STATISTICAL ANALYSIS PLAN

Study Code: AXI-IIG-02

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

Investigational Product	AG-013736 (AXITINIB)
Indication Studied	Advanced G1-G2 neuroendocrine tumors of nonpancreatic origin
EudraCT No	2011-001550-29
Phase of Study	II-III
Sponsor: company and address	GETNE (Grupo Español de Tumores Neuroendocrinos)
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Approved by

Name Role	Name Role

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Statement:

By signing this document, I acknowledge that I have read the Statistical Analysis Plan and approve of the planned statistical analysis described herein.

I agree that the planned statistical analyses are appropriate for the objective of the study and are consistent with the methodology described in the protocol, clinical development plan, and all regulatory guidelines.

I also understand that any subsequent changes to the statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

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1. LIST OF ABBREVIATIONS

1.1 Abbreviations

AE	Adverse Event
AJCC	American Joint Comitee on Cancer
BEV	Bevacizumab
BID	Two times a day (Latin bis in die)
CCRm	Carcinoma colorrectal metastásico
CECs	Circulating endothelial cells
CPEs	Endothelial Progenitor circulating cells
CR	Complete response
CREC	Clinical Research Ethics Committee
CRF	Case Report Form
CYP3A4	Cytochrome P 450 3A4
DP	Disease progression
ECG	Electrocardiogram
FOLFOX	LV + 5-FU + Oxiplatin
FOLFIRI	5-Fluoracil + Leucovorin + irinotecan
5-FU	5-Fluorouracil
GCP BCP	GOOD/BEST CLINICAL PRACTICES
HIF	Hypoxia-induced factor
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IM	Intramuscular
IUE	Intrauterine exposure
ITT	Intention to treat
IV	Intravenous
LV	Leucovorin
mCRC	Metastatic colorectal carcinoma

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NET	Neuroendocrine tumor
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PDGF	Platelet-derived growth factor
PDGFR	PDGFR β PDGF receptor β
PFS	Progression-free survival
PO	Per os, orally
PP	Per Protocol
PR	Partial response
Q3	Quartile 3
QT	QT interval on the ECG
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria In Solid Tumours
RT	Radiotherapy
RTK	Receptor of tyrosine kinase
SAE	Serious Adverse Event
SD	Standard Deviation
SP	Safety Population
TTP/THP	Time to progression
ULN	Upper normal limit
UPC	Urine protein:creatinine ratio
VEGF	Vascular endothelial growth factor
VEGFR2	VEGF receptor 2
XELOX	Capecitabine + Oxaliplatin

2. INTRODUCTION (INTRODUCCION)

2.1 Background & Rationale

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.

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.

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 micro vessel 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.

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 authors3 have correlated VEGF expression with increased angiogenesis and metastasis and diminished duration of progression-free survival in correlated with reduced disease-free survival in pancreatic endocrine tumors.

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, sorafenib, everolimus, bevacizumab, and pazopanib, among others. Two new targeted agents have been approved in recent years, sunitinib6 and everolimus, 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) (sunitinib) 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.

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, is capable of improving 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 similar to 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.

2.2 Study Objectives

This statistical analysis plan describes the methods and statistical models to be applied for the generation of the statistical report. As a reference, the study protocol v7.0 (dated on 21 March 2018) has been used in order to prepare this document

2.2.1 Primary Objective

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

2.2.2 Secondary Objectives

- Evaluate the objective response rate (ORR) (measured according to RECIST 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 (OS).
- Explore potential biomarkers (circulating tumour cells, circulating endothelial cells, hypertension, and other serum or tumoral biomarkers of angiogenesis).

2.2.3 Safety Objective

- Evaluate the safety and tolerability of axitinib (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.0)

2.3 Study Design

This is a 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.

2.3.1 Eligibility and Randomization

Patients are randomized to receive sandostatin LAR with axitinib or sandostatin LAR with placebo until disease progression or unacceptable toxicity occurs. Randomization has been 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%).

2.3.2 Eligibility criteria

Subjects might 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 < 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 ≥ 1500 cells/mm^3.
    - Platelet count ≥ 75,000 cells/mm^3.
    - Hemoglobin ≥ 9.0 g/dL.
    - AST y ALT ≤ 2.5 x upper limit of normal (ULN), except if liver metastases exist, in which case AST and ALT ≤ 5.0 x ULN is allowed.
    - Total bilirubin ≤ 1.5 x ULN.
    - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min.
    - Proteinuria < 2+ by reactive strip. If the reactive strip is ≥ 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 ≥ 18 years.
12. ECOG performance status 0-2.
13. Life expectancy ≥ 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 ≤ 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. Lactating women may not participate in this study.
17. Signed and dated informed consent document stating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to recruitment.
18. 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.

Subjects might be evaluated with regards 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[3] 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.

2.3.3 Withdrawals

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 treatment 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, at the discretion of Investigators, that continued study drug dosing is not in the subject's best interest.
- Progression disease.

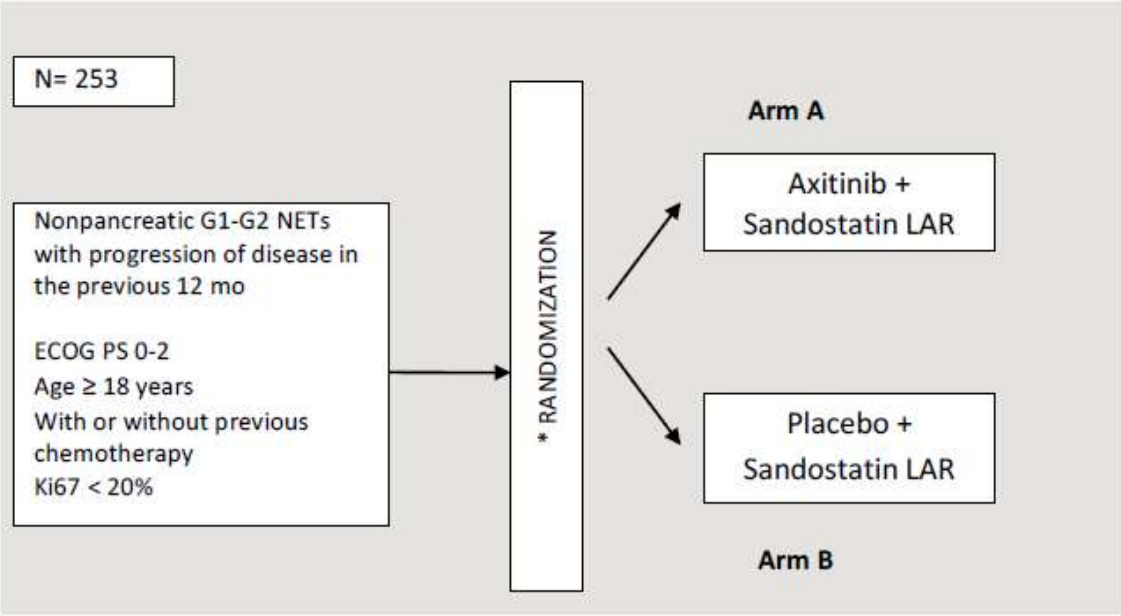
2.3.4 Study treatment

Patients will be randomly assigned in a double-blind design with a 1:1 ratio to receive:

✓ Experimental Arm: sandostatin LAR 30 mg IM every 28 days + Axitinib 5 mg PO twice a day (BID)

✓ Control Arm: sandostatin LAR 30 mg IM every 28 days + Placebo PO twice a day (BID).

Figure 1 Study Design



2.3.4.1 Dosage and regimens

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, were 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 was administered in cycles of 4 weeks' duration.

Sandostatin LAR 30 mg is administered intramuscularly every 28 days.

Patients who tolerated axitinib/placebo without presenting any drug-related adverse events of grade 2 or higher according to CTCAE over a period of 2 consecutive weeks might 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 was receiving antihypertensive medication, in which case the dose was not increased).

Patients who experienced a reaction to the drug above grade 2 according to CTCAE should receive a dose modified according to protocol guidelines. Concomitant medications that were 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 was consulted with and authorized in writing by the medical coordinator of the study.

Figure 2 **Available Axitinib /Placebo Dose Levels**

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

2.3.4.2 Treatment duration

Treatment under study (sandostatin LAR with axitinib or sandostatin LAR with placebo) has been constant until disease progression or unacceptable toxicity occurred. The estimated follow-up period is 24 months after end of treatment.

2.3.5 Replacement of Patients

No patient replacement is contemplated during the course of this study.

3. STUDY(ANALYSIS) POPULATIONS

The **study population** will be made up with patients diagnosed of neuroendocrine carcinomas advanced whose origin is not pancreatic, in first or second-line treatment.

3.1 Intent-to-treat population (ITT)

The intent to treat population (ITT) is defined as those subjects who were randomized to the study treatment.

3.2 Safety population (SP)

The Safety Population is defined as those subjects who were randomized to the study treatment and received at least 1 dose of investigational product

3.3 Per Protocol Population (PP)

The Per Protocol population is defined as those subjects who are in the ITT population, received at least 1 dose of investigational product and had a baseline radiological assessment and at least one additional tumor size evaluation.

3.4 Other populations

No other populations have been defined for this study.

3.5 Screening Failures

Patients with any screening failure who were randomized to either study treatment arms will be analyzed in the ITT population, otherwise (if not randomized) the patient will not be analyzed.

4. STUDY ENDPOINTS AND DERIVED VARIABLES

4.1 Baseline and demographic characteristics

- Age: will be computed as the time elapsed (in years) between birth and randomization date
- Time from diagnosis: will be computed as the time elapsed (in months) between the diagnosis date and randomization date.
- Number of previous lines for previous anticancer treatment: will be computed as number of different systemic antineoplastic treatment regimens registered in a patient not taking into account surgery and radiotherapy.

4.2 Efficacy endpoints

- PFS Time: will be computed as the time elapsed (in months) between the randomization date and the date of the first progression observed or death date for any cause (if it happens before the progression)
- Overall Survival Time: will be computed as the time elapsed (in months) between the randomization date and the death date for any cause.
- TTP Time: will be computed as the time elapsed (in months) between randomization date and the first observed progression date (Radiological or clinically, whichever comes first)
- Best Overall Response: will be computed as the best response presented according to RECIST 1.1 criteria from randomization to disease progression (DP).
- Objective Response Rate: will be computed as the proportion of patients who show as best overall response a complete response (RC) or partial response (PR).
- Duration of Response: will be measured as the time elapsed (in months) from the date of the first documented PR or CR (whichever occur first) until the date of the first documented PD or death from any cause. Only subjects who achieve CR or PR will be included in this analysis.
- Biochemical Response (5-OH-Indoleacetic Acid (5-HIAA). Chromogranin A (CgA) and Enolase (ENE): In patients with elevated baseline NET tumor markers, biochemical response will be defined as a decrease of > 50% in the levels of CgA or 5-HIAA or ENE, each assessed individually as compared to their respective baseline values as proposed by (Alexandria T. Phan, et al, 2017).
  - ✓ Elevated baseline NET tumor markers are defined as those baseline values for 5-OH-Indoleacetic Acid , Chromogranin A and Enolase) that are greater than each respective ULN.

4.3 Safety endpoints

4.3.1 Exposure of Study Medication

- Treatment duration: will be computed as the time elapsed (in months) from the start date of study treatment until the last dose date +28 (cycle duration) divided by 28.

4.3.2 Adverse Events

- Severity and frequency of associated Adverse Events/Serious Adverse Events (TEAEs/SAEs), Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).
- Treatment related to study drug AE is defined as those AEs whose relationship with study drug therapy is related or unknown as recorded in the eCRF.
- TEAE leading to study drug modification is defined as those AEs whose action taken dose reduced, increased, dose interrupted as recorded in the eCRF.
- AE leading to study drug withdrawn is defined as those AEs whose action taken is withdrawn is as recorded in the eCRF.

4.4 Other derived variables

Any other derived variable necessary for analyses will be described and justified in the final statistical study report.

5. GENERAL STATISTICAL METHODS

5.1 Sample Size

The sample size of the first part of the study was calculated according to the Simon screening procedures for phase II randomized clinical trials, (Simon R, 1985) 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-002, which was 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 contemplated the enrollment of 148 additional patients, for a total of 253 patients.
- Patients have followed the same protocol as in the first part of the study.
- No additional analyses (with more mature data) have been made of the patients enrolled in the first part until the end of the study.
- **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.

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 (HR) 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).

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.

5.2 Patients' disposition

5.2.1 Patients´ disposition and withdrawals

Patients disposition will be summarized by treatment arm, absolute and relative frequencies of patients included in each of the populations of analysis will be shown. Patients excluded from these populations will be described in a listing, including the cause of exclusion.

Absolute and relative frequencies will be also summarized by site. Patients who discontinue treatment prematurely will be displayed in a listing, indicating the reason for such discontinuation.

The number and percentage of patients who complete study drug treatment will be summarized by treatment group. Reasons for premature discontinuation of treatment will be tabulated.

In addition, the number and percentage of patients who complete the study will be summarized by treatment group. Reasons for prematurely discontinuing from the study will be tabulated.

As appendix, a listing with all patients included in the study, will be displayed. It will contain the following information: ID patient/site, age/sex, population indicator, treatment completion, study completion, and for those patients who discontinue treatment the reason for such discontinuation.

5.2.2 Protocol Deviations

Subjects are deemed to be a Protocol Deviation if they could present any of the following reasons:

- Not met any of the inclusion/exclusion criteria.
- Signed and dated informed consent document.
- Omission and delays of the study tests, assessments or procedures when these are systematical (not justified).
- Omission, delays of study visits when they are systematical (not justified).
- Any other deviation from what is established in the protocol that may be considered to affect the evaluation of the objectives of the study

All protocol deviations will be listed

5.3 Summary of Statistical Methods

Since this clinical trial has two treatment arms, statistical analyses will be presented and compared by treatment group. Both descriptive and inferential statistics will be used.

Continuous variables will be summarized using the number of cases, mean, standard deviation (SD), mean 95% CI, median, Q1, Q3, minimum and maximum. Shapiro-Wilk test will be used to check whether the measure deviates from a normal distribution.

Categorical variables will be summarized in contingency tables by presenting the number and percentage of patients in each category. Depending on the variable, a two-sided 95% CI may be provided.

Fisher's exact test (2-sided) or chi-squared test will be used to explore associations of categorical data. For continuous variables, these comparisons will be done using the parametric t-Student test if the variable follows a normal distribution or the non-parametric Wilcoxon-test (Mann-Whitney test) otherwise.

In order to explore the correlation between two continuous variables, Pearson or Spearman correlation tests will be applied (depending on the Gaussian distribution of data). In case of categorical variables, Chi-square or Fisher exact test will be used instead. Agreement index between 2 binary variables will be assessed by means of Cohen's kappa coefficient (κ) and in case of 2 ordinal variables Tau- Kendall coefficient will be considered.

Survival analyses (PFS, OS, TTP and duration of response) will be computed with a Kaplan-Meier model. As a result, survival curves, median and its 95 %CI, number of events distribution and censored cases, estimated survival probability by time intervals, and estimators for Log-Rank Test will be displayed. A Cox model will be adjusted in order to control odds factors, and Hazard Ratio (HR) and its corresponding 95% CI will be showed.

A significance level of 0.05 for all test in contrast will be used.

5.3.1 Analysis of Baseline & Demographics

Demographic and baseline data analyses will be performed on the ITT population. Statistical Analyses of this section will be produced in accordance with 5.3 section and will be displayed by treatment arm.

Age (definition in 4.1Baseline and demographic characteristics) and Gender will be summarized by descriptive statistics.

5.3.1.1 Baseline characteristics

Vital signs: Weight (kg), Height (cm), temperature (ºC), pulse (beats per minute), Systolic and Diastolic BP (mm Hg) will be summarized by descriptive statistics.

Smoking habits: Absolute and relative frequency of smoking habits will be tabulated. Number of cigarettes per day will be summarized by descriptive statistics.

5.3.1.2 Physical examination

Number and proportion of patients with normal/abnormal results in physical examination will be tabulated broken down by System and treatment arm.

5.3.1.3 Oncologic history and histologic confirmation of neuroendocrine carcinoma

Time since diagnosis (definition in 4.1Baseline and demographic characteristics**¡Error! No se encuentra el origen de la referencia.**), Primary Tumor Location, Metastasis location, TNM Staging and Grade will be summarized by descriptive statistics.

Different tumor locations will be also classified as follows:

- Esophagus
- Stomach
- Duodenum
- Jejunum-Ileum
- Gall bladder

- Biliary tract
- Colon
- Rectum
- Lung
- Unkown origin
- Other (non gastrointestinal nor lung; i.e. thymus, gynecological, genitourinary…..)

Primary tumor location will also be analyzed grouped as follows:

- Esophagogastric
- Gall bladder and biliary tract
- Small bowell: duodenum and jejunum-ileum
- Large bowell: colon and rectum
- Lung
- Unknown
- Other

And further grouped as follows:

- ✓ Gastrointestinal: esophagogastric, gall bladder and biliary tract, small and large bowell
- ✓ Lung
- ✓ UK and other

5.3.1.4 Previous anticancer treatment

The number and proportion of patients who received a previous cancer treatment will be tabulated, indicating the number of registered treatments per patient and number of previous lines.

As appendix, a listing with previous anticancer treatment received will be displayed. It will contain the following variables: ID patient/site, age/sex, treatment arm, type, agents, intent, onset and end date and best overall response.

5.3.1.5 Previous relevant medical history

The number of patients affected for any relevant surgical or medical disease (not related with the disease of study) will be analyzed by treatment arm. Number and proportion of patients will be tabulated broken down by SOC, Preferred Term and treatment arm.

As appendix, a listing with all the relevant affections not related with the study disease will be displayed by patient. It will contain the following variables: ID patient/site, age/sex, treatment arm, Medical-surgical affection, start and end date, ongoing indicator, and concomitant medication indicator.

5.3.1.6 Signs and Symptoms

The number of patients who had any sign or symptom in the 14 days prior to the beginning of the study treatment will be tabulated by treatment arm, indicating the number of signs/symptoms reported by patient. Signs and Symptoms will be only available for phase II patients (Stage 1)

As appendix, a listing with signs and symptoms presented will be displayed by patients. It will contain the following variables: ID patient/site, age/sex, treatment arm, symptom, specification, grade, onset and end date and ongoing indicator.

5.3.1.7 ECOG and ECG

ECOG performance status and Electrocardiogram evaluation results (normal; Significant abnormal, Non-significant abnormal) will be summarized by descriptive statistics.

5.3.1.8 Laboratory values at baseline

Baseline parameters for Hematology, Biochemistry and Hemostasis will be summarized by treatment arm.

5.3.1.9 Tumoral Markers

For those patients with measures of baseline NET tumor markers (5-OH-Indoleacetic Acid Chromogranin A and Enolase), the following outcomes will be summarized by treatment arm:

- Number and proportion of patients with elevated baseline NET tumor markers (> 1x ULN).
- Number and proportion of patients with elevated baseline NET tumor markers (> 2*ULN) as proposed by (Oberg K, Anthony L, Sideris L, et al, 2011).
- Number and proportion of patients with clinically significant baseline NET tumor markers

5.3.1.10 Ki-67 Determination

For those patients with baseline Ki-67 measure, the following outcomes will be summarized by treatment arm:

- Ki-67 determination (%).
- Number and proportion of patients with Ki-67 <5% and ≥5%.
- Number and proportion of patients with Ki-67 (<3% and 3–20% as proposed by AJCC guidelines

5.3.2 Efficacy Analyses

Efficacy analyses will be performed on the **ITT and PP populations.** Statistical Analyses of this section will be produced in accordance with section 5.3Summary of Statistical Methods and will be displayed by treatment arm.

5.3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the Progression-Free Survival (PFS). Is defined as the time elapsed (in months) between the randomization date and date of the first progression observed or the death date from any cause (if it happens before the progression)

Patients who progress or die will be considered as events except if the event occurs after the start of a new line of treatment, in which case the patient will be censored with the date of the last reported tumor evaluation prior to the start of the new therapy. If the patient is lost to follow-up or has more than one tumor evaluation not available between the date of the last evaluation and the date of progression, death or start of a new therapy, the patient will be censored on the date of the last tumor evaluation valid prior to evaluations not available. Finally, if a patient would not have tumor assessments after baseline, the patient will be censored on Day 1.

A summary table with the number of cases, number of events (and type of event), number of censored patients, median and its confidence interval of 95% (CI 95%), the p-value corresponding to apply the Log-Rank Test and the results of the Cox model (Hazard Ratio (HR), p-value and estimate and confidence interval of 95%), by treatment arm will be displayed. Besides this, PFS Kaplan-Meier curves will be included. In addition, **PFS at 6, 12- and 24-months rate** will be computed and analyzed by treatment arm, 95 % CI for the rate computed will be also provided based on PFS Kaplan-Meier life table.

5.3.2.2 Secondary Efficacy Endpoints

Best Overall Response (according to RECIST 1.1 criteria) will be computed as the best response presented according to RECIST 1.1 criteria from randomization to disease progression (DP). Results will be summarized in a contingency table. 95% Clopper- Pearson CI for every percentage will be provided.

Objective Response Rate (definition in 4.2 Efficacy endpoints) will be computed and summarized by treatment arm, 95% Clopper- Pearson CI will be provided.

Duration of disease response (definition in 4.2 Efficacy endpoints) will be computed and summarized by treatment arm.

5.3.2.2.1 Overall Survival

Overall Survival (OS) will be assessed by treatment arm. Is defined as the time elapsed (in months) from the date of randomization of the patient up to the date of death from any cause. If the patient would not die, will be censored at the last contact date.

A summary table with the number of cases, number of events (and type of event), number of censored patients, median and its confidence interval of 95% (CI 95%), the p-value corresponding to apply the Log-Rank Test and the results of the Cox model (Hazard Ratio, p-value and estimate and confidence interval of 95%), by treatment arm will be displayed. Besides this, OS Kaplan-Meier curves will be included.

Time to Progression (TTP) will be assessed by treatment arm. Is defined as the time elapsed (in months) from the randomization date until the first observed progression date (radiological or clinic, whichever comes first). For patients without documented progression or death related with progression 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.

A summary table with the number of cases, number of events (and type of event), number of censored patients, median and its confidence interval of 95% (CI 95%), the p-value corresponding to apply the Kaplan-Meier method and the results of the Cox model (Hazard Ratio, p-value and estimate and confidence interval of 95%), by treatment arm will be displayed. Besides this, TTP Kaplan-Meier curves will be included.

5.3.2.2.2 Biochemical Response

Percent change from baseline will be computed and summarized by treatment arm for CgA, hydroxyindoleacetic acid (5-HIAA) and Enolase.

Additionally,biochemical response as number and proportion of patients with a decrease of > 50% in the levels of CgA , 5-hydroxyindoleacetic acid (5-HIAA) and Enolase separately will be also provided together with its 95% Clopper- Pearson CI.

5.3.2.2.3 Functional Response Rate

Evaluate the functional response rate using F-DOPA-PET (optional, depending on availability).

5.3.2.2.4 Potential biomarkers

Potential biomarkers (circulating tumor cells, circulating endothelial cells, hypertension, and other serum or tumoral biomarkers of angiogenesis) will be explored.and analysed by i+12 Institute of the Doce de Octubre Hospital in Madrid. Outcomes will be provided in a separate report different from Final Statistical Report.

5.3.3 Safety Analyses

Safety analyses will be performed on the **Safety population**. Statistical Analyses of this section will be produced in accordance with 5.3 Summary of Statistical Methods and will be displayed by treatment arm.

5.3.3.1 Treatment exposure

Treatment Duration (months), (definition in section4.3 Safety endpoints) will be computed and summarized by treatment arm.

5.3.3.1.1 Treatment Administration

Total cumulative administered dose (mg), Absolute Dose intensity (mg/week) and Relative Dose Intensity (mg/week) (definition in section 4.3 Safety endpoints) will be computed and summarized by treatment arm.

Number of cycles administered per patient will be computed and summarized by treatment arm. Number and proportion of patients with each number of cycles received will be also summarized by treatment arm.

5.3.3.1.2 Delays, reductions and modifications

The number and proportion of patients with delays, reductions, interruptions, and dose suspensions will be analyzed by treatment arm. The total number of cycles affected by each of these actions will be analyzed. Reasons for Delays, reductions, interruptions, and dose suspensions will also be described

5.3.3.2 Adverse events

Adverse events (AE) will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later and presented by primary System Organ Class (SOC) and Preferred Term (PT).

AEs will be graded according to NCI CTCAE, Version 4.0. For events of varying severity, the most severe grade as documented on the eCRF will be used in the summaries.

A global summary table with the AEs generated by treatment arm, indicating the number and proportion of patients who presented:

- At least one AE.
- At least one serious adverse event (SAE),
- At least one adverse event which grade is 3-4,
- At least one adverse event related with study treatment.
- At least one adverse event that leads to treatment withdrawn.
- At least one adverse event that leads to treatment modification.
- At least one adverse event grade 3 or 4 related with study treatment.
- At least one adverse event serious and grade 3 or 4.
- At least one adverse event serious, grade 3 or 4 and related to study treatment
- At least one adverse event that leads to death

Total number of AEs, Serious and related with study treatment will be also analyzed by treatment arm.

Incidence of serious and non-serious, related and non-related with sandostatin and axitinib AEs will be tabulated by Primary System Organ Class (SOC) and Preferred Term (PT), sorted by decreasing total incidence of SOC and PT within SOC.

When calculating the incidence of AEs, or any sub-classification thereof by treatment, causality, severity, etc, each subject will only be counted once (corresponding to the maximum toxicity grade) and any

repetitions of adverse events will be ignored; the denominator will be the corresponding total population size in each treatment arm or Safety population for Overall.

As appendix, a listing with all adverse events will be included. This listing will contain the following variables: ID patient/site, age/sex, treatment arm, SOC term, PT term, onset and end date, severity, and relationship with study drug, action taken, seriousness and seriousness criteria.

5.3.3.2.1 Adverse events: Worst grade by patient related

Incidence of AEs related with sandostatin and axitinib AEs will be tabulated by Primary System Organ Class (SOC) and Preferred Term (PT), sorted by decreasing total incidence of SOC and PT within SOC.

5.3.3.2.2 Adverse events: Worst grade by patient unrelated

Incidence of AEs non-related with sandostatin and axitinib AEs will be tabulated by Primary System Organ Class (SOC) and Preferred Term (PT), sorted by decreasing total incidence of SOC and PT within SOC.

5.3.3.3 Serious adverse events (SAEs)

5.3.3.3.1 Serious adverse events: Worst grade by patient related

Incidence of SAEs related with sandostatin and axitinib will be tabulated by Primary System Organ Class (SOC) and Preferred Term (PT), sorted by decreasing total incidence of SOC and PT within SOC.

5.3.3.3.2 Serious adverse events: Worst grade by patient unrelated

Incidence of SAEs non-related with sandostatin and axitinib will be tabulated by Primary System Organ Class (SOC) and Preferred Term (PT), sorted by decreasing total incidence of SOC and PT within SOC.

5.3.3.3.3 Deaths

The number and proportion of death patients be showed by treatment arm. Cause of death will also be summarized.

Patients who die due to Toxic death will be summarized. Adverse Events related to Toxic deaths will be described

5.3.3.4 Vital Signs

Vital signs at screening and EoT will be analyzed using descriptive statistics for continuous variables, due to extensive amount of cycles, a listing with vital signs by patient and cycle will be provided.

5.3.3.5 Physical Exam

Physical Exam will be summarized only at Screening and EoT, due to extensive amount of cycles, a listing with abnormal results by, patient Organ/System and cycle will be provided.

5.3.3.6 ECOG performance status

ECOG performance status will be summarized only at Screening and EoT, due to extensive amount of cycles, a listing with ECOG by patient cycle will be provided.

5.3.3.7 ECG

Frequencies of overall ECG evaluation (normal; Significant abnormal, Non-significant abnormal) will be provided over time1.

5.3.3.8 Clinical laboratory evaluation

Laboratory parameters (Hematology, Biochemistry and Hemostasis) will be graffically analyzed over time point by line plots with mean (SD) .A listing with only clinically significant parameters by patient, lab parameter and cycle will be provided.

Shift tables for changes from the baseline toxicity gradeto cycle1 and the worst post-baseline toxicity grade during all study will also be provided. The toxicity grade of selected laboratory values will be determined using the CTCAE v4.0.

5.3.3.9 Prior and Concomitant medication

Previous medications will be coded with WHO-DRL and will be summarized by therapeutic subgroup and Anatomical Therapeutic Chemical (ATC) subgroup (levels 1, 3 and 4) by each treatment arm. Concomitant medications will be included in all periods that they were taken in.

The number and proportion of patients who have received prior and concomitant medications will be summarized by treatment arm.

As with previous medication, concomitant medication will be summarized for each treatment arm by therapeutic subgroup and chemical subgroup (ATC levels 1,3 and 4). Patients taking the same medication multiple times will be counted once per medication in each investigational period.

As appendix, a listing with all concomitant medication will be included. This listing will contain the following variables: ID patient/site, age/sex, treatment arm, Drug, route, dose (units), onset and end date, ongoing indicator and indication.

5.3.4 Exploratory Analyses

Exploratory Analyses will be performed on the **ITT and PP populations.**

Biochemical response will be correlated with ORR (Kappa Agreement Index), and Best Overall Response will be correlated with CgA , taking the following cut-points (Moonjin Kim, Lee Sujin, et al, 2015):

- Partial response (PR) was defined as ≥ 50% decrease in plasma CgA compared to the baseline CgA
- Stable disease (SD) was defined as a decrease <50% or an increase < 25%
- Progressive disease (PD) was defined as an increase ≥ 25%.

[1] ECG is planned at screening and End of Treatment also all Italian patients have to do an electrocardiogram every 12 week.

Tau-Kendall coefficient will be used as an indicator of agreement for both measures of response.

5.3.4.1 Reduction of tumour size

A waterfall plot will be displayed per treatment arm in order to show percent growth or reduction of the tumor, sum of diameter (mm) maximum percentage of change from baseline will be computed for each patient and represented in a vertical bar from worst value, such as greatest progression of disease, on the left side of the plot, to the best value, i.e., most reduction of tumor, on the right side of the plot .Bars will be also printed with different colors depending on the Best Overall Response achieved by every patient.

5.3.4.2 Multivariate analysis for PFS

The following variables at baseline will be used as covariate in a Cox model with PFS as independent variables in order to test any influence over survival:

- Demographics: Age and Gender
- Time from diagnosis: (<12 and ≥12 months)
- Primary Tumor Location
- Metastasis location: Number of involved organs, patients with liver metastasis or other specific locations (i.e. bone, peritoneum)
- Ki-67, categorized as (<3%, 3-20%; <5%, 5-20%)
- ECOG functional status
- Elevated baseline NET tumor markers 5-HIIA or CgA levels elevated or not separately.
- Number of previous lines of treatment.
- Functioning Tumor (Yes/no)

As a result, a Forest Plot will be displayed with different covariates at ordinate axis and their corresponding value of odds ratios (O.R) and their 95% C.I.

5.3.4.3 Changes in biomarker concentrations over time

A mixed model for CgA and 5-HIIA percent change from baseline will be fitted separately with treatment arm as fixed effect and either CgA and 5-HIIA baseline values as covariate.

Least square means estimated fold changes over baseline and associated 95% CIs derived from the mixed model will be used to represent changes over time and treatment arm by a line plot chart.

5.3.5 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.

5.3.5.1 General imputation method

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. Regarding efficacy variables summarized at the end of the study, if the end-of-treatment visit is not performed, the last available value of the variable after randomization will be used.

Concerning 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.

5.3.5.2 Missing dates

In case of any incomplete dates (missing day) necessary for the analysis, first day of the month and year indicated in each case will be imputed.

Just in case the previous imputation generated an incoherence considering the rest of dates reported for any patient, the day imputed would be the corresponding day according to the rest of dates for the same patient.

For those subjects without a documented progression or death at the time of the analysis, PFS will be censored at the date of the last evaluation tumor. If the subject does not have any tumor assessment after the baseline, then will be censored at day 1.

5.3.6 Subgroup analyses

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 (phase II) and the second subgroup (phase III).

PFS will be also analyzed by primary tumour location, Ki-67, categorized as (<3%, 3-20%; <5%, 5-20%), Functioning Tumor (Yes/no), Elevated baseline NET tumor markers 5-HIIA or CgA levels elevated or not separately.

5.3.7 Interim Analyses

An interim analysis was performed of the data collected through March 2015 for the patients on Stage I (Phase II). A blind analysis will be performed, 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 could be replicated by a centralized blind review. This review was made with the same cutoff date as that used in the analysis conducted in March 2015 and was also considered as an interim analysis. The analysis of the results of the centralized blind assessment was evaluated by an IDMC. The investigative team was not informed of the preliminary results to minimize observational bias and ensure full independence

5.3.8 Principal Efficacy Analysis

An additional analysis (with more mature data) will be conducted for the patients enrolled in the first part (Stage I) and the second (Stage II) before end of study. This analysis will be focus on the principal efficacy analysis (PFS) and Response. Also a reduced analysis of Baseline & Demographics data will be conducted.

5.4 Reporting conventions

Descriptive Statistics will be reported to 2 decimal places. All percentages will be rounded and reported to a single decimal point (xx.x %). A percentage of 100% will be reported as 100%. Estimated parameters derived from a model (i.e regression or ANCOVA) and coefficients will be reported to 3 decimal places.

P-values greater than 0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as “<0.0001”.

Population sizes may be presented for each classification factor as totals in the column header as (N=xxxx), where appropriate.

The AEs will be coded using MedDRA, version 21.1 or later.

All units’ measurements will be summarized in the International System of Units.

5.5 Study timelines

Final Statistical Report will be delivered one month from DataBase Lock.

5.6 Technical Details

The study protocols: v3.0 (11-APR-2013), v4.0 (17-FEB-2015), v5.0 (29-JAN-2016), v6.0 (16-NOV-2016) and v7.0 (21-MAR-2018) has been used as a reference for this document. SAS programs, SAS Logs and SAS outputs generated during the creation of the Statistical Report will be archived in the PIVOTAL’s File System.

5.7 Software

All analysis and reporting will be undertaken using SAS® for Windows Version 9.4.

6. REFERENCES

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