protocol and agree to lead this clinical study in accordance with the provisions included on it, and ethical principles stated in the latest version of the Declaration of Helsinki, Good Clinical Practice (GCP) regulations of the International Conference on Harmonization (ICH), and applicable legal requirements.

Sponsor's Representative and Global Study Principal Investigator Signature:

_____ _____

Dr. Rocío García-Carbonero Date