A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated metastatic pancreatic neuroendocrine tumours (pNET) previously untreated.

PROTOCOL CODE: GETNE-1408

EudraCT No.: 2014-004072-30

VERSION: 5.0 (23 November 2016)

SPONSOR: Spanish Task Force Group For Neuroendocrine Tumours (*Grupo Español de Tumores Neuroendocrinos* - GETNE)

INVESTIGATOR: [redacted]

BIOMARKER STUDY:

[redacted]

PROTOCOL SIGNATURE PAGE

Protocol: GETNE-1408

VERSION: 5.0 (23 November 2016)

I have read this protocol and agree to direct this trial in accordance with all the stipulations of the protocol and the Declaration of Helsinki.

Sponsor's signature

[signature]

[redacted]

Coordinating investigator's signature

[signature]

[redacted]

I have read this protocol and agree to direct this trial in accordance with all the stipulations of the protocol and the Declaration of Helsinki.

Principal Investigator at the Hospital _____

Name:

. SUMMARY

1.1 *Type of Application*

A phase II, open-label, non-controlled, multicenter prospective clinical trial in treatment-naïve patients with well- and moderately-differentiated advanced or metastatic pancreatic neuroendocrine tumours. The study includes analysis of serological and tumour tissue biomarkers.

1.2 *Sponsor details*

Spanish Task Force Group For Neuroendocrine Tumours (*Grupo Español de Tumores Neuroendocrinos* - GETNE)

1.3 *Trial Title*

A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated Metastatic Pancreatic Neuroendocrine Tumours (pNET) previously untreated.

1.4 *Protocol code:* *GETNE - 1408*

1.5 *EudraCT No.:* 2014-004072-30

1.6. *Coordinating investigator*

[redacted]

1.7 *Principal Investigators*

The list of Principal Investigators and participating sites is provided in a separate document.

1.8 *Sites where the trial is to be conducted*

10 Spanish hospitals will participate in the study.

1.9 *Name of the Organisation responsible for Monitoring*

MFAR (Marketing Farmacéutico & Investigación Clínica)

[redacted]

1.10 *Trial treatment*

Single arm of TH-302 administered at 340 mg/m^2 by intravenous infusion on days 8 and 22 in combination with sunitinib given orally at doses of 37.5 mg per day continuously in 28-day cycles.

Pharmaceutical form:

- Sunitinib: hard gelatin capsules of 25 and 12.5 mg. Oral administration.
- TH-302: the dose will be adjusted according to body surface area and will be administered by intravenous infusion over 30 to 60 minutes. In the event of weight variation > 10%, the body surface area will be recalculated and the dose readjusted.

The physical and chemical properties of sunitinib and TH-302, as well as the list of excipients, are included in the Investigator's Brochure.

1.11. *Design and Phase of Clinical Trial*

Phase II, open-label, non-controlled, multicenter, prospective clinical trial.

1.12 *Primary and Secondary Objectives*

The main purpose of the study is to determine the safety and activity of TH-302 in combination with sunitinib in patients with a well- or moderately-differentiated metastatic pancreatic neuroendocrine tumour (pNET). Drug activity will be measured according to the objective response rate (ORR), as measured by RECIST criteria version 1.1, with assessments performed every 8 weeks, regardless of delays due to adverse events. ORR is defined as the percentage of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST criteria v1.1, relative to the total analysis population. Confirmed responses are those that persist in a repeat imaging study conducted ≥ 4 weeks after initial documentation of response.

The secondary objectives of the study are:

- Progression-free survival
- Time to tumour progression
- Duration of response
- Overall survival
- Safety of TH-302 treatment in combination with sunitinib.
- Prognostic/predictive value of biomarkers analysed in peripheral blood and in paraffin-embedded tumour tissue.

1.13 *Disease under study*

Patients with a well- or moderately-differentiated metastatic pancreatic neuroendocrine tumour (pNET) (grade 1-2 of histological differentiation and Ki67 ≤ 20%) who are naïve to systemic treatment, with the exception of somatostatin analogues.

1.14 *Total Number of Patients*

It is estimated that 43 patients will be enrolled in the study.

1.15 *Duration of Treatment*

Treatment with TH-302 in combination with sunitinib will continue until disease progression, unacceptable toxicity, non-compliance with the protocol, the patient's withdrawal of informed consent or at the discretion of the investigator.

1.16. *Schedule and planned end date*

Recruitment is expected to last for 24 months, followed by a 20-month follow-up period.

- Date of submission to central IEC for research with medicinal products: November 2014/January 2015.
- Data of submission/AEMPS approval: November 2014/January 2015
- Estimated date of enrolment of first patient: February 2015
- Study end date: January 2019
- Data analysis period: 4 months
- Database closure: April 2019
- Date for the final study report: June 2019
- Publication date: June 2019

1.17 *Table of Trial Determinations*

Determinations outline: (ANNEX 1)

2. PROTOCOL TABLE OF CONTENTS

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3. STUDY RATIONALE

3.1. *Epidemiology and classification of pancreatic neuroendocrine tumours (pNET)*

pNETs represent a heterogeneous tumour group classified according to their functional capacity and histological differentiation (1) (Annex 2). The prevalence of neuroendocrine tumours (NET) has increased in recent years at an estimated rate of 35/100,000/year, of which approximately 30% are pNET. In particular, the incidence of pNET is 0.32/100,000/year (2). Most are non-functioning tumours. Those that are functioning are identified according to the hormone secreted, and some are found outside the pancreas.

The 5-year survival rate is 80%; 60-100% for localised disease, 40% for locally advanced disease and 25% for metastatic disease (which can reach 60% in reference sites).

3.2. *Therapeutic options for managing metastatic pancreatic neuroendocrine tumours (pNET)*

Treatment goals in the management of pNETs are symptom control and limiting tumour growth in order to positively affect patient survival.

In the context of cytotoxic drugs, it appears that pNETs are more sensitive to chemotherapy than other NETs, including carcinoid tumours. For decades, cytotoxic therapy was the only available treatment option, with streptozotocin as the first drug to demonstrate NET activity, being approved in 1976 by the FDA (Food and Drug Administration). Its combination with fluoropyrimidines, particularly doxorubicin, further increased its activity, and it became the standard treatment for well- and moderately-differentiated tumours. These combinations achieved a pNET response rate of between 35-69%, with median overall survival of up to 26 months (3), (4). However, this goal was not always measured according to radiological assessments, but also clinical ones, so its interpretation was limited and no definite correlation was found between these data and those obtained in reviews of routine clinical practice (5). A second cytostatic agent that is key in the treatment of pNETs is temozolomide, an alkylating agent, the benefit of which appears to be correlated with MGMT enzyme deficiency. The combination of temozolomide and capecitabine studied in retrospective reviews, such as the one published in 2011 with 30 treatment-naïve patients with pNET (6), showed an objective response rate of 70%, a median progression-free survival (PFS) of 18 months and an overall 2-year survival rate of 92%.

In high-grade, poorly-differentiated tumours, the standard treatment regimen comprises the combination of platinum and etoposide, which, in retrospective reviews and prospective studies, achieves a high response rate of between 56-67%, but they are unfortunately not as durable as expected (7).

The pNET population was represented in the CLARINET phase III study, which randomised 204 patients with G1/G2 non-functioning GEP-NETs, to receive lanreotide Autogel 120 mg (N = 101) versus placebo (N = 103) (8). The first endpoint - PFS - was achieved by showing a 53% reduction in the risk of progression in favour of somatostatin analogues (HR 0.47; 95% CI 0.30-0.73, p = 0.0002). Subgroup analysis according to the location of the primary demonstrated a PFS for pNET patients (N = 91) that had not been achieved in the arm with lanreotide Autogel and 12.1 months in the placebo arm (HR 0.58; 95% CI 0.32-1.04, p = 0.0637).

In recent years, data from two phase III studies with targeted therapy against vascular endothelial growth factor receptor (VEGFR), sunitinib, and the mammalian target of rapamycin (mTOR), everolimus, in pNET patients, has broadened the therapeutic horizon for these patients. The improved PFS demonstrated led to the approval of both drugs by the EMA and the FDA.

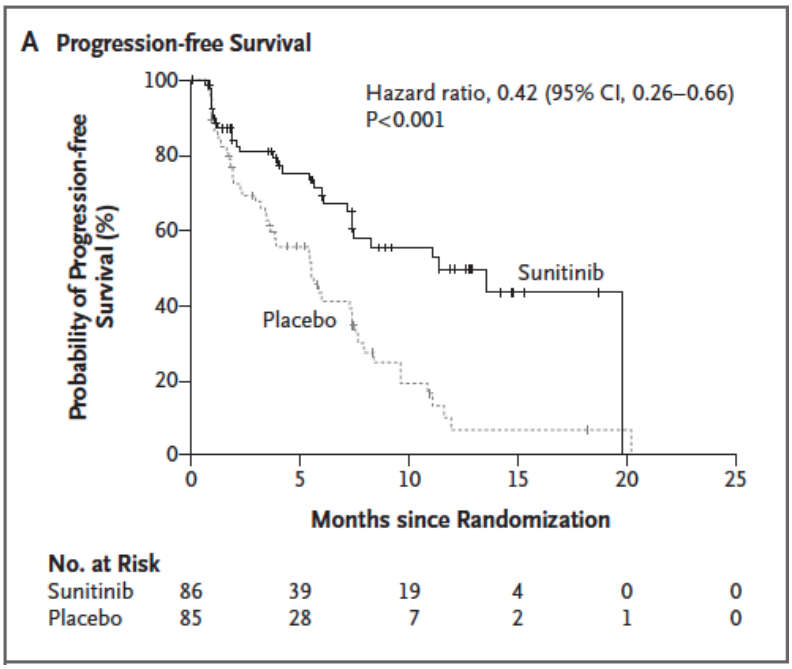
The PI3K/AKT/mTOR pathway is also key in tumour development, as it regulates the metabolism, growth, cell proliferation and angiogenesis, integrating multiple signalling pathways. Its activation can be responsive to VEGFR, PDGFR and insulin-like growth factor receptor (IGFR) stimulation, and it is regulated through two tumour suppressor genes (TSG) - TSC2 and PTEN. As everolimus deregulates this molecular pathway in pNET, use of the drug should be developed against these tumours. Thus, based on the phase II results published in 2008 with two cohorts of 60 patients treated with octreotide and everolimus at doses of 5 and 10 mg daily, a response rate of 27% was observed in pNET patients with a median PFS of 63 weeks (9). Based on these results, a second phase II study was developed, called RADIANT-1, targeting pNET patients who had progressed during or after chemotherapy and who received everolimus 10 mg/day, being stratified according to prior treatment with octreotide (115 patients in monotherapy and 45 patients in combination) (10). The results for both strata showed a response rate of 9.6% and 4.4%, respectively, and PFS was 9.7 vs. 16.7 months, respectively, for both arms. In a third phase III study, RADIANT-3, 410 pNET patients were randomised to receive everolimus 10 mg/day vs. placebo (11). The results of the study demonstrated significantly improved PFS with everolimus of 11.4 months versus 5.4 months (HR 0.34; $p<0.0001$).

Unfortunately, patients ultimately progress and the development of new active drugs, as well as the development of predictive biomarkers of progression, is vital. The first study to analyse the sequence of therapeutic targets was the PAZONET study, the results of which were presented at ESMO 2012 (12). A total of 44 patients were enrolled who had previously received treatment with a tyrosine-kinase inhibitor (TKI) and/or mTOR inhibitor, and who were treated with pazopanib 800 mg/day allowing concomitance with somatostatin analogues. The results showed that pazopanib was active in this patient arm with a clinical benefit of 83% for those previously treated with TKI, 89% with an mTOR inhibitor and 60% with both drugs. The PFS in these three subgroups was 12.1 months, 6.8 months and 4.1 months, respectively. For the overall population it was 9.5 months.

3.3. *Sunitinib in Pancreatic Neuroendocrine Tumours*

In pNET, there is a high expression of VEGF and VEGFR2-3, PDGFR alpha and beta, cKIT and EGFR, and hypoxia is a key event in the regulation of tumour angiogenesis. This constitutes a strong rationale when it comes to developing anti-angiogenic drugs for these tumours. In clinical studies, the activity of sunitinib on NET was first demonstrated in a phase I study where the 3 enrolled NET patients, all of whom had been previously treated, showed reduced tumour lesions to varying degrees, being exceptional in one patient with a higher partial response (21 weeks) and two long-lasting minor responses (13). Thereafter, a multicenter, phase II study was conducted in patients with carcinoid tumours and pNET (14). Results from the 66 pNET patients showed an objective response rate of 16.7% and a stable disease rate of 68%. The time to progression and overall survival at one year was 7.7 months and 81.1%, respectively. To definitively confirm this benefit, a phase III study versus placebo was developed, in which 171 patients of the 340 initially estimated were finally randomised against independent data monitoring (15). The benefit in terms of PFS was 11.4 months for the sunitinib arm at a dose of 37.5 mg/day versus 5.5 months for the placebo arm (HR 0.42; $p<0.001$). Efficacy data on patients in routine clinical practice treated with sunitinib were consistent with those obtained on selected populations in clinical trials (16).

Figure 1. PFS results of the phase III study of sunitinib vs. placebo in pNET patients.



3.4. *TH-302 (Preclinical and Clinical Development in Solid Tumours)*

- ***Introduction***

(1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) diamidophosphate (also known as TH-302) is a nitroimidazole-triggered prodrug of a brominated version of isophosphoramide mustard (Br-IPM) (17). TH-302 is able to diffuse into hypoxic tissues without activation by NADP(H) quinone oxidoreductase (DT-diaphorase). It is preferentially activated under severe hypoxic conditions that are unlikely to be present in healthy tissue but in solid tumours (18).

The molecule TH-302 is activated by a process that involves a one electron reduction at the 2-nitroimidazole site of the prodrug, mediated by ubiquitous cellular reductases such as the NADPH-cytochrome P450, to generate a radical anion prodrug (RP). In the presence of oxygen (normoxia) the radical anion prodrug reacts rapidly with oxygen to generate the original prodrug and superoxide (SO). In these situations, TH-302 is relatively inert, remaining intact as a prodrug. However, under hypoxic conditions, (<0.5% O2), the radical anion prodrug can either fragment directly or undergo further reduction at the nitroimidazole site of the prodrug, causing Br-IPM to be released (Figure 2). Br-IPM can then act as a DNA alkylating agent and form DNA crosslinks, causing damage through the presence of γH2AX. Br-IPM can diffuse through normoxic tissues and act as a cytotoxic agent in these regions. Previously, other alkylating mustards such as ifosfamide or cyclophosphamide had already demonstrated activity in many tumours.

Tumours often contain highly hypoxic regions that are known to be resistant to chemotherapy and radiotherapy. These regions develop due to the creation of irregular and aberrant blood vessels that prevent adequate oxygenation and penetration of the majority of chemotherapy treatments, which act on highly proliferating cells adjacent to the blood vessels, but not on the relatively quiescent cells found in the hypoxic regions. For this reason, they are resistant to these regimens of cytostatic drugs (19). In contrast, the prodrug TH-302 is activated in conditions of severe hypoxia, and not in the majority of normal tissues with a similar structure (20). Recent preclinical findings support the hypothesis of the induction of hypoxia within the tumour developed by anti-angiogenic drugs, which could constitute a synergistic effect with TH-302.

The molecular formula of TH-302 is C9H16Br2N5O4P and the molecular mass is 449 g/mol.

Figure 2. TH-302 activation pathway diagram

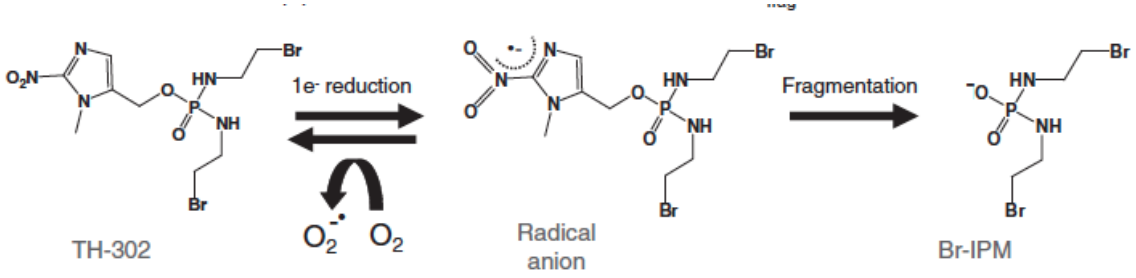


Figure obtained from *Meng, F., et al. Molecular and cellular pharmacology of the hypoxia-activated prodrug TH-302. Mol Cancer Ther. 2012;11:740–51*

- ***Preclinical Data***

In preclinical investigations, TH-302 as monotherapy or in combination with numerous cytotoxic drugs has shown broad activity in murine models (21). In particular, TH-302 has shown consistent activity in cell lines from neural crest derived tumours such as melanoma and glioblastoma/astrocytoma (TH-302 Investigator's Brochure).

TH-302 is very active *in vitro*, as demonstrated in proliferation studies of H460 lung carcinoma cells (22), where TH-302 activity is related to dose-exposure and oxygen dependence, which practically achieves linearity (23). This activity is also observed in H69 small-cell lung cancer cells (SCLC), B16-F10 melanoma, SKMEL-5 melanoma, HT-29 colon cancer, HCT116 colon cancer, MES-SA uterine cancer, DX5 uterine cancer, ACHN renal cancer and PC-3 prostate cancer in anoxic conditions (CI50 from 0.1 to 10 μM) and weakly cytotoxic in the presence of air (CI50 > 80 μM). Consistent results are obtained in clonogenic models.

In vivo studies demonstrate activity both as monotherapy and in combination with other cytostatic drugs (cisplatin, paclitaxel or 5-fluorouracil) (22).

The effect of TH-302 has been studied in many murine xenograft models (H82 small-cell lung cancer, H460 and Calu-6 non-small cell lung cancer, A375 and Stew2 melanoma, 786-0 renal cell and PLC/PRF/5, Hs766t and BxPC-3 pancreatic cancer). The cytotoxic activity of TH-302 increases *in vivo* in hypoxic conditions, as shown by excision methods and tumour growth models. Acute (single dose) or chronic (for 2 weeks) treatment with TH-302 demonstrates selective reduction in tumour volume of the hypoxic regions in xenograft models, with their corresponding increase in necrotic compartments (20). TH-302 achieves a significantly greater benefit in combination with chemotherapy, and even the complete eradication of some tumours, including metastatic ones (24).

With regard to the combination with anti-angiogenic drugs, the rationale starts from the knowledge of hypoxia induced by these agents that, in tumour progression, provide a more aggressive phenotype. The study of murine xenograft models in human 786-O renal cell carcinoma, melanoma A375, H460 non-small cell lung cancer and hepatocellular carcinoma PLC/PRF/5, investigated the synergistic activity of TH-302 in combination with sunitinib or sorafenib (25). Both anti-angiogenic drugs increased hypoxia detected in the tumour tissue, and was time and dose-dependent. In the 786-O renal cell model, the activity of sunitinib (40 mg/kg) increased when combined with TH-302 (50 mg/kg) in terms of tumour growth control, from 38% to 75%. In addition, no significant weight loss was identified when combining anti-angiogenic drugs with TH-302, which is an indicator of toxicity. In conclusion, the synergism reached in terms of the anti-tumour efficacy of the combination of sunitinib or sorafenib with TH-302 by selective action on hypoxic tissue induced by anti-angiogenic drugs, forms the basis for the future clinical development of this combination.

- ***Pharmacokinetic data and preclinical safety***

TH-302 does not act as a substrate for the clinically relevant efflux pumps studied: MDR1 (ABCB1), MRP1 (ABCC1) and BCRP (ABCG2). Reductase expression and homologous recombination-dependent repair (HRD) affect *in vitro* cytotoxicity caused by TH-3026.

The first pharmacokinetic data for TH-302 and its active metabolite Br-IPM in preclinical studies were obtained from mice, rats, dogs and monkeys (26). The drug was delivered as a single oral, intravenous and intraperitoneal dose, and the safety of the drug was subsequently analysed by repeated doses. Following intravenous administration of the drug, rapid distribution throughout the body was identified, with a volume of distribution similar to or greater than total body water (0.542 l/kg in mice vs. 1.67 – 5.09 l/kg in rats, 1.98 l/kg in dogs and 2.92 l/kg in monkeys), as well as rapid clearance (3.28 – 7.66 l/h/kg) with an effective half-life of between 10 and 50 minutes. TH-302 remained stable when incubated with liver microsomes from mice, rats, dogs, monkeys and humans. TH-302 is mainly eliminated renally and faecally, based on observations in rats and dogs. A tissue distribution study on rats demonstrated that TH-302 distributes quickly to tissues following intravenous administration. The highest concentrations of radioactivity related to TH-302 were found in the kidneys and the small intestine. However, low but quantifiable radioactivity levels were observed in the brain and spinal cord. Protein binding was low (< 55%) and independent of plasma concentration.

The first toxicity data after one or multiple doses of TH-302 were gathered from rats and dogs. As the preclinical efficacy data indicated that the Cmax might be important for anti-tumour activity, a 30-minute intravenous infusion was chosen for these toxicity studies, in order to obtain rapid drug concentration peaks and support the use of the 30 minute infusion in clinical practice. Toxicity at non-fatal doses was mainly haematological, accompanied in male rats by moderate weight loss. All of these changes were fully reversible within 2 weeks during the recovery period.

Based on these results, TH-302 was administered in rats in multiple doses of 12.5, 25 and 50 mg/kg, according to Good Laboratory Practice (GLP), where each rat received a 30-minute infusion once a week for 3 weeks. The primary toxicity was haematological and reversible, and was only significant at the 50 mg/kg dose. Dry and flaky skin was also observed at this dose on the top and soles of the feet, as well as excessive salivation. None of these results was present at the end of the recovery period. The histopathology showed bone marrow hypocellularity in the high-dose group and tongue epithelial dysplasia in the mid-, and especially the high-dose groups. These changes disappeared completely. In the study with dogs treated intravenously with 4, 8 or 16 mg/kg of TH-302, leukopenia and neutropenia were observed, in particular at the highest dose. These changes were completely reversible. In the study with rats treated intravenously with 12.5 mg/kg or 50 mg/kg of TH-302, the main toxicities were haematological and reversible.

- ***Clinical data in solid tumours***

The first phase I study in humans was conducted in 57 patients treated with TH-302 administered intravenously in 2 different regimens (17). The first regimen, involving 37 patients, was weekly for 3 weeks with 1 week rest, and a dose escalation of 7.5 to 575 mg/m^2. The second regimen, involving 20 patients, was introduced subsequently and independently, with doses administered tri-weekly and a dose escalation of 670 to 940 mg/m^2. The maximum tolerated dose (MTD) of TH-302 was 575 mg/m^2 for the weekly regimen, or 670 mg/m^2 for the tri-weekly regimen. The most common adverse events in the weekly treatment regimen (>= 20%) were fatigue, nausea, skin rash, constipation, anorexia, vomiting, stomatitis and dyspnoea. Haematological toxicity was rarely significant, 3 events were grade > 0 anaemia (6%), thrombocytopenia (5%) and neutropenia (4%). From the 240 mg/m^2 dose, anti-emetic prophylaxis was required for moderately emetogenic models. Dose-limiting toxicity (DLT) was mucosal and cutaneous toxicity, as well as dehydration. In the weekly regimen, the DLT was grade 3 mucosal and cutaneous toxicity at a dose of 670 mg/m^2. In the tri-weekly regimen, the DLT was grade 3 fatigue and joint pain in one patient, and grade 3 vaginitis/proctitis, stomatitis and pain in another patient at a dose of 940 mg/m^2. The pharmacokinetic data showed that plasma concentrations of TH-302 and its active metabolite Br-IPM increased in proportion to the administered dose. The elimination half-life was 0.81 hours for TH-302 and 0.70 hours for Br-IPM. The low plasma concentrations of the active metabolite (1% - 2% of the concentration of TH-302) are explained by the rapid distribution of TH-302 one hour after administration and not being susceptible to activation by liver enzymes or DT-diaphorase. Two partial responses were identified in a patient with metastatic small-cell lung cancer and another patient with melanoma at doses of 480 and 670 mg/m^2 in weekly regimen. Disease stability was identified in 18 patients treated with the weekly regimen, and in 19 patients treated with the tri-weekly regimen.

Administration of TH-302 in combination with different chemotherapy regimens - docetaxel, pemetrexed and gemcitabine - was investigated in a triple-arm, phase I/II dose escalation study (TH-CR-402) with an expansion cohort that included patients with castration-resistant prostate cancer (CRPC) (docetaxel), non-small cell lung cancer (NSCLC) (pemetrexed) and pancreatic cancer (gemcitabine).

The starting dose of TH-302 in each of the treatment arms was 240 mg/m^2.

In the phase I/II study with docetaxel, after the determination of the MTD, the cohort was expanded to 26 patients with CRPC and NSCLC after first line progression, who received TH-302 on days 1 and 8 plus docetaxel 75 mg/m^2 on day 1 for 21-day cycles (27). The MTD of TH-302 in combination with 75 mg/m^2 docetaxel was 340 mg/m^2. DLTs at higher doses of TH-302 were: afebrile grade 4 neutropenia, grade 3 infection (pneumonia) with grade 3 neutropenia and febrile grade 3 neutropenia and diarrhoea. The recommended dose of TH-302 was 340 mg/m^2. In terms of responses achieved, of the 4 evaluable CRPC patients, one partial response was observed and two disease stabilisations. Of the two evaluable NSCLC patients, 1 achieved partial response and the other achieved stable disease.

In the case of the combination with pemetrexed, after reaching the MTD, patients with NSCLC in second line were enrolled, receiving TH-302 on days 1 and 8 with pemetrexed 500 mg/m^2 on day 1 of each 21-day cycle (28). The 29 patients enrolled showed a DLT that was grade 4 thrombocytopenia or grade 3 oral stomatitis. The recommended dose of TH-302 for the combination was 400 mg/m^2. Of the 26 patients eligible for response assessment, 35% showed a partial response and another 35% showed stable disease.

In the third gemcitabine arm, the 38 patients enrolled were treated with TH-302 followed by gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of each 28-day cycle (29). The DLTs were grade 4 thrombocytopenia and grade 4 neutropenia, as well as grade 3 pain caused by perianal rash and oesophagitis. The MTD was 340 mg/m^2. The 17 patients with a pancreatic tumour who received first-line treatment had a partial response rate of 35% and a stable disease rate of 59%.

The TH-302 study was expanded to include 214 patients with adenocarcinoma of the pancreas in phase II (TH-CR-404), with 2 different TH-302 doses (240 mg/m^2 – N = 71- or 340 mg/m^2 – N = 74- on days 1, 8, 15) in combination with gemcitabine (1000 mg/m^2) versus gemcitabine as monotherapy (N = 69) in 28-day cycles (1:1:1) (30). Crossover to the combination of TH-302 with gemcitabine arm was permitted after progression in randomised patients. The first endpoint - PFS - was 3.6 months for the gemcitabine arm vs. 5.5 months for the gemcitabine with TH-302 240 mg/m^2 arm (HR 0.64; 95% CI: 0.43, 0.96; p = 0.031) vs. 6.0 months for the gemcitabine with TH-302 340 mg/m^2 arm (HR 0.58; 95% CI: 0.39, 0.87; p = 0.008). The response rate was 12% for the gemcitabine arm, 17% for the gemcitabine with TH-302 240 mg/m^2 arm, and 27% for the gemcitabine with TH-302 340 mg/m^2 arm. Based on the safety and efficacy data in this phase II study, a phase III study (MAESTRO) is currently in progress, evaluating TH-302 in the same regimen and dosage (340 mg/m^2 of TH-302 on days 1, 8, and 15 of a 28-day cycle with gemcitabine), and on the same patient population evaluated in the randomised phase II study (study TH-CR-404) (NCT01746979).

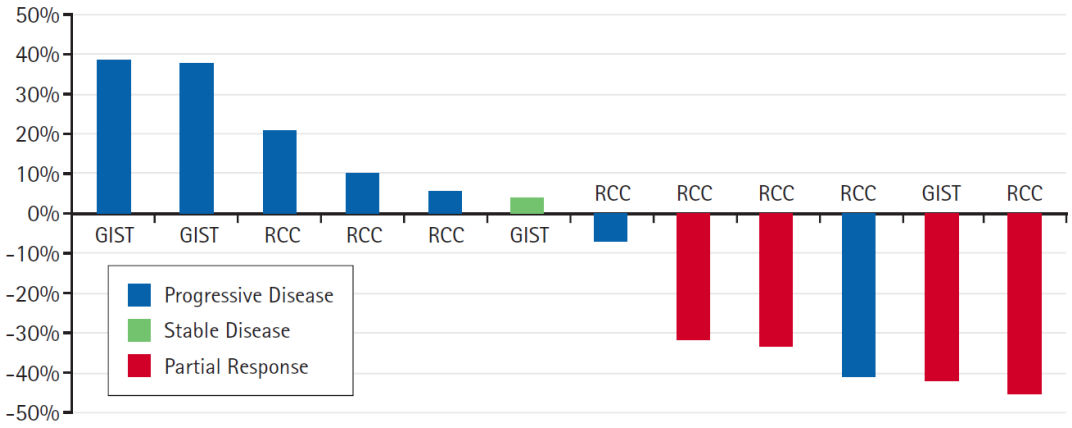
Based on hypoxia markers detected in metastatic soft tissue sarcomas and its significant resistance to chemotherapy, the phase I study TH-CR-403 was conducted for this population (31). Patients were administered a starting dose of TH-302 of 240 mg/m^2 on days 1 and 8 in the dose escalation phase with doxorubicin 75 mg/m^2 on day 1 of every 21-day cycle. 16 patients were enrolled. Although there was no DLT with the starting dose, 3 patients experienced transient grade 4 neutropenia and were therefore permitted to add prophylaxis with granulocyte colony-stimulating factor (G-CSF) on day 8 of each cycle. The MTD was 300 mg/m^2 and the DLTs at 340 mg/m^2 were grade 4 thrombocytopenia and febrile grade 4 neutropenia with grade 3 infection. Five patients (33%) had a partial response according to RECIST criteria. Data from the expansion cohort showed the following response rates (N = 89): complete response (2%), partial response (34%), disease stability (48%) and disease progression (DP) (16%).

Survival rate to 6 months was 62%. Median overall survival was 17.5 months (95% CI: 16.1 months until an unattained upper limit) and the overall survival rate at 1 year was 70%.

With these encouraging results (better than doxorubicin as monotherapy), a randomised phase III study (TH-CR-406) was conducted to assess the administration of TH-302 at doses of 300 mg/m^2 weekly in combination with a routine doxorubicin regimen (NCT01440088).

From the work which identified an increase in the hypoxic fraction with sunitinib at 40 mg/m^2 in 786-0 renal cell carcinoma murine models, and the activity of TH-302 in hypoxic tissues, its research in humans began with the conduct of a phase I dose-escalation clinical trial (32). This study combined TH-302 with sunitinib in patients with renal cell carcinoma, gastrointestinal stromal tumour (GIST) and pancreatic neuroendocrine tumour (pNET) in first line or successive. GIST and pNET were only included in the dose escalation phase. The recommended dose of sunitinib was 50 mg daily for 28 days in 42-day cycles (6 weeks) in combination with TH-302 at a dose 340 mg/m^2 by intravenous infusion on days 8, 15 and 22 of each 42-day cycle (6 weeks). There was no DLT at a dose of 240 mg/m^2 (N = 4), 1 DLT was observed at 340 mg/m^2 (N = 6), which was a grade 2 stomatitis. Grade 3/4 neutropenia and thrombopenia was observed in 3 and 5 patients, respectively. The most common adverse events associated with TH-302 were nausea and mucositis. Preliminary data showed synergistic activity of sunitinib plus TH-302 in patients with renal cell carcinoma progressing to sunitinib (figure 3).

Figure 3. Change in tumour volume with the combination therapy sunitinib+TH-302.



3.5. Biomarkers

To date, no validated predictive marker has been identified in pancreatic neuroendocrine tumours. The importance of this research lies in being able to identify patients optimally to ensure as personalised a global approach as possible.

Although VEGF is considered to be the driving force behind angiogenesis in pNET, many studies have proven the involvement of other molecules such as PDGF, cKIT or mTOR. Initial data from patients with neuroendocrine tumours treated with sunitinib (33), (34) has been obtained by measuring circulating biomarker levels in the plasma, such as VEGF, soluble VEGF receptor-2 (sVEGFR-2), interleukin-8 (IL-8) and sVEGFR-3. In one of the studies, sVEGFR-2 and sVEGFR-3 levels dropped significantly by 30% after the first cycle, in 60% and 70% of patients, respectively. The reduction in sVEGFR-3 levels in the first cycle was greater in the subgroup of patients with partial response (N = 11). Elevated IL-8 levels were also identified in those patients with reduced tumour size.

Recently, a phase II study in pNET patients in first line or after progression and treated with pazopanib at a dose of 800 mg/24h, also included a biomarker expression analysis (35). Patients with some degree of VEGFR-2 expression tended towards longer PFS compared to those who did not express this protein (median 12.18 vs. 11.56 months; HR 0.95).
In 101 patients with a renal cell carcinoma treated with sunitinib, 16 SNPs (single nucleotide polymorphisms) have been evaluated, belonging to 9 genes that affect the pharmacodynamics [VEGFR2 (rs2305948, rs1870377), VEGFR3 (rs307826, rs448012, rs307821), PDGFR-α (rs35597368) and VEGF-A (rs2010963, rs699947, rs1570360) and IL8 (rs1126647), and pharmacokinetics [CYP3A4 (rs2740574), CYP3A5 (rs776746)], transport [ABCB1 (rs1045642, rs1128503, rs2032582] and [ABCG2 (rs2231142)] and metabolism [CYP3A5*1, CYP3A4] of sunitinib. The results defined a possible group of patients with VEGFR3 and CYP3A5*1 polymorphisms who had a lower response and worse tolerance to sunitinib (36).

The HIF-1 pathway is a crucial angiogenesis regulator involving other molecules such as VEGF, PDGF, angiopoietins (Ang-1 and Ang-2), DLL4 and metalloproteinases (37). Carbonic anhydrase (CAIX) is another factor associated with the activity of HIF-1α and which regulates tumour pH and cell survival, together with cell adhesion. The expression of these key proteins in tumour hypoxia and their determination in pNET patients where this phenomenon is widely described, may contribute predictive information for incorporation in clinical practice.

Finally, TH-302 has been associated with hypoxia, which is why hypoxia markers (vascular microdensity, carbonic anhydrase IX, etc.) are potential candidates to predict which patients will be more likely to respond and which are not.

3.6. *Rationale for the Clinical Development of this Study*

NETs are highly vascular tumours exhibiting a high expression of proangiogenic molecules, such as VEGF. Many inhibitors of this pathway, such as monoclonal antibodies (bevacizumab) or tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib) have shown activity in pNET.

Despite these advances, a wider range of treatment options and the complexity of the treatment algorithm for pNET, the tumours may exhibit primary or acquired resistance after an initial response that make them insensitive to treatment with these drugs (38), (39).

Primary resistance to anti-angiogenic drugs may develop by the expression of proangiogenic factors that are relatively insensitive to VEGF-mediated inhibition (including c-MET, fibroblast growth factor (FGF), angiopoietins, and ephrins), or by the formation of blood vessels by other molecular pathways or the prior infiltration by inflammatory cells that express pro-inflammatory factors and cytokines that promote angiogenesis and which protect the blood vessel from VEGF-mediated inhibition. Acquired resistance may develop through the hypoxia-induced activation of alternative proangiogenic pathways such as angiopoietins, ephrins or FGF, or increase mesenchymal marker levels. These new receptors and molecular pathways seem to continue signalling through PI3K/AKT/mTOR (a finding that could potentially suggest secondary sensitivity to mTOR inhibitors), the recruitment of cells from bone marrow that contribute to VEGF-independent tumour vascularisation, pericyte-mediated protection or the invasion of non-tumour tissue with vessels that are more mature and less responsive to anti-VEGF therapy.

The mechanisms described that lead to an increase in the release of pro-angiogenic factors include accumulation of intratumoral HIF-1α. (40).

In conclusion, pancreatic neuroendocrine tumours (pNET), which exhibit significant vascularisation, are sensitive to anti-angiogenic therapy, although with poor responses. In contrast, the chemotherapy regimens achieve a high objective response rate, although they are not sustainable over time. Therefore, the development of therapeutic targets against hypoxia, including reducible prodrugs, targets against HIF-1 and genetic engineering with anaerobic bacteria gives cause for optimism in overcoming resistance mechanisms of cell survival in hypoxic areas versus conventional chemotherapy.

Based on all the data presented above, the purpose of this study is to demonstrate the activity of TH-302 under hypoxic conditions, such as in neuroendocrine tumours, after sunitinib-induced response, which may be consolidated and prolonged to overcome an established resistance mechanism. The study shall try to determine the synergism and safety of this combination, in order to achieve improved and longer-lasting responses in unresectable, locally advanced or metastatic well- or moderately-differentiated pNET in first-line therapy.

4. STUDY OBJECTIVES

4.1. *Primary Objective*

Objective response rate (ORR).

4.2 *Secondary Objectives*

Progression-free survival (PFS)
Time to progression (TTP)
Response duration (RD)
Overall survival (OS)
Safety
Serological and tumour tissue biomarkers

5. STUDY DESCRIPTION

5.1. Design

This is a prospective, non-randomised, open-label, single-arm, phase II study that will assess the efficacy and safety of TH-302 plus sunitinib in patients with well- and moderately-differentiated metastatic pancreatic neuroendocrine tumours (pNET) who are naïve to systemic treatment other than somatostatin analogues. The study will include a serological biomarker analysis to investigate its clinically beneficial prognostic and predictive role.

The study will be conducted at 10 Spanish university sites belonging to the Spanish Task Force Group for Neuroendocrine Tumours (GETNE) network. GETNE will act as the study sponsor.

Once the patient has signed the informed consent form, he/she should be registered in the study, regardless of whether he/she meets the eligibility criteria, using the electronic data collection platform provided for the trial, at the following web address:

[redacted]

In the event that the patient meets all of the inclusion criteria and none of the exclusion criteria, an enrolment confirmation email will be sent with the corresponding patient number. The trial treatment may only be initiated once this confirmation has been received.
If any problems are detected with the tool during the enrolment process, or if the confirmation email is not received, please contact as soon as possible:

Marketing Farmacéutico & Investigación Clínica [Pharmaceutical Marketing & Clinical Research]
[redacted]

For more information concerning the enrolment procedure, please refer to the enrolment procedure available in the site's investigator files.

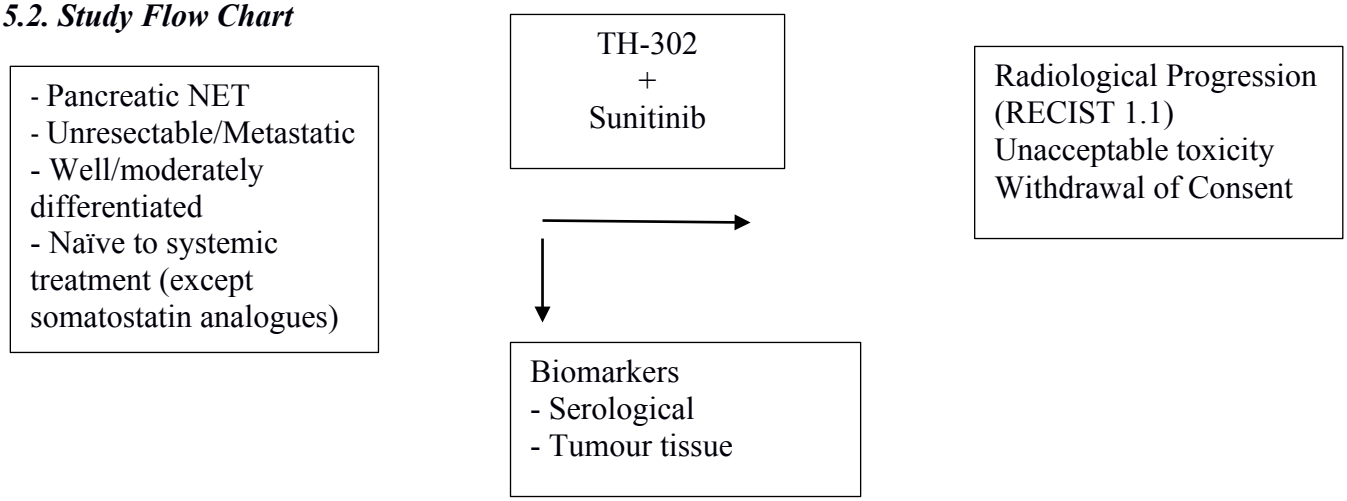
The tumour sample must be found and sent to [redacted] to perform the determinations detailed in this protocol. In addition, for patients who give their consent for the translational sub-study, blood samples (peripheral blood) must be collected prior to administration of the study medication and within the time limits defined in this protocol. These must be processed as laid out in section 8.1.

For more information about the shipment of the biological samples, please refer to the biological sample shipment procedure available in the site's investigator files.

The study treatment is TH-302, administered at doses of 340 mg/m^2 by intravenous infusion on days 8 and 22 in combination with sunitinib given orally at 37.5 mg per day continuously from day 1 through to day 28 of a 28-day treatment cycle. Patients will receive the study treatment until radiological progression is confirmed according to RECIST criteria version 1.1, or until treatment discontinuation is considered to be in the best interests of the patient, at the discretion of the investigator (these decisions will balance maximum benefit with acceptable tolerability). Patients will continue taking the study treatment at the discretion of the investigator should they experience clinical benefit.

Tumour response will be assessed every 8 weeks, regardless of any delay which may arise due to toxicity. To prevent the introduction of bias associated with treatment duration, compliance with the assessment schedule is essential.

5.2. Study Flow Chart



5.3. Study Duration and Schedule

Patient enrolment will take place over a period of 24 months, and a follow-up period of 20 months.

It is estimated that the study schedule will be as follows:

- Date of submission to central IEC for research with medicinal products: November:November 2014/January 2015.
- Data of submission/AEMPS approval: November 2014/January 2015
- Estimated date of enrolment of first patient: February 2015
- Study end date: January 2019
- Data analysis period: 4 months
- Database closure: April 2019
- Date for the final study report: June 2019
- Publication date: June 2019

5.4. Sample Size

It is estimated that a total of 43 eligible patients will be enrolled in the study (having received at least one dose of treatment). The design will follow *Simon's two-stage design* for phase II studies, with a baseline number of 18 patients. The combination of TH-302 with sunitinib will be considered as inactive in terms of the response rate if less than 5% of patients are responders, with a response rate threshold of 20%. These figures are based on the results shown with other drugs for the treatment of pNET.

Should a response be identified in at least 3 out of every 18 patients treated, recruitment will continue up to 43 patients in order to be able to better estimate the response rate. If the study shows a response in at least 8 patients, the treatment is likely to continue its research development.

The likelihood of terminating the study after the first part with 18 patients enrolled is 0.42 if the response rate is 10%, and 0.06 if the response rate is 25%.

The likelihood of not accepting the null hypothesis and considering the combination of TH-302 with sunitinib active with a response rate less than 5% is 5% (Type I or alpha error).

The likelihood of not rejecting the null hypothesis and considering the combination of TH-302 with sunitinib inactive with a response rate greater than 5% is 20% (Type II or beta error). The statistical power of the study will be 0.80.

6. TREATMENT

6.1 Treatment Administration

6.1.1. Sunitinib

Sunitinib will be provided by the Trial Sponsor. Sunitinib will be administered at a dose of 37.5 mg per day (1 capsule of 25 mg and 1 capsule of 12.5 mg) orally for 28 days on an ongoing basis. It must always be taken at the same time every day (or as close as possible) and capsules must be swallowed whole. Food does not appear to affect the bioavailability of the drug. A 37.5 mg dose was chosen based on the approved dose of sunitinib for the treatment of pancreatic neuroendocrine tumours (pNET). If the patient requires a sunitinib dose reduction, the dose adjustment stated in section 6.3 will be followed.

On days when TH-302 is also administered, sunitinib must be taken 2 hours before, or at least 2 hours after TH-302 infusion. Given its hypoxia-inducing ability in highly vascular tumour tissue and its TH-302-enhancing effect, sunitinib will be administered as monotherapy in the first week of treatment.

If, for any reason, the patient skips a dose or vomits after ingestion, a double dose should not be taken the following day. Treatment will resume on the following day with the usual daily dose. In contrast, if for any reason an additional dose is taken, the following day's dose should be skipped.

The study drug will be supplied in 25 mg and 12.5 mg capsules. The study drug must be handled and stored safely and as specified on the label. The label on the bottles will indicate the study protocol number, the medication or bottle number, the contents, instructions for use, storage instructions, the clinical trial declaration and the name of the sponsor. The patient number will be allocated to a bottle upon hand over.

Patients will be instructed as to its correct administration and that it must be kept at room temperature (15-25 ºC) and out of the reach of children. Site staff must ensure that the patient understands the instructions for correct outpatient use of the drug.

Patients will receive enough medication until the next visit, and must return the containers with any surplus medication for it to be accounted for. This will take place on day 1 of each cycle prior to dispensation of medication for the next cycle. Any surplus medication returned by the patient for it to be accounted for will not be dispensed again, and the number of surplus sunitinib tablets will be recorded. If the dose is modified during a medical visit, the patient will return all surplus prior medication.

The patient will be questioned about treatment compliance at each study visit. For a patient to be deemed to adequately comply with the study treatment, at least 80% of the prescribed doses must be administered. The recording of these activities will comply with current regulations and guidelines.

6.1.2 TH-302

TH-302 will be provided by the Sponsor. The TH-302 dose administered will be 340 mg/m^2 by intravenous infusion over 30-60 minutes, on days 8 and 22 of each cycle. The dose should be adjusted according to body surface area. In the event of patient weight variation > 10%, the body surface area will be recalculated and the TH-302 dose readjusted. If the patient requires a TH-302 dose reduction, the dose adjustment stated in section 6.3 will be followed.

The TH-302 medicinal product is supplied in a 10 ml glass bottle and must be diluted prior to administration with a 5% commercial glucose solution (containing 278 mmol/L dextrose) for injection to a total volume of 500 ml (1000 ml for a total dose ≥ 1000 mg) per infusion to obtain the final desired concentration. The 5% glucose solution will not be provided.

Each dose of TH-302 will be prepared in an infusion bag without di-(2-ethylhexyl) phthalate (DEHP) with 5% glucose solution for clinical use and administered intravenously using an infusion pump and DEHP-free IV delivery system.

TH-302 should be administered under free-flow intravenous fluid, preferably through a central venous catheter, especially in the presence of extravasation risk factors. Administration through the small vessels in the hands or feet is not recommended.

Detailed instructions on dilution and administration are included in the pharmacy files. Preventive treatment will be added prophylactically for nausea or vomiting, following a regimen for moderately emetogenic chemotherapy.

Cases of perivascular erythema and hyperpigmentation at the infusion site have been reported. Severe cellulitis and tissue necrosis may manifest due to TH-302 extravasation during its administration. The necessary recommended and preventive measures should be taken for the administration of cytostatic drugs, thereby preventing complications during infusion. If any signs or symptoms of extravasation appear, the TH-302 infusion should be stopped and continued in another vein. The patient should be monitored closely to assess the evolution of the skin lesion given the progressive nature of extravasation lesions, and a plastic surgeon should be consulted if necessary.

Infusion reactions have also been observed during the administration of TH-302 characterised by swelling of the lips and urticaria, which respond to treatment with steroids and antihistamines. Include a steroid (such as dexamethasone or equivalent) in the pre-infusion antiemetic regimen is recommended. Signs and symptoms of hypersensitivity include fever, myalgia, headache, rash, pruritus, urticaria, angioedema, chest discomfort, dyspnoea, cough, cyanosis and hypotension. If the nature and severity of the reaction require the infusion to be discontinued, it should be determined whether it is an IgE-mediated process. If symptoms such as obstruction of the upper airways or hypotension are presented that suggest anaphylaxis or an anaphylactoid reaction, the investigator will assess whether to administer an antihistamine (such as slow intravenous or intramuscular diphenhydramine 25-50 mg orally, or equivalent) and a low-dose steroid (such as intravenous hydrocortisone 100 mg or equivalent). If the event is clearly anaphylactic, the administration of epinephrine (1/1000, 0.3-0.5 ml subcutaneously, or equivalent) should be considered, in addition to the standard treatments. In the case of bronchospasm, the administration of inhaled β-agonists will be assessed.

Depending on intensity, idiosyncratic reactions may also be treated with an antihistamine and steroids at low doses. Post-infusion reactions of the study drug will be assessed and treated in a similar way. Whenever a study drug infusion reaction occurs, the investigator should consult the medical monitor to determine the most suitable procedure for future infusions.

TH-302 must be handled and stored safely and as specified on the label and in the Investigator's Brochure. The label on the bottles will indicate the study protocol number, the medication or bottle number, the contents, instructions for use, storage instructions, the clinical trial declaration and the name of the sponsor. The patient number will be allocated to a bottle upon hand over.

6.2. Duration of Treatment

Treatment with TH-302 in combination with sunitinib will continue until disease progression, unacceptable toxicity, non-compliance with the protocol, the patient's withdrawal of informed consent or at the discretion of the investigator. **In case of withdrawal of the study medication for toxicity, the patient will continue follow-up according to the scheduled study activities, and the investigator following the patient shall be responsible for initiating another systemic treatment option if deemed appropriate.**

6.3. Titration of the Study Drug

All dose modifications must be conducted according to the most severe preceding toxicity, as classified by the *National Cancer Institute Common Terminology Criteria for Adverse Events* (NCI-CTCAE, version 4.0).

As far as possible, an attempt should be made to follow the dose and scheduled regimen. However, in case of an adverse event, administration of the study drug should be titrated as described below.

The patient should notify the investigator of the date of onset of any adverse signs and symptoms.

Dose modifications to both treatments may be required in 3 different situations:

- During a cycle: treatment is discontinued until recovery and the dose is reduced, if necessary, during a particular treatment cycle.
- Between different cycles: treatment administration is delayed in the next cycle due to persistence of residual toxicity at the beginning of a new cycle.
- During the following cycle: the dose is reduced in the following cycle, taking into account the toxicity exhibited in the previous cycle.

In the event of treatment delay, proceed as follows:

- On day 1 of a cycle, if the administration of sunitinib must be postponed, the whole cycle must be delayed.

- On days 8 or 22, if the administration of both drugs must be postponed, that dose must be skipped.
- On days 8 or 22, if the administration of just 1 drug must be postponed, that dose will be skipped and the cycle will not be delayed, but rather the other drug will be administered on its own.

6.3.1. Discontinuation of Treatment

The treatment will be temporarily discontinued until the resolution of ≤ grade 2 toxicity. Depending on the duration of treatment discontinuation, this will either lead to the loss of all subsequent scheduled doses within the same cycle, or even delay the start of the next cycle. If the patient recovers from the adverse event within the same cycle, therapy may be continued in that cycle. Any missed doses for toxicity will not be made up for within the same cycle.

Dose reduction when reintroducing the treatment is determined below (section 6.3.3), unless, in the event of disagreement, the investigator prefers to discuss it with GETNE [redacted] If a dose is reduced within a cycle, the patient should return to the site to receive the new treatment dose.

If treatment discontinuation lasts > 4 weeks, for reasons other than study treatment toxicity (non-cancer surgery, etc.), GETNE must be consulted before reintroducing the study drug [redacted]

Treatment will be discontinued permanently in the following situations:

- The patient requires more than 2 dose-reduction steps.
- The patient requires more than 4 weeks delay (one full cycle) to restart treatment due to study treatment toxicity.

In patients for whom recovery from treatment toxicity involves treatment suspension lasting more than 4 weeks, or delaying a treatment cycle, but there is a clear clinical benefit in the opinion of the investigator, reintroduction of the treatment may be discussed with GETNE [redacted]

Patients who discontinue treatment with TH-302 may continue receiving sunitinib as monotherapy within the trial.

Under no circumstances may patients receive TH-302 as monotherapy. In the event that the administration of sunitinib must be discontinued, the administration of TH-302 will also be discontinued.

Patients who permanently discontinue TH-302 and sunitinib will abandon active treatment and enter the follow-up phase.

6.3.2. Reintroduction of Treatment

The study treatment will not be reintroduced until the following parameters with the adjusted dose are met, as described in section 6.3.4.:

- For TH-302, neutrophil count ≥ 1,500 mm³, with no evidence of fever (Temp. ≥ 38 ºC)
- For Sunitinib, neutrophil count ≥ 1,000 mm³.
- Platelet count ≥75,000 mm3 (see section 6.3.3.)
- Haemoglobin ≥ 9 g/dl on day 1 of the cycle and haemoglobin ≥ 8 g/dl in the weeks thereafter. If haemoglobin < 8 g/dl, the appropriate measures, in accordance with routine clinical practice, must be taken before continuing with the treatment.
- Non-haematological toxicity recovery to grade ≤ 1 or baseline. Treatment reintroduction may be considered with ≤ grade 2 toxicity recovery at the discretion of the investigator, and if this decision does not compromise the safety of the patient.
- QTc interval < 501 msec and after correcting potential reversible causes of the disorder, such as electrolyte disturbances or concomitant medications that prolong the QTc. If the QTc interval continues > 480 msec, an ECG must be performed more regularly at the discretion of the investigator, in accordance with routine clinical practice, until the QTc interval ≤ 480 msec.
- ALT (and/or AST) value < 3 x ULN (< 5 in the event of liver metastases) and a total serum bilirubin value ≤ 1.5 x ULN. Patients who exhibit these parameters for more than 2 weeks must permanently discontinue the study treatment.

6.3.3. Dose Reduction

Titration is not required in patients with grade 1 or 2 treatment-related toxicity. Despite this, investigators should always treat their patients according to their medical judgement and based on individual circumstances.

2 dose-reduction steps are permitted depending on the type and severity of toxicity. If the investigator deems it to be necessary, the reduction of the two dose levels can be performed directly, without needing to wait for a time between both.

Patients requiring more than 2 dose reductions will abandon the treatment phase and enter the follow-up phase.

All adjustments or dose modifications should be clearly documented in the patient's medical record and in the CRF (Investigational product administration).

Once a patient's dose has been reduced, all subsequent cycles will be administered at that same dose, unless a further reduction is required. Dose reescalation will not be permitted as part of the study. Specific cases will be discussed with the study's coordinating investigator [redacted]

Table 1. Available dose levels with TH-302 and sunitinib

DOSE LEVEL	TH-302 DOSE	SUNITINIB DOSE
Starting	340 mg/m^2 D8, 22	37.5 mg/24h D1-28
-1	280 mg/m^2 D8, 22	37.5 mg/24h D1-28
-2	280 mg/m^2 D8, 22	37.5 mg/24h D1-22, plus a rest week (3 weeks on / 1 week off)

6.3.4. Dose Titration According to the Type and Severity of Toxicity

Table 2. Titration according to haematological toxicity

ABSOLUTE NEUTROPHIL COUNT (ANC) (/µl)	AND /OR	PLATELET COUNT (/µl)	DOSE LEVEL WHEN REINTRODUCING TH-302		SUNITINIB
			Day 8	Day 22	
≥ 1500	AND	≥ 100,000	Starting	Starting	Starting
1000-1499	AND	75,000-99,999	Delay	Delay	Starting
500-999	OR	50,000-74,999	Delay and reduce one level in following cycles	Delay and reduce one level in following cycles	Reduce one level
< 500	OR	< 50,000	Delay and reduce one level in following cycles	Delay and reduce one level in following cycles	Reduce one level

Table 3. Titration according to non-haematological toxicity

TH-302			
Toxicity grade	**Toxicity**	**Discontinuation**	**Dose after recovery**
Grade 2	Except for asthenia, alopecia, nausea, vomiting and diarrhoea	Until ≤ grade 1 recovery	Starting
	Unacceptable skin abnormality	Until ≤ grade 1 recovery	Reduce **one** level (-1)
Grade 3	Except for nausea and vomiting	Until ≤ grade 1 recovery	Reduce **one** level (-1)
Grade 4	Potentially fatal (drug-related)	Permanent discontinuation	N/A
	Others such as non-life threatening asthenia or pulmonary embolism	Until ≤ grade 1 recovery	Reduce **two** levels (-2)

Table 4. Titration according to non-haematological toxicity

Sunitinib			
Toxicity grade	**Toxicity**	**Discontinuation**	**Dose after recovery**
Creatinine > x2 upper limit of normal (ULN)	Irrespective of the cause	Until creatinine ≤ x2 upper limit of normal (ULN)	Reduce **one** level (-1)
Grade 2	Except for asthenia, alopecia, nausea, vomiting and diarrhoea	Until ≤ grade 1 recovery	Starting
Grade 3	Except for nausea and vomiting	Until ≤ grade 1 recovery	Reduce **one** level (-1)
Grade 4	Potentially fatal (drug-related)	Permanent discontinuation	N/A
	Others such as non-life threatening asthenia or pulmonary embolism	Until ≤ grade 1 recovery	Reduce **one** level (-1)

Table 5. Titration according to ECG QTc interval prolongation

	Presence of a reversible cause	**Unidentified reversible cause**
G2 QTc interval prolongation	- Treat the reversible cause. - ECG monitoring. * - If first event, continue TH-302 at the same dose if QTc < G2 (≤ 480 msec) - If relapse, G2 or QTc > 480 msec more than two cycles after correction of the possible causes, and with no other identifiable cause, the dose will be titrated after consulting a cardiologist and GETNE, in accordance with the available TH-302 safety data and the investigator's good medical practice.	- ECG monitoring.* - If first event, continue TH-302 at the same dose. - If relapse or QTc > 480 msec more than two cycles after correction of the possible causes, and with no other identifiable cause, the dose will be titrated after consulting GETNE, in accordance with the available TH-302 safety data and the investigator's good medical practice.
G3 QTc interval prolongation	- Treat the reversible cause. - ECG monitoring. * - Discontinue treatment until QTc ≤ 500 msec. - Reintroduce TH-302 at the same dose - If G3 recurs, future dose titration will be performed after consulting a cardiologist and GETNE, in accordance with the available TH-302 safety data and the investigator's good medical practice.	- ECG monitoring. * - Discontinue treatment until QTc ≤ 500 msec. - Reintroduce treatment with one-level dose reduction. - If G3 recurs, despite dose reduction, future dose titration will be performed after consulting a cardiologist and GETNE, in accordance with the available TH-302 safety data and the investigator's good medical practice.
G4 QTc interval prolongation	Permanent treatment discontinuation	Permanent treatment discontinuation
* In the event of a QTc interval prolongation and during treatment discontinuation, the frequency of performing control ECGs should be increased to once a week (the same day each week), together with electrolytes analysis, until the QTc interval ≤ 480 msec (≤ G1).		

6.3.5. Medication Errors or Overdose

Medication errors may be due to a timing error or the drug dosage. These cases should be recorded as an adverse event (AE) or severe adverse event (SAE), as appropriate, in the CRF.

Should a medication error occur, GETNE must be notified immediately [redacted]

Examples of a medication error:

- Medication errors that involve patient exposure to the drug (dispensation/administration of expired medication, dispensation of commercial sunitinib or TH-302 or not allocated for this trial, etc.)
- Medication errors or practices not in accordance with the protocol and that may or may not involve the patient participating in the study (deviations from relevant temperatures, trial medication stock mismatches, etc.).

An SAE will be reported where a patient voluntarily or accidentally ingests more than 60 sunitinib tablets in a single cycle (for example, more than 4 tablets in more than 2 days within a cycle or more than 4 tablets in one day).

An AE will be reported in cases where a patient voluntarily or accidentally ingests 58 or 60 sunitinib tablets in a single cycle. The event will be recorded in the CRF.

Any TH-302 dosage error which leads to > 20% of the expected dose should be considered a TH-302 overdose.

6.3.6. Concomitant treatment

All concomitant medication, including any drug administered within 4 weeks (28 days) prior to the day 1 visit and 30 days after the last dose of the study drug, must be recorded in the case report form, together with the reason for administration.

The patient should be informed about the importance of consulting the investigator prior to taking additional medications.

Concomitant medication includes any vitamins, herbal remedies, over-the-counter drugs and prescribed medicines.

Any additional treatment that becomes necessary during the study, and any change to concomitant drugs, must be recorded in the corresponding section of the case report form, including the name, dose, duration and indication of each drug.

Should medication be administered intermittently, or in relation to an adverse event, this adverse event should be recorded on the adverse event form of the case report form.

- **Disallowed concomitant treatment:**
  - Other oncology drugs (chemotherapy, immunotherapy, targeted therapy) during the treatment phase, whether approved healthcare drugs or under clinical trial.
  - Drugs that are known to cause QT interval prolongation, given the risk of developing polymorphic ventricular tachycardia. (Annex 4)
  - Strong or moderate CYP3A4 inhibitors

If, during the study, a patient requires treatment with one of these drugs for a limited period of time, TH-302 and sunitinib will not be administered simultaneously. Treatment will be reviewed together with the medical monitor, who will supply the dosage rules based on the half-life of the medicinal products, TH-302 and sunitinib, in addition to other clinical considerations. The medical monitor will advise the investigator, who will assess the search for alternative medicines.

- **Concomitant treatment not recommended:**
  - Chronic immunosuppressant treatment, including systemic corticosteroids. Short courses of topical/inhaled or systemic corticosteroids are permitted
  - Herbal products

For up-to-date information on drug interactions (substrates, inhibitors or inducers), visit the following website:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classSub

- **Permitted concomitant treatment**
  - Treatment with somatostatin analogues (octreotide LAR or lanreotide Autogel) at doses established in the summary of product characteristics and with the aim of controlling the symptoms of the patient's underlying disease
  - Any treatment for pre-existing comorbidities, complications or symptomatic control, taking into account the precautions mentioned above, and recorded in the patient's medical record and in the CRF.
  - Stimulation of colony formation, following standard treatment and institutional guidelines. Its use is not allowed as primary prophylaxis, but is allowed as secondary treatment or prophylaxis, in the event that the alternatives of dose reduction or treatment delay are not deemed appropriate.
  - Transfusion of red blood cells/platelets or erythropoietin for supportive treatment of anaemia or for the prompt treatment of thrombopenia, following standard treatment and institutional guidelines.
  - Hormone replacement therapy within 2 months prior to study enrolment shall not constitute an exclusion criterion. The same dose must be maintained throughout the course of the study.
  - Palliative radiotherapy of non-target lesions is permitted, if necessary, while taking part in the study. The location, total dose received and treatment dates should be recorded in the case report form.

7. PATIENT SELECTION

7.1. *Inclusion Criteria*

1. Age ≥ 18 years capable of giving informed consent.

2. ECOG performance status (Eastern Cooperative Oncology Group) 0 or 1

3. Pancreatic neuroendocrine tumours (pNET) diagnosed histologically with a Ki67 ≤ 20% (well- or moderately-differentiated tumours).

4. Evidence of unresectable or metastatic disease. Locally advanced disease must not be amendable to surgical resection or radiation therapy with curative intent.

5. Prior systemic therapy is not permitted. Patients may be treated with somatostatin analogues prior to or during the trial. Concomitant or prior interferon (IFN) treatment is not permitted.

6. Tumour progression documented by CT scan, MRI or octreoscan within 12 months prior to the baseline visit.

7. Measurable disease by RECIST 1.1 criteria. Measurable lesions that have been previously radiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

8. The patient must be able to consume the medication orally.

9. Life expectancy more than 12 weeks.

10. The required laboratory values corresponding to adequate organ function and bone marrow are as follows.

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN), or AST and ALT ≤ 5 x ULN if liver function abnormalities are secondary to underlying malignancy.
- Total serum bilirubin ≤ 1.5 × ULN
- Serum albumin ≥ 3.0 g/dl
- Absolute neutrophil count ≥ 1500/µl.
- Platelets ≥ 100,000/µl
- Haemoglobin ≥ 5.6 mmol/l (9 g/dl)
- Creatinine clearance > 40 ml/min (Cockroft and Gault Formula)

11. Suitable cardiac function:

- 12-lead ECG with no pathological findings (non-clinically significant abnormalities are permitted)
- Normal echocardiogram/MUGA normal (LVEF ≥ 50%)

12. Informed consent with date and signature indicating that the patient (or legal representative) has been informed of all study aspects prior to enrolment.

13. The patient must be able to comply with the required study visits, treatment, laboratory tests and other study procedures.

7.2. *Exclusion Criteria*

Patients must NOT meet any of the following exclusion criteria:

1. Previous treatments with chemotherapy, anti-VEGF monoclonal antibodies, tyrosine kinase inhibitors (TKI), mTOR inhibitors or interferon (IFN) administered for advanced disease.
2. Prior treatment with another hypoxia-activated drug under clinical trial.
3. Major surgery, radiotherapy or systemic therapy within 4 weeks prior to study enrolment, except palliative radiotherapy for non-target metastatic lesions.
4. Prior high-dose chemotherapy requiring haematopoietic stem cell rescue.
5. Immunosuppressive drugs such as cyclosporine, tacrolimus, azathioprine, or long-term corticosteroids taken concurrently or within 3 months prior to study enrolment.
6. Treatment, within 7 days prior to study enrolment, with known strong CYP3A4 inhibitors or inducers, or drugs that prolong the QT interval.
7. Prior radiation therapy to > 25% of the bone marrow.
8. Treatment within another clinical trial.
9. Uncontrolled brain metastatic disease, spinal cord compression, carcinomatous meningitis or leptomeningeal disease. Patients should have completed surgery or radiation therapy for existing brain lesions, should not have documented increase in size of said lesions over the three months prior to the first study treatment dose, and should be asymptomatic.
10. Diagnosis of any second malignancy within the last 3 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
11. Clinically significant cardio/cerebrovascular disease within 12 months prior to treatment initiation, including:
    - Myocardial infarction
    - Severe/unstable angina
    - Coronary/peripheral artery bypass graft
    - Congestive heart failure NYHA (New York Heart Association) Class III or IV, or patients with a history of congestive heart failure NYHA class III or IV, unless an echocardiogram or MUGA scan within 3 months prior to screening shows a left ventricular ejection fraction ≥ 45%.
    - Significant cardiac valvular heart disease.
    - Cerebrovascular accident including transient ischaemic attack.
    - Pulmonary thromboembolism.
12. Cardiac arrhythmias (NCI CTCAE version 4.0 grade ≥ 2), atrial fibrillation of any grade, or QTc interval > 450 msec for males or > 470 msec for females.
13. Hypertension that cannot be controlled despite optimal medical therapy (> 150/100 mmHg)
14. Chronic obstructive pulmonary disease (COPD) or any lung disease accompanied by hypoxaemia or oxygen saturation < 90% after a 2-minute walk.
15. Current treatment with therapeutic doses of acenocoumarol (administration of low doses of acenocoumarol up to 2 mg/24 h for deep vein thrombosis prophylaxis is permitted).
16. Known human immunodeficiency virus (HIV) infection.

17. Pregnant or breast-feeding. All female patients of childbearing age must have a negative pregnancy test (blood or urine) prior to study enrolment.
18. Prior allergic reaction to ingredients structurally similar to TH-302 or sunitinib or to any of the drugs' excipients.
19. Non-healing wound, fistulae, active stomach ulcer or bone fractures.
20. Any condition (medical or psychiatric) or reason that, in the opinion of the investigator, would interfere with the patient's ability to participate in the clinical trial, by placing the patient at excessive risk or by complicating the interpretation of the safety data, therefore being unsuitable for enrolment in the study.

7.3 *Criteria for treatment withdrawal*

The patient may withdraw the informed consent and stop treatment at any time during the study, for any reason. The investigators and medical monitors may discontinue treatment for reasons of safety and/or lack of compliance, as detailed below. These patients will attend the follow-up safety visit. Patients who discontinue treatment will be followed up to determine radiological progression, subsequent neuroendocrine tumour treatments and survival.

Treatment withdrawal due to adverse events or safety reasons:

- Any unacceptable adverse event that cannot be appropriately managed by medical intervention or which, in the opinion of the investigator or the clinical monitor, poses excessive risk for the patient if the current dose is continued.
- Any unacceptable toxicity according to the protocol (see section 6.3. Safety assessment. Titration of the Study Drug.)
- Disease progression based on protocol criteria.
- Patients who, in the opinion of the investigator or clinical monitor, clearly fail to comply with the requirements of the protocol.
- Patient's absence from follow-up.
- Administration of chemotherapy or immunotherapy not envisaged by the protocol but that, in the opinion of medical staff, is required by the patient.
- Study ended by GETNE
- Patients who experience a treatment delay greater than 4 weeks will discontinue treatment and enter the follow-up phase, unless there is an obvious clinical benefit in the opinion of the investigator and after discussing it with GETNE [redacted]
- Whenever possible, after permanent treatment discontinuation, the patient should continue with the follow-up assessments as scheduled after the last treatment dose received. Any permanent treatment discontinuation must be recorded in the eCRF.

8. METHODOLOGY

8.1. *Translational Section. Determination of Biomarkers.*

Sample Collection

Tumour block collection

A paraffin-embedded tumour block will be requested and sent to [redacted] for the hypoxia marker expression study.

Collection of peripheral blood samples

10 ml of peripheral blood will be taken from each patient during the baseline visit and placed in EDTA tubes, to be sent to the Spanish National Cancer Research Centre for polymorphism study.

Handling and storage of samples

Tumour block

The paraffin blocks will be stored at room temperature under routine site conditions after the patient has signed the informed consent form, at which point they will be sent to the reference site.

Peripheral blood samples

The blood samples will be stored at -20 °C from the moment of extraction, and will be sent periodically to the reference site.

Sample shipping

Tumour block

The paraffin blocks will be sent with the periodic deliveries at room temperature (< 25 ºC).

Peripheral blood samples

The blood samples will be sent all together and correctly identified in dry ice to the reference site.

Centralised receipt of samples

The paraffin-embedded tumour samples will be received by [redacted]

The samples will be received from Monday to Friday, from 08:00 to 15:00.

Peripheral blood samples will be received by [redacted] for the attention of:

[redacted]

The samples will be received from Monday to Friday, from 08:00 to 15:00.

Sample processing

Tumour block
The paraffin blocks will be analysed by specialised pathologists as they are received. The expression of hypoxia-related proteins such as CAIX, HIF2A/HIF-1alpha, VEGF, CYP2W1 and c-myc will be assessed centrally and retrospectively in immunohistochemistry.

Peripheral blood:
DNA will be isolated from the peripheral blood, following the instructions of the "FlexiGene DNA kit" (Qiagen), and the concentration of the DNA extracted will be quantitated by the "PicoGreen® dsDNA quantitation reagent" (Invitrogen). The DNA will be stored at -20 ºC until genotyping.

Genotyping will be carried out by standard techniques (for example, "TaqMan Probes", or "KASPar SNP Genotyping System") using 15 ng of genomic DNA. Fluorescence detection and allele assignment will be performed using the "7900HT Detection System" by Applied Biosystems. The results obtained will be used to create a genetic database, which will collect the genotypes of each patient enrolled in the study.

The list of polymorphisms to genotype includes variants in the following candidate genes:

VEGFR2 (rs2305948 and rs1870377), *VEGFR3* (rs307826), *IL8* (rs1126647), *CYP3A4* (rs35599367 and rs67666821), *CYP3A5* (rs776746), *ABCB1* (rs1045642, rs1128503 and rs2032582), *POR* (rs1057868 and c.1705_1706insG). If a polymorphism of particular relevance and related to the effectiveness of sunitinib or TH-302 appears in the literature as the study progresses, its inclusion in the study could be considered.

The procedure for coding and shipping samples is detailed in a separate document.

9. STATISTICAL ANALYSIS

9.1. *Descriptive Analysis*

The descriptive analysis of patient characteristics will include demographic data, disease-specific data and prior treatments. Qualitative data will be described with absolute frequencies and corresponding percentages. Quantitative data will be studied using the mean ± standard deviation, median, minimum and maximum values. The response percentages will be estimated using confidence intervals of 95%.
In the safety analysis, adverse events will be specified according to the maximum grade described at the discretion of the investigator and defined by NCI-CTCAE, version 4.0 (see section 10.2.3.), including adverse events described from treatment initiation until 28 days following its completion.

The following safety analysis data will be presented:

- Temporary and permanent treatment discontinuations due to an adverse event.
- Deaths.
- Adverse Events (AEs) and Serious Adverse Events (SAEs).
- Hospitalisations.
- Use of concomitant medication and growth factors.

9.2. *Inferential Analysis*

The objective response rate corresponding to the percentage of patients in which there is confirmation of a complete response (CR) or a partial response (PR) according to RECIST criteria, in relation to the total analysis population, will include a confidence interval of 95%. The association between the marker expression profiles analysed in plasma and in tumour tissue for treatment response (yes/no) will be assessed using logistic regression models and univariate and multivariate Cox regression, establishing the corresponding *hazard ratio* and confidence interval at 95%. The predictive value (of genetic biomarkers, in plasma and tumour tissue) of each model will be estimated using an area under the ROC curve.

The survival analyses will be performed using the Kaplan-Meier method presented with the corresponding graph, as well as by Cox regression analysis to obtain the *hazard ratios* and confidence intervals for the associations. For patients without documented progression or death at the time of analysis, the PFS will be censored at the last date of tumour assessment. For patients who have not died at the time of analysis, the OS will be censored.

All statistical tests are bilateral, two-tailed tests, and all values with $p < 0.05$ will be considered significant.

10. ASSESSMENT CRITERIA

10.1. *Efficacy Assessment*

Objective response rate (ORR)

This will be assessed according to RECIST version 1.1 criteria, to be performed every 8 weeks, regardless of treatment delays caused by treatment toxicity.
The ORR is defined as the percentage of patients in which there is confirmation of a complete response (CR) or a partial response (PR) according to RECIST criteria, in relation to the total analysis population.
A response is confirmed for patients in whom the response persists in an imaging test repeated ≥ 4 weeks after initial documentation of response.

Progression-free survival (PFS)

This is defined as the time between the start of study treatment to the date of first objective evidence of radiological progression or patient death from any cause; whichever comes first.

Time to progression (TTP)

This is defined as the time between the start of study treatment to the date of first objective evidence of radiological progression.

Response duration (RD)

This is defined as the time between the first recorded objective response (CR or PR), which is subsequently confirmed, to the first objective evidence of radiological progression or death from any cause.
RD will only be calculated in the subgroup of patients with objective response (CR + PR).

Overall survival (OS)

This is defined as the time between the start of study treatment to the date of death from any cause.
If confirmation of death could not be obtained, survival will be censored with the date of the last visit at which time the patient was known to be alive.

Safety

See Safety Assessment section below.

Biomarkers:

They assess the correlation between radiological response and the patient's clinical course and the following expression levels:

- ENO1 (enolase 1) in plasma (it will be performed locally at the same time as chromogranin at each participating site)

- SNPs (single nucleotide polymorphisms) related to the activity and metabolism of sunitinib and TH-302 *VEGFR*2 (rs2305948 and rs1870377), *VEGFR*3 (rs307826), *IL*8 (rs1126647), *CYP3A4* (rs35599367 and rs6766682 1), *CYP3A*5 (rs776746), *ABCB*1 (rs1045642, rs1128503 and rs2032582), *PO*R (rs1057868 and c.1705_1706insG). If a polymorphism of particular relevance and related to the effectiveness of sunitinib or TH-302 appears in the literature as the study progresses, its inclusion in the study could be considered.
- Hypoxia markers related to paraffin-embedded tumour tissue (HIF1- α, CYP2W1 and c-Myc).

10.2 *Safety Assessment*

10.2.1. Safety Analysis

The safety period runs from the date of the signature of the informed consent form until 28 days after the last dose of the study drug. Safety will be evaluated according to adverse event reports, the frequency of treatment discontinuations due to adverse events, and laboratory or ECG tests. Descriptive analysis will be used.

10.2.2. Adverse Events

An adverse event is defined as any unwanted or unintended symptom, sign, disease or experience (including a clinically significant laboratory result of any grade according to the common terminology criteria for adverse events *[CTCAE] of the National Cancer Institute, version 4.0*) that emerges or worsens during the course of the study, whether related or not to the study drug.
The assessment of adverse events will include type (symptoms from the medical history, physical examination findings or laboratory/ECG/radiological/other diagnostic procedure abnormalities), prevalence, severity/seriousness, time and their link.

Examples of adverse events are the following:

- Deterioration (excluding mild fluctuations) of the nature, intensity, frequency, or duration of a pre-existing condition.
- Development of an intercurrent illness during the study.
- Development of symptoms that may or may not be associated with the use of a concomitant medication or the study drug.
- Injury or accidents: if a medical condition is known to have caused the injury or accident, both the medical condition as well as the accident should be recorded as two independent medical events (e.g., in the event of a fall caused by dizziness, both the “fall” and the “dizziness” must be recorded separately).

The following situations will not be classified as adverse events:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). However, the disease precipitating the procedure is an adverse event.
- Pre-existing conditions or diseases present or detected prior to the first administration of the study drug that do not deteriorate.
- Circumstances in which no unwanted medical events manifest (e.g., hospitalisation for elective surgery, hospitalisations for social circumstances and/or convenience).

The relationship between the adverse event and the study drug:

The reasonable possibility of a link between the adverse event and the study drug will be determined. In cases where the study site investigator is unable to make an objective judgement, the opinion of the clinical monitor should be sought. The following definitions will be used:

- Not related: There is no possible relationship to the study drug. The temporal relationship between drug exposure and the start/evolution of the adverse event is unreasonable or incompatible, or a causal relationship to the study drug is implausible.

- Unlikely: If the study drug is deemed not to be reasonably related to the adverse event, but a causal relationship cannot be ruled out. Although the temporal relationship between exposure to the study drug and the start/evolution of the adverse event does not exclude causality, there is a clear alternative cause that is more likely to have caused the adverse event than the study drug.

- Possible: The causal relationship to the study drug is not clear. The temporal relationship between drug exposure and the start/evolution of the adverse event is reasonable or unknown, information regarding the discontinuation of exposure or re-exposure is unknown or ambiguous, and although there are no other potential causes, a causal relationship with the study drug does not seem likely.

- Likely: There is a high degree of certainty for the causal relationship between the study drug and the adverse event. The temporal relationship between drug exposure and the start/evolution of the adverse event is reasonable, the response is clinically compatible with discontinuation of exposure, other causes have been ruled out and the event must be conclusive from a pharmacological or phenomenological point of view, adopting a re-exposure procedure if necessary.

- Definite: The causal relationship is clear. The temporal relationship between drug exposure and the start/evolution of the adverse event is reasonable, the response is clinically compatible with discontinuation of exposure, other causes have been ruled out and the event must be pharmacologically or phenomenologically conclusive, adopting a re-exposure procedure if necessary.

For the purposes of expedited reporting, the categories "definite", "probable" and "possible" will be considered related to the study medication, and the categories "improbable" and "not related" shall be considered unrelated to the study medication.
The site's principal investigator, or the person delegated by said investigator, is responsible for determining the relationship of the adverse event to the study medication.

Recording and reporting of adverse events:

All adverse events experienced by patients, regardless of their relationship to the study drug, must be reported in full on the adverse event page of the case report form and in the patient's medical record, adopting the appropriate medical terminology. The severity, the result and relationship to the study drug will be determined and documented in the case report form.
Should a patient discontinue the study drug due to an adverse event, this must be recorded in the case report form. In the event of patient death caused by disease progression, the data will be included in the efficacy analysis, unless the investigator feels that the event is related to the study medication. Adverse events will be monitored until they have been resolved, or until they have stabilised and/or reached a new baseline level. If an adverse event has not been resolved before the end of the study, the investigator and the medical monitor will perform a clinical assessment to determine whether its follow-up is justified.

The site investigator must record all directly observed adverse events and all adverse events that were spontaneously reported.
It should be noted that the intermittent or on-demand use of any medicine (and specifically any newly-prescribed medication) throughout the study could precipitate the onset of an adverse event that would have to be recorded on the case report form, both on the adverse event form as well as the concomitant medication form.

Adverse events will be recorded on the case report form from patient enrolment after the informed consent form has been signed, during the study treatment and 28 days following the end of treatment. During the long-term follow-up, following the 28-day period after the end of treatment, adverse events (AEs) related to the study treatment or procedures will be recorded, even after study completion, until stabilisation or until the outcome is known, unless the subject is documented as "lost to follow-up". In addition, should the patient sign the informed consent form but not receive treatment, adverse events will be recorded that the investigator considers to be related to the study procedures.

10.2.3. Intensity Grading of Adverse Events

Adverse events and their severity will be assessed based on *National Cancer Institute Common Terminology Criteria for Adverse Events* (NCI-CTCAE, version 4.0). These criteria can be consulted at the following address:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

10.2.4. Serious Adverse Events (SAEs):

A serious adverse event (SAE) or reaction is any harmful medical event that, regardless of the dose:

- Results in the death of the patient.
- Is life-threatening to the patient or potentially fatal (i.e., the patient is at immediate risk of death at the time of the event).
- Requires patient hospitalisation or the prolongation of existing hospitalisation.
- Results in permanent or significant disability or incapacity.
- Causes a defect, congenital malformation or results in cancer.

In addition, medical and scientific judgement should be used to decide whether other situations should be considered as a serious adverse event, although they do not meet the above criteria, such as those that endanger the patient's life or require intervention to prevent any of the above outcomes.
It must not be confused with the term "severe", which indicates the intensity of the adverse event.

Recording and Reporting of Serious Adverse Events (SAEs):

Information on SAEs, whether related to the treatment or not, will be collected and recorded on the SAE form of the corresponding case report form. SAEs, as defined above, must be recorded from the date the informed consent form was signed, and the pharmacovigilance contact person must be notified immediately, within 24 hours of awareness by the study site, by fax to

Marketing Farmacéutico & Investigación Clínica

[redacted]

The initial report must state the site name and number, the name of the investigator, the patient ID number and initials, patient demographics, study drug administration data and everything known about the serious adverse event, including date of onset, intensity, treatment and relationship to the study drug. If the patient dies, the report should include the cause of death and its potential relationship to the study drug, in addition to the autopsy findings (if available).

This includes the determination of one or more SAE criteria, a detailed description of the event, relevant clinical reports (without names or other patient identifiers), the date of death and an autopsy report (where applicable, and if available), the updated investigator assessment regarding the relationship of the study drug to the SAE, and actions taken.
The Sponsor will send the safety reports to the health authorities in an appropriate manner, in accordance with the applicable laws and regulations.
SAEs must also be reported by the investigator to the responsible Independent Ethics Committee (IEC), in accordance with regulatory requirements.
The assessment of the expected SAEs considered to be reportable to the health authorities and Ethics Committees, which were specified above, will be carried out by the Sponsor in accordance with the "Guide for the investigator" section of the most up-to-date version of the Investigator's Brochure for TH-302. The updated version of the Investigator's Brochure will be provided by Threshold.

The notification of a suspected SAE must not be delayed in order to obtain further information. The follow-up report will be completed with the collection of any additional data after the initial report. This report will also be issued should the event be resolved, in the absence of significant changes, or should the situation stabilise. This report will be issued in the following 24 hours.

Through the study's principal investigator, the sponsor (GETNE) will assess the SAEs, taking into account the product safety reference documents, and will report, through the CRO, those SAEs that meet the expedited reporting criteria (serious, unexpected and related to the study medication) with the help of the monitor. The sponsor is responsible for notifying the competent authorities (Spanish Agency of Medicines and Medical Devices - AEMPS, central IEC, hospital IEC, competent bodies of the Autonomous Communities) and the principal investigators/institutions involved in the study, and this will be carried out within the time scales determined by current Spanish legislation. The maximum period for notification shall be 15 calendar days from the time the sponsor learns of the suspected adverse reaction. However, if the unexpected serious adverse reaction leads to the patient's death, or endangers the patient's life, the sponsor shall inform the AEMPS within 7 calendar days from the time it became aware of the situation. Said information shall be completed, as far as possible, within the following 8 calendar days.
All SAEs will undergo a follow-up until the following situations are reached:

- Event resolution
- Event stabilisation.
- Restoration of the baseline situation and, if available, a baseline value.
- The event can be attributed to products other than the study treatment or factors not related to the study.
- It is not possible to obtain further information.

All unresolved SAEs at the conclusion of the study must be followed up, to determine the end result.

SAEs will be recorded from the time the patient signs the informed consent form until the follow-up safety visit, 28 days after the last dose of the study drug, or until the start of administration of an investigational or medical drug, whichever comes first.

Fatal events (regardless of their relationship to the study drug) will be recorded as serious adverse events up to the follow-up safety visit (28 days after discontinuation of the study drug) or until the start of further treatment, whichever comes first. Fatal events that occur after the follow-up safety visit (28 days after discontinuation of the study drug) or upon initiation of an investigational or medical drug, whichever comes first, will not be recorded as serious adverse events but will be recorded on the corresponding case report form.
In the event of death, the main cause of death (the event that led to death) should be recorded and reported as an SAE. The result of this event will be recorded as "Fatal"; the death will not be recorded as a separate event. It may only be notified as an event if there is no cause of death (for example: sudden death, unexplained death). In this case, the death in itself could be reported as an SAE.

This event will not be reported expeditiously as an SAE within 24 hours, but will be recorded in the case report form and analysed as a study objective. The death of a patient is not an adverse event in itself, but an outcome of an adverse event. All patient-death reports must include an adverse event as a cause of death (if known).

The sponsor will inform the investigators as soon as possible of any safety information that might affect patients.

Reporting pregnancy

Women of childbearing potential who are sexually active must use an effective contraception method during the course of the study, so as to minimise the risk of failure. Before enrolment in the study, women of childbearing potential will be informed of the importance of avoiding pregnancy during their participation in the study, and the potential risk factors of an unwanted pregnancy.

All women of childbearing potential MUST have a negative pregnancy test within 7 days prior to enrolment.
In addition, all women of childbearing age will be asked to immediately contact the investigator if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during their participation in the study.

If, after initiating administration of the investigational medicinal product, it is discovered that a study patient is pregnant or may have been pregnant at the time of exposure to the product, the investigational medicinal product will be permanently discontinued as appropriate (e.g., dose reduction if required for the safety of the patient). The investigator must immediately inform the sponsor of this event in accordance with the SAE reporting procedures, and the pregnancy must be recorded on a pregnancy form (Annex 7).

Initial information on a pregnancy must be reported immediately to the sponsor and information about its outcome must be provided once it is known. Completed pregnancy follow-up forms must be sent to the sponsor, in accordance with the SAE reporting procedures.

The sponsor must be informed of any pregnancy that occurs in a female partner of a male study participant. Information on this pregnancy will be collected on the pregnancy form (Annex 7).

Pregnancies must be reported to:

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[redacted]

The treatment discontinuation and follow-up procedures laid down in the protocol must be applied to the patient, unless contraindicated for pregnancy (e.g., x-rays). If indicated, other appropriate pregnancy follow-up procedures will be considered.

In addition, the investigator must inform the sponsor of any pregnancy, and follow-up on information regarding the course of the pregnancy, including a perinatal and neonatal outcome. Infants should be monitored for a minimum of 8 weeks

11. STUDY PROCEDURES

11.1. *Schedule of Assessments*

See Annex I.

11.2. *Baseline Visit (Days -28 to -1)*

At this visit the patient should be informed about all aspects of the study, including visits and tests to be performed. The patient will be asked to sign and date the informed consent form prior to performing any study procedure.
The informed consent form must be signed within 4 weeks before the start of the study medication. The original signed and dated informed consent form must be stored by the investigator in the patient's medical record and the patient must be provided with a copy.
The investigator will assess and confirm the eligibility of each patient, and all inclusion criteria must be met, but none of the exclusion criteria.
All the results of the tests undertaken during screening must be available before deciding whether a patient is eligible.

The specific baseline visit procedures envisaged by the protocol are as follows and must be performed within 28 days of initiating study treatment, or, failing that, screening must be repeated.

- Medical history.
- 12-lead ECG.
- Vital signs (blood pressure, heart rate, temperature, height and weight).
- A full physical examination.
- Complete blood test (See schedule of assessments, Annex I).
- NET markers (chromogranin A, enolase 1 and others depending on the tumour type).
- Urinalysis.
- Performance Status (ECOG Performance Status) (Annex 3).
- Concomitant medication.
- Echocardiogram/MUGA.
- Thoracic, abdominal, and pelvic CT scan (bone scan).
- Extraction of peripheral blood sample (biomarker analysis in blood).
- Tumour block for diagnosis of well- or moderately differentiated neuroendocrine tumour for biomarker analysis.

Patients should start the study treatment within two working days following the baseline visit.

11.3 ***Day 1 visit*** (may occur on the same day as the baseline visit if all baseline visit test results are available).

- Confirm that all the screening period and baseline visit procedures have been carried out.
- Confirm that the patient meets the inclusion criteria and none of the exclusion criteria.
- Instruct the patient regarding the administration of the study medication and provide the study medication for a complete cycle, i.e., 28 days.

11.4 *Treatment Visit*

- Days 1, 8, 15 and 22 of each cycle:
  - Physical examination.
  - Signs and symptoms.
  - ECOG performance status.
  - Vital signs (blood pressure, heart rate, temperature, height and weight). Recalculate body surface area if the variation has been shown to be greater than 10%.
  - Complete blood test (See schedule of assessments, Annex I).
  - Recording of adverse events.
  - Recording of concomitant medication.
  - Accounting for medication.
  - Administration of the study intravenous medication (TH-302 is not administered on D1 or on D15) and dispensation of oral medication.

- Visit every 8 weeks (from D1 C1 onwards):
  - NET markers (chromogranin A, enolase 1 and others depending on the tumour type) (+/- 1 week).
  - Thoracic, abdominal, and pelvic CT scan reassessment (+/- 1 week).
  - If reassessing via bone scan, perform every 24 weeks.

These procedures will not be postponed in the event of cycle delays and must be performed every 8 weeks until disease progression, regardless of whether the patient has completed the treatment.

11.5 *End-of-Study Treatment Visit*

This visit will take place once disease progression has been identified, in the event of unacceptable toxicity or if the patient decides to withdraw their consent to continue in the study. The end of treatment visit must take place 4 weeks after concluding treatment, irrespective of the cause of treatment discontinuation.

The following procedures will be performed:

- Physical examination.
- Signs and symptoms.
- ECOG performance status.
- Complete blood test (See schedule of assessments, Annex I).
- NET markers (chromogranin A, enolase 1 and others depending on the tumour type).
- Urinalysis.
- Echocardiogram/MUGA.
- Recording of adverse events.
- Recording of concomitant medication.
- 12-lead ECG (only if clinically indicated).
- Thoracic, abdominal, and pelvic CT scan (if applicable).
- Bone scan, if clinically indicated.
- Drug accountability.

11.6 *Follow-up*

The following procedures will be performed during follow-up until disease progression:

- ECOG performance status.
- Thoracic, abdominal, and pelvic CT scan and/or bone scan (if applicable).
- Cancer treatment received.

Tumour assessment must be performed every 8 +/- 1 weeks until disease progression, irrespective of whether the patient has completed the treatment.

After disease progression, the overall survival secondary endpoint will be performed following the site's usual practices (in terms of scheduling visits), and must be continued until death or end of the trial, whichever occurs first.

12. ETHICAL ASPECTS

12.1. *Legal Considerations*

This clinical study will be conducted in accordance with the protocol, the principles established in the latest revised version of the Declaration of Helsinki (Annex 5) and in accordance with applicable regulatory legislation, in particular, the ICH harmonised tripartite guideline on good clinical practice 1996 and Royal Decree 223/2004 on Clinical Trials, regulating clinical trials with medicinal products in Spain, which incorporates the whole of European Directive 2001/20/EC on the approximation of provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use.

12.2. *Patient's Informed Consent*

Before the screening assessment, the patient will be informed about the nature of the study drug and will receive the relevant information concerning the purpose of the study, the potential benefits and potential adverse events. The patient will be informed of the procedures to be undertaken and the potential risks to which he/she could potentially be exposed.

Then, the patient (or, in the case of disabled patients, his/her legal representative) must read (or be informed orally before witnesses) and sign two copies of the informed consent form that will have previously been approved. The patient will receive a signed copy of the informed consent form. The patient may withdraw from the study at any time without it affecting his/her ongoing medical care. Verification that the patient has given written informed consent will be recorded in the patient's CRF.

12.3. *Respect for Confidentiality*

The investigator will be responsible for storing the appropriate information about each patient (for example, name, address, telephone number, social security number and study ID number) so that the health authorities may have access to said information if necessary. These records shall be kept confidential for as long as required by local legislation.

The highest levels of professional conduct and confidentiality will be maintained at all times, ensuring compliance with national data protection legislation.

The patient's identity in the study documents will be coded, and authorised personnel, the sponsor, the study monitor, and the investigator's staff at each site will have access to personal details that could identify the patient if required for the data verification processes. The patient study codes will be assigned by the study sponsor through the monitor, and will be created by assigning a unique identity number to each patient enrolled in the study. These codes will be safeguarded by the study sponsor and monitor. Personal details that could identify the patient will be kept confidential.

12.4. *Liability Insurance*

The sponsor has taken out an insurance policy to cover the liability of the investigator and other parties participating in the study:

Insurance Company: [redacted]

[redacted]

13. STUDY DOCUMENTATION

13.1 *Files*

The investigator must maintain adequate and accurate records to ensure that the study is fully documented and to allow the study data to be subsequently checked. These documents are:

- Copies of completed CRFs, informed consent forms and the source documents.
- Investigator's file containing the protocol and any amendments, investigational medicinal product information as well as copies of essential documents.
- Records related to the investigational medicinal product(s).

In addition, all original source documents supporting CRF entries must be readily available.

The patients' original medical documentation would include the patients' hospital/medical records, doctors'/nurses' notes, the appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, letters from specialists and patients' screening and enrolment forms.

13.2 *Case Report Form*

The principal investigator or a study team authorised representative must complete and sign an electronic CRF for each patient enrolled in the study. This also applies to patients who do not complete the study (even during the screening period prior to enrolment, if completion of a CRF has been started). If a patient withdraws from the study, the reason must be indicated in the CRF. If a patient withdraws due to a treatment-limiting adverse event, every effort should be made to clearly document the result.

The database will be managed to allow the eCRF to generate further information requests that the investigator will be obliged to answer by confirming or modifying the data asked about. The requests, with their responses, will be managed through the eCRF. The eCRF must be kept up-to-date in order to allow the monitor to review the patients' status during the course of the study. Procedures and controls will be employed to ensure the confidentiality of electronic records.

13.3 *Monitoring*

The study will be monitored by the company MFAR. The accuracy of data collected in the CRFs shall be guaranteed by the monitor by verifying the data recorded in the CRF against data recorded in the medical record or in other documents such as laboratory reports, images, drug dispensation records, or any other source document containing information regarding the progression and follow-up of patients during their participation in the study.

Data to be verified shall be set out in the data verification plan, drawn up by the monitor and approved by the sponsor. The planned frequency of monitoring for each site will also be established.

To ensure data accuracy, precision and completeness, GETNE:

- Will provide the material with the necessary information to properly coordinate the study procedures.
- Will provide a training session for the investigator's team that will include a review of the protocol, the completion of the eCRF and study procedures.
- Will conduct regular site visits to review study progress, investigator and patient compliance with procedures and to address any urgent problems.
- Will remain in contact with the site for any query via e-mail, phone and/or fax.
- Will review and evaluate the CRF entries to detect any possible errors.
- Will ensure the quality of the data.

To ensure data accuracy for the safety of the patient, the investigator must include the original laboratory reports, imaging tests, medical reports and medical notes taken at each visit.

13.4.- *Publication of results*

The sponsor undertakes to promptly disseminate the results through the usual scientific means (conferences and publications), under the responsibility of the scientific coordinator and translational study coordinator. The study coordinator reserves the right to select his/her position in the different publications and reports that the study may envisage. The translational study coordinator will hold an assured position amongst the study authors. The remaining positions will be assigned to the participating investigators according to a rigorous order of recruitment.

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ANNEXES

ANNEX 1. SCHEDULE OF ASSESSMENTS

	Screening (28 days)	Cycles				End of treatment (at 4 weeks +/- 1) after the end of treatment	Follow-up until progression (every 8 weeks until progression)	Post-progression follow-up
		Day 1 (D1)	Week 2 (D8)	Week 3 (D15)	Week 4 (D22)			
Informed consent [1]	X							
Inclusion/exclusion criteria	X							
Medical record and demographic data[2]	X							
Physical examination (weight, height and vital si	X	X	X	X	X	X	X	
Signs/symptoms		X	X	X	X	X	X	
ECOG performance status (Annex 3)	X	X	X	X	X	X	X	
Haematology and haemostasis[4]	X	X	X	X	X	X	X	
Full clinical chemistry[5]	X	X	X	X	X	X	X	
NET markers[6]	X	Every 8 weeks from D1C1 until progression and end of treatment visit.						
Pregnancy test[7]	X ≤ 7 days)							
12-lead ECG[8]	X		X[8]		X[8]			
Urinalysis	X					X		
Echocardiogram/MUGA[9]	X					X		
Recording of adverse events	X	X	X	X	X	X	X	
Recording of concomitant medication	X	X	X	X	X	X	X	
Sunitinib dispensation record		X						
Dose record/sunitinib compliance		X	X	X	X			
TH-302 administration			X		X			
CT image tumour measurements[10]	X	Every 8 weeks from D1C1 until progression and end of treatment visit.						
Collection and freezing of blood sample for marker tests[11]	X							
Shipment of tumour sample for marker tests[12]	X							
Post-study survival[13]								X

1. Patients will be required to sign two copies of the informed consent form. The patient must indicate his/her degree of consent with respect to the use of biological samples.

2. Medical record and demographic data: Includes but is not limited to: specific cancer history, date of diagnosis, type of primary tumour with histological diagnosis, previous surgical procedures and dates, and any other relevant medical history within the last 6 months.

3. Physical examination: weight, height, body surface area and vital signs: heart rate, blood pressure, body temperature.

4. Haematology and haemostasis: haematocrit, haemoglobin, platelet count, white blood cell count, red blood cell count, neutrophil count and lymphocyte count. Coagulation will include prothrombin time (PT), the international normalised ratio (INR) and activated partial thromboplastin time (APTT). This will be conducted at the baseline visit (≤ 7 days) and at each pre-treatment visit (+/- 3 days prior to day 8 and +/- 1 day prior to day 22 of each cycle). It will also be conducted +/- 1 day prior to day 15 to ensure a weekly follow-up of the patients.

5. Clinical chemistry: AST, ALT, GGT, alkaline phosphatase, direct and total bilirubin, urea, calcium, chloride, creatinine, glucose, LDH, phosphorus, magnesium, potassium, sodium, albumin at the baseline visit (≤ 7 days) and at each pre-treatment visit (+/- 3 days prior to day 8 and +/- 1 day prior to day 22 of each cycle). It will also be conducted +/- 1 day prior to day 15 to ensure a weekly follow-up of the patients.

6. Enolase 1, chromogranin A (or peptide secreted functionally) tumour markers at baseline visit, every 8 weeks (+/- 1 week) and at the end-of-study visit.

7. Urine and blood pregnancy test in female patients of childbearing age. This will be conducted within 7 days prior to the day 1 visit and whenever pregnancy is suspected.

8. 12-lead electrocardiogram: before every test, the subject must be at rest for approximately 10 minutes. The subject should be in a semi-lying or supine position; the same position must be adopted for all subsequent ECG tests.

In the first cycle, an ECG will be performed at day 8 and at day 22 immediately after completion of the TH-302 infusion. Thereafter, an ECG will be performed at the discretion of the investigator

9. Baseline and end-of-study visit echocardiogram, and if clinically indicated.

10. Thoracic, abdominal, and pelvic CT scan within 28 days prior to study enrolment and subsequently every 8 +/- 1 weeks and at the end-of-study visit. For tumour reassessments, the same exploratory technique used in the baseline examination must be adopted. A baseline bone scan may be performed within 28 days prior to day 1 of the first cycle, if there is a clinical suspicion of bone metastases. In the event of bone metastases, a reassessment bone scan will be performed every 12 weeks until week 24 and thereafter every 24 weeks until the end of treatment. Margin of +/- 14 days with reference to the scheduled visit.

An MRI may only be performed in exceptional circumstances and only in cases when a CT scan is not possible.

11. Blood sample for the analysis of genetic markers that will be sent to [redacted]. Only the tubes from the baseline visit will be sent.

12. Paraffin-embedded tumour sample for marker analysis that will be sent to [redacted]

13. Determination of overall survival of patient (living/death/lost to follow-up). According to the site's usual practices, until the end of the trial.

ANNEX 2. WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS (GEP-NETs)

WHO	Tumour	Grade	Mitosis (10 HPF)	Ki67 index (%)
WHO 1	**NET**	G1	< 2	≤ 2
WHO 2	**NET**	G2	2-20	3-20
WHO 3	**NEC**	G3	> 20	> 20
	MANEC **Tumour-like lesions**			

WHO: World Health Organization; NET: Neuroendocrine tumour; NEC: Neuroendocrine carcinoma; HPF: High-power Fields.

ANNEX 3. PATIENT PERFORMANCE STATUS SCALE: ECOG SCALE.

GRADE	
0	Fully active, able to perform all pre-disease activities without restrictions.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a sedentary nature.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Out of bed > 50%.
3	Capable of only limited self-care and personal hygiene. Bedbound > 50%.
4	Completely disabled. Incapable of self-care. Totally confined to bed or chair.
5	Dead.

ANNEX 4. NON-PERMITTED CONCOMITANT MEDICATION

I. Drugs that cause QT interval prolongation, with the risk of developing polymorphic ventricular tachycardia

Amiodarone	Domperidone	Pentamidine
Arsenic trioxide	Droperidol	Pimozide
Astemizole	Erythromycin	Probucol
Azithromycin	Flecainide	Procainamide
Chloroquine	Halofantrine	Quinidine
Chlorpromazine	Haloperidol	Sotalol
Cisapride	Ibutilide	Sparfloxacin
Citalopram	Levomethadyl	Terfenadine
Clarithromycin	Mesoridazine	Thioridazine
Disopyramide	Methadone	Vandetanib
Dofetilide	Moxifloxacin	

II. Strong or moderate CYP3A4 inducers

CYP3A4 enzyme-inducing drugs

Bosentan	Glutethimide	Rifabutin*
Carbamazepine*	St John's Wort*	Rifampicin*
Dexamethasone	Modafinil	Rifapentine*
Efavirenz	Nafcillin	Sulfadimidine
Felbamate*	Nevirapine*	Sulfinpyrazone
Phenobarbital*	Omeprazole	Troglitazone
Phenytoin*	Primidone*	Troleandomycin

*Strong CYP3A4 enzyme inducers

CYP3A4 enzyme-inhibiting drugs

Amprenavir*	Fosamprenavir*	Grapefruit or any product containing grapefruit*
Atazanavir*	Gestodene	Posaconazole*
Boceprevir*	Indinavir*	Ritonavir*
Clarithromycin*	Itraconazole*	Saquinavir*
Clotrimazole	Ketoconazole*	Telaprevir*
Conivaptan*	Lopinavir*	Telithromycin*
Delavirdine*	Mibefradil* (withdrawn USA)	Troleandomycin
Diltiazem	Miconazole*	Verapamil*
Erythromycin*	Nefazodone*	Voriconazole*
Ethinylestradiol	Nelfinavir*	Grape or any product containing grape*
Fluoxetine	Nicardipine	

* Strong CYP3A4 enzyme inhibitors.

ANNEX 5. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI.

Ethical Principles for Medical Research Involving Human Subjects.

Adopted by the
18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification, added by the WMA General Assembly, Washington 2002
Note of Clarification, added by the WMA General Assembly, Tokyo 2004
59th WMA General Assembly, Seoul, Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that: "A physician shall act in the patient's best interest when providing medical care".

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are under-represented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be

impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention.

Patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.

This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ANNEX 6. Serious Adverse Event Report Form

ANNEX 7. Pregnancy Report Form.

ANNEX 8. Sample shipment form

I. **Tumour block. Hospital** [redacted]

"A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated advanced pancreatic neuroendocrine tumours (pNET) previously untreated. Prognostic and predictive biomarker research". Determination of biomarkers: [redacted] TUMOUR BLOCK ☐ Site of origin: Investigator of the site of origin:	PATIENT CODE DATE OF SAMPLE COLLECTION LOCATION OF TUMOUR BLOCK ANATOMOPATHOLOGICAL DIAGNOSIS

II. Plasma sample for [redacted]

"A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated advanced pancreatic neuroendocrine tumours (pNET) previously untreated. Prognostic and predictive biomarker research". Determination of biomarkers: [redacted] BLOOD SAMPLE ☐ Site of origin: Investigator of the site of origin:	PATIENT CODE ☐☐☐☐ DATE OF SAMPLE COLLECTION ☐☐☐☐ LOCATION OF TUMOUR BLOCK ANATOMOPATHOLOGICAL DIAGNOSIS

ANNEX 9. Informed Consent

PATIENT INFORMATION SHEET/
INFORMED CONSENT FORM

Study title: A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated advanced pancreatic neuroendocrine tumours (pNET) previously untreated.
Prognostic and predictive biomarker research.

Study code: GETNE-1408

Sponsor: GETNE

Investigator Details: _____

Hospital: _____

Contact telephone, in case of any doubts: _____

Dear patient,

We are inviting you to participate in this clinical trial because you have been diagnosed with a pancreatic neuroendocrine tumour. Below we explain, in a summarised form, information about the study which you are being invited to participate in, the purpose of which is to understand the activity and safety of sunitinib and TH-302 treatment in combination, in patients with your disease. The activity and safety of the treatment proposed here will be studied by analysing specific markers in your tumour and blood samples, as it is possible that they indicate the progression of your disease and the treatment response (targeted molecular analysis).

TH-302 is an investigational drug which has not yet been approved for marketing by the Spanish Medicines Agency. It will be provided by Threshold, which supports this project.

A total of 43 patients will participate in the study. Your participation in the study is entirely voluntary, and the relationship with the medical team looking after you will in no way be affected should you decide not to participate. You are free to withdraw consent for participation in the study at any time, without having to provide justification and without it affecting your ongoing medical care. Should you not wish to receive the proposed study treatment, your doctor will inform you of alternative treatment options available for your particular case. You are hereby reminded that you may speak with third parties before signing this form. Please do not hesitate to speak with your doctor should you have any questions.

This study has been issued a favourable opinion by the corresponding Independent Ethics Committee (IEC) and has been approved by the Spanish Agency of Medicines and Medical Devices (AEMPS), pursuant to current legislation, Royal Decree 223/2004, of 6 February, which regulates clinical trials with medicinal products. It will be conducted in compliance with the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines. The sponsor undertakes to ensure compliance with the principles established by Law 14/2007 regarding Biomedical Research, and Royal Decree 1720/2007, which approves the regulation implementing Organic Law 15/1999.

Your participation in the clinical trial will not involve any expense for you over and above what you would incur if you did not participate in it. Sunitinib and TH-302 will be provided to you free of charge by the Sponsor. Visits to the site, examinations and other procedures related to the study will not cost you anything. If you experience any problem which requires medical attention, your doctor will examine you and will provide you with medical care.

The sponsor may cancel the study due to various reasons. In this case, you will be informed of this circumstance.

INTRODUCTION

Pancreatic neuroendocrine tumours represent a heterogeneous group of tumours. The proportion of the population presenting this type of tumour has increased in recent years. Treatment goals of current treatments in the management of this type of tumour are symptom control and limiting tumour growth. If you agree to participate in this study, specific biological markers from tumour tissue and blood samples taken at the baseline visit will be analysed, which could help predict the course of pancreatic neuroendocrine tumours and the response to the treatment that you will be administered (targeted molecular analysis). It is unlikely that the study results will benefit you directly. However, the results derived from this study could benefit other patients who suffer from this disease by allowing those patients who are going to benefit from this treatment to be selected.

Pancreatic neuroendocrine tumours are characterised by the formation of blood vessels (angiogenesis) that allow the tumour cells to continue to grow. For this reason, research has focussed in recent years on the development of drugs which inhibit the formation of new blood vessels, such as sunitinib, which has already been approved in the USA and Europe for the treatment of pancreatic neuroendocrine tumours because of its proven activity and survival benefit. However, certain tumour cells can survive this low-oxygenation setting caused by the destructive action of sunitinib on the blood vessels. Based on this hypothesis, the potential role of TH-302, a prodrug active in conditions of severe hypoxia (low oxygen levels) that causes cell death, has been investigated. The results have shown anti-tumour activity of this drug in combination with other chemotherapeutic agents and other drugs, such as sunitinib.

METHODOLOGY

Your doctor will ask you questions about your medical records, in particular about your personal history and concomitant medication. You will undergo a comprehensive study prior to entry into the trial, which will include the following procedures: complete physical examination (height, weight and vital signs), measurement of the functional status index, an electrocardiogram, echocardiogram, a complete laboratory tests, including urinalysis, pregnancy test and radiological tests to understand the circumstances of your disease.

If you agree to participate in the study, a tumour tissue sample that has already been extracted for your diagnosis will be sent to [redacted], and it will be necessary to take one blood sample (10 ml) at the start of the study that will be sent to [redacted]. There, a molecular analysis will be conducted to investigate its relationship to treatment response. By signing this consent form, you agree to this collection, processing and transfer.

During the treatment period, you must visit the hospital every week to evaluate tolerability and treatment response. Every 8 weeks, a full reassessment of tumour progression will be conducted. The investigators may discontinue the treatment for safety reasons and/or lack of compliance, unacceptable toxicity, growth of the disease, or if your doctor considers that it is in your best interest to receive another treatment for your disease, which is different from the study treatment.

Once treatment has ended, irrespective of the reason, you must attend an end-of-study visit. This visit will comprise another comprehensive study incorporating vital signs, medical history (collection of relevant clinical data by your doctor, including personal and family history regarding the disease), a physical examination, and comprehensive laboratory and radiological tests. Thereafter, you will be examined approximately every 8-12 weeks to check on your health and disease status.
It is important to attend all the scheduled study visits and to tell your doctor should you experience any incident or side effects.

At the end of your participation in the clinical trial, you will receive the best and most suitable treatment available for your disease, in the opinion of your doctor. In this situation, it is possible that you may not continue to be administered the study medication.

STUDY TREATMENT

This study proposes just one treatment regimen. Once you have agreed to participate in the trial, you will be registered, using the enrolment list, and you will be assigned an enrolment number which will identify you throughout the clinical trial. You will receive the treatment regimen proposed for this trial (TH-302 + Sunitinib) in the form detailed below:

TH-302:
Prior to the administration of TH-302, the doctor will perform laboratory tests and the appropriate assessment procedures to check that it is safe for you to receive the treatment. TH-302 is administered intravenously on days +8 and +22 of each 28-day cycle (it will not be administered on day +1 or on day +15 of the cycle) at the Day Hospital over 30-60 minutes. During infusion of the drug, you must check for any signs or symptoms (itching, stinging, redness, pain) that might be suggestive of extravasation of the drug (leakage of the fluid from the blood vessel that contains it), in order to proceed with proceeding to interrupt treatment early and initiate the appropriate therapeutic measures.

Sunitinib:
Prior to the administration of Sunitinib, the doctor will perform laboratory tests and the appropriate assessment procedures to check that it is safe for you to receive the treatment. Sunitinib is administered daily at a dose of 37.5 mg per day for 28 consecutive days, which constitutes a treatment cycle. Sunitinib will be dispensed by the hospital pharmacy, at a frequency to be determined by your doctor.

ALTERNATIVE TREATMENTS AVAILABLE

The standard treatment for your disease may include one or several of the agents listed below: Streptozotocin, Doxorubicin, Temozolomide, Capecitabine, Sunitinib and Everolimus, either as single agents or in combination.

Regimens with Streptozotocin and 5-Fluorouracil or Adriamycin are particularly used in the chemotherapy of well-differentiated tumours.

In high-grade, poorly-differentiated tumours, the standard treatment regimen comprises the combination of Cisplatin/Carboplatin and Etoposide.

In recent years, the results from studies with Sunitinib and Everolimus in pNET patients has broadened the therapeutic horizon. The benefit demonstrated has led to the approval of both drugs by the European and American Medicine Agencies.

In this case, your doctor will inform you of the advantages and disadvantages of these medicines, and together you will decide on the best alternative. Your doctor will also inform you of the consequences of not administering any treatment at all.

RISKS AND BENEFITS

Direct benefits due to your participation in this clinical trial cannot be guaranteed.

A reduction, stabilisation or, in very exceptional circumstances, the disappearance of your tumour could be obtained with any of the standard treatments which are currently available. However, in the treatment of pancreatic neuroendocrine tumours, such as the one you present, the main objective is the duration of disease control. We therefore hope to be able to improve the control of this disease with the treatment proposed in this study.

The results of this study may help investigators to gain a better understanding of the advantages and disadvantages of using this treatment in patients suffering from your condition, which may benefit patients with the same disease in the future.

Besides having desirable effects, medicines may also have undesirable effects (side effects). The medications given may have no side effects, or one or more side effects. As a general rule, we recommend you contact your doctor if you experience any symptoms as he/she will be better able to assess their importance and what is best for you.

In the case of TH-302, the most commonly-reported side effects are: fatigue, nausea, vomiting, mucositis, skin abnormality, immunosuppression, anaemia and reduced platelet count.

The most frequently detected side effects with Sunitinib are: fatigue, increased blood pressure, thrombosis or bleeding, oral aphthous ulcers, immunosuppression, anaemia, changes in bowel movements or a reduced platelet count.

Regarding **pregnancy and lactation:**

Women

It is not known whether the medicine under study, TH-302, affects breast milk or the foetus. For this reason, both women who are breastfeeding and pregnant women cannot take part in this study. Given that the drugs in this study may affect the foetus, you must not fall pregnant or breastfeed a child while you are participating in the study.
If you are fertile, you must have a negative pregnancy test before being enrolled in the study.

Unless you are sterile due to surgical or other reasons, you should use two effective birth control methods, accepting this condition when you sign the consent form. This control must be maintained throughout the treatment period and for at least 6 months after you have received the last dose of the drug. You must use these methods of birth control unless you maintain complete sexual abstinence.

Male patients

It is not known whether TH-302 affects sperm. For this reason, and given the risks, you must avoid fathering a child during your participation in this study. Even if you have been surgically sterilised (e.g. vasectomy), you must agree that if you maintain sexual relations you will do so using a barrier contraception method (latex condom with spermicide) from the moment you sign the consent form, throughout the study treatment period and for up to 6 months after having received the last dose of the drug.

All participants (Males or Females)

If you think you have fallen pregnant, or that you have made your partner pregnant during the study, you must inform the study doctor immediately. He/she will explain the possible risks for the foetus and the various options for continuing with the pregnancy or not. If you fall pregnant during this study, the treatment with the drug that you are receiving will be discontinued and it is possible that you will be withdrawn from some study procedures, but not from the follow-up carried out by the study doctor. The study doctor will request permission to stay in contact with you throughout the duration of your pregnancy.

Any new information discovered during your participation with regard to the trial drugs that may affect your decision to continue participating in the trial will be communicated to you as soon as possible by your doctor and, if necessary, a new consent form will be signed.

INSURANCE

The Sponsor of the clinical trial (*Grupo Español de Tumores Neuroendocrinos* - Spanish Task Force Group for Neuroendocrine Tumours) has taken out a civil liability insurance policy that complies with the provisions of current legislation (RD 223/2004) with the company HDI Hannover International, with policy no. 130/001/009658, which will provide compensation and indemnity in case your health is impaired or lesions occur.

CONFIDENTIALITY

Your medical documentation may need to be made available to others working on behalf of the sponsor, to members of the Independent Ethics Committee and to Regulatory Health Authorities.

By signing this consent form, you grant this access for this study. However, the Sponsor will take steps to protect your personal information and will not include your name on any form, report, publication or future disclosure by the Sponsor. You will be identified by a code within the study. If you withdraw from the study, we will not collect any further personal information about you, but it may be necessary to continue using the information already collected. By taking part in this study, you agree not to restrict the use of the data or results derived from this research.

The Sponsor undertakes to ensure compliance with the principles established by Organic Law No. 15/1999 on the protection of personal data and to facilitate the practice of the rights of access, rectification, cancellation and opposition. To exercise these rights, you must contact the Site where the trial was conducted. If study data is transferred to third parties (other countries), at least the same level of data confidentiality as that exercised in Spain will be maintained.

SUB-STUDY WITH BIOLOGICAL SAMPLES

Introduction:

Human body cells contain a wide variety of substances, including genetic material. The genetic material is like an “instruction book” which serves to duplicate cells, among other things. It also contains the biological information which directs the development of an individual. This genetic material is found inside cells, arranged in structures called chromosomes. Each small part of the genetic material that forms the chromosomes is called a gene. Genes tell the cell how to make proteins and other substances that organise the biological work of each cell. Genes also determine some characteristics of individuals and are sometimes responsible for some people developing certain diseases and responding to specific treatments with medicines. When genetic material is used to investigate the causes of diseases or to understand how people respond to medicines, this research is called genomic research. It is used to help develop new treatments and diagnostic tools.

We are contacting you to request your consent for the extraction and use of your samples in order to perform genetic analyses to identify genes or genetic markers (simple tests used on blood or tumour samples which provide crucial information for the diagnosis and for a better treatment selection), of which you are a carrier and which may determine your response to the treatment regimen proposed in the previously-described clinical trial.

It is our intention that you receive correct and sufficient information so that you can evaluate and judge whether or not to participate in this sub-study. To this end, please read this information sheet carefully and we will clarify any doubts you may have following this explanation. You may also discuss it with whomever you wish.

Objective of the sub-study:

The objective of this sub-study with biological samples is to study specific biomarkers (simple tests used on blood or tumour samples), which will allow patients who will benefit the most from the different treatment options for pNET to be selected.

Sample collection:

A sample of your tumour will be coded and sent to [redacted] where the determinations of this sub-study will be carried out.

Once you have been enrolled in the trial and before starting treatment, approximately 10 ml of blood will be taken from you. This will be frozen, coded and sent to [redacted], for the sub-study determinations to be carried out.

Use and destination of samples at the end of the research:

Samples will only be used by the Sponsor and/or investigators working for the Sponsor, and only for the research described above. Samples will be stored in the same laboratories where the determinations are carried out. 6 years after the date the blood sample is drawn, genetic information derived from the study will be made public and may be consulted, but your identity will be kept confidential so that your genetic data cannot be linked to you. After this period, the genomic material, i.e. the samples, will be destroyed or kept for subsequent use in this line of research or any further research, provided that you sign your express authorisation for storage of this material in a biobank (you will be informed by your doctor of the details of the receiving biobank as soon as the specific information is available). Under no circumstances and at no time will samples be used for direct profit, either by the sale of the material itself or the sale of the rights to perform studies on said samples.

Expected benefits

Direct benefits due to your participation in this sub-study with samples cannot be guaranteed.
The blood and tumour samples of patients participating in clinical trials, such as GETNE 1408, are extremely important, as they are linked to accurate clinical information of these patients. This information, including whether the cancer responds to treatment or if it reappears in the future, can be used together with the information discovered in the laboratory in order to help answer questions about this type of cancer and its treatment

Drawbacks and risks of participating in the sub-study

Obtaining the tumour tissue does not pose any additional risk to you as a sample that will be obtained/was obtained at the time of surgery for your disease will be used.

The blood sample will be taken following the same procedure as that used to take other blood tests. There may be stinging and swelling on your skin at the puncture site and a bruise may form at the puncture site. The risks of this practice are the same as those that you would be exposed to if you were not participating in the study.

If necessary, you may be contacted after the study in order to gather new data and obtain further samples.

Confidentiality

The processing, reporting and transfer of personal data from all the research participants will be in compliance with the provisions of Organic Law 15/1999, of 13 December, on personal data protection, and its implementing regulation. In line with this legislation, you are entitled to access, modify, object to and cancel said data, for which you should contact your study doctor.

Your data and samples collected for the study will be identified by a code, and, throughout the course of the study, this code will be the only way in which your data will be linked to the study information. Only your clinical trial doctor/collaborators will be able to link this data with you and your medical records. Therefore, your identity will not be revealed to anyone, except in the case of a medical emergency or a legal requirement.

Access to your personal information will be restricted to the study doctor/collaborators, health authorities, the Independent Ethics Committee, and personnel authorised by the sponsor, when they need to check the data and study procedures. However, they will always maintain the confidentiality of such information in accordance with current legislation. This check will be performed, as far as possible, in the presence of the principal investigator or collaborators responsible for guaranteeing the confidentiality of medical record data pertaining to subjects participating in the clinical trial.

Only the data collected for the clinical trial that contains no information that directly identifies you (e.g. name and surnames, initials, address, social security number, etc.) will be disclosed to third parties or other countries. If this disclosure occurs, it will be for the study purposes described and the degree of confidentiality and requirements set forth in current legislation in Spain as a minimum will be guaranteed.

If you decide to participate in the study with biological samples, the information will be collected and entered into the study database. The scientific personnel and doctors of GETNE and individuals who work with the people carrying out the study may need to examine your medical record to ensure that the study is being conducted correctly. However, your data will be kept confidential in accordance with Spanish legislation.

More information

This sub-study complies with Law 14/2007, of 3 July, on Biomedical Research and Royal Decree 1716/2011, of 18 November, which establishes the basic requirements of authorisation and functioning of biobanks used for biomedical research and the handling of biological samples of human origin and they regulate the functioning and organisation of the National Register of Biobanks for biomedical research.

In accordance with this regulation, you can request access to the genetic information obtained from your samples in this study through your study doctor. It is important to know that this research data is exploratory and/or preliminary. It may have no impact on your wellbeing and should not be used to guide your diagnosis, prognosis or medical care. This type of preliminary or exploratory data will not be able to be individually interpreted by your doctor or any specialist, so no individual advice associated with it will be given. If you decide to request your genetic data, ask your doctor about the implications that this information may have for you and your family.

It is possible that results which may have an impact on both you and members of your family will be obtained from conducting this study. You may refuse to be notified of these results. In addition, if you decide not to be informed of these results, your study doctor may contact members of your family in the event that the results might affect them. If you decide to be notified of results of the study that may affect members of your family, you will be advised to inform them.

If you would like to know the results, your doctor will provide you (or will tell you where you can be provided) with genetic counselling for both you and your family members.

Both this document, and the research sub-study, have been reviewed and issued a favourable opinion by your Hospital's Ethics Committee.

You will be given a copy of this document as part of the files of this research project, separate from the findings of the research project. Thank you for having read this document and for considering participating in the study. Please do not hesitate to contact your doctor should you have any queries.

If you agree to participate, please sign this sheet, which will be kept in your medical record.

WRITTEN INFORMED CONSENT FORM

Study title: A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated advanced pancreatic neuroendocrine tumours (pNET) previously untreated.
Prognostic or predictive biomarker research.

I, …… (full name)

- Have been informed of this study.
- Have read and understood the information sheet given to me.
- Have been able to ask questions about the study and have received satisfactory replies to my questions.
- Accept that Sponsor employees or people acting on the Sponsor's behalf and the competent authorities can review my medical record for data verification purposes.
- Consent to the collection and processing of my personal data according to the conditions specified in the Information Sheet.
- Have received a copy of this document.

I have spoken to: ……..... Contact telephone no.: .....
(full name of the investigator)

- Understand that my participation is voluntary.
- Understand that I may withdraw from the study:
  - Whenever I want.
  - Without having to give explanations.
  - Without this having any effect on my medical care.

☐ I freely grant my consent to participate in the study.

☐ I wish to donate tumour tissue samples for the corresponding analysis.

☐ I wish to donate a blood sample for the corresponding analysis.

☐ I consent to my sample being used for research purposes in this and other lines of research.

Participant

(full name) (signature) (date)

Investigator (the person obtaining the consent must sign and date the form at the same time as the participant)

(full name) (signature) (date)

You will be given a signed and dated copy of this consent form. First copy or original for the investigator.

LEGAL REPRESENTATIVE'S ORAL INFORMED CONSENT

Where applicable, for example in subjects with severe dementia, state the name and signature of the subject's legal representative.

Study title: A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated advanced pancreatic neuroendocrine tumours (pNET) previously untreated.
Prognostic or predictive biomarker research.

I, …… (full name) as ……(relationship to the participant) of …….... (name of participant)

- Have been informed of this study.
- Have read and understood the information sheet given to me.
- Have been able to ask questions about the study and have received satisfactory replies to my questions.
- Accept that Sponsor employees or people acting on the Sponsor's behalf and the competent authorities can review my medical record for data verification purposes.
- Consent to the collection and processing of my personal data according to the conditions specified in the Information Sheet.
- Have received a copy of this document.

I have spoken to: ……..... Contact telephone no.: .....
(full name of the investigator)

- Understand that my participation is voluntary.
- Understand that I may withdraw from the study:
  - Whenever I want.
  - Without having to give explanations.
  - Without this having any effect on my medical care.

I freely give my consent to take part in the study.

☐ I wish to donate tumour tissue samples for the corresponding analysis.

☐ I wish to donate a blood sample for the corresponding analysis.

☐ I consent to my sample being used for research purposes in this and other lines of research.

Representative

(full name) (signature) (date)

Investigator (the person obtaining the consent must sign and date the form at the same time as the participant)

(full name) (signature) (date)

You will be given a signed and dated copy of this consent form. First copy or original for the investigator.

ORAL INFORMED CONSENT BEFORE WITNESSES

If the subject or the subject's legal representative cannot read, the signature of an impartial witness is required, and in this event the following form must be signed.

Study title: A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated advanced pancreatic neuroendocrine tumours (pNET) previously untreated.
Prognostic or predictive biomarker research.

I, …… (full name) hereby declare under my responsibility that …….... (full name of participant)

- Has been informed of this study.
- Has been able to ask questions about the study and I have received satisfactory answers to my questions.
- Accepts that Sponsor employees or people acting on the Sponsor's behalf and the competent authorities can review my medical record for purposes of data verification.
- Consents to the collection and processing of my personal data according to the conditions specified in the Information Sheet.
- Has received a copy of this document.
- Has been informed of this study.
- Has read and understood the information sheet given to me.
- Has been able to ask questions about the study and I have received satisfactory answers to my questions.
- Accepts that Sponsor employees or people acting on the Sponsor's behalf and the competent authorities can review my medical record for purposes of data verification.
- Consents to the collection and processing of my personal data according to the conditions specified in the Information Sheet.
- Has received a copy of this document.

Has spoken to: ……..... Contact telephone no.: .....
(full name of the investigator)

- Understands that his/her participation is voluntary.
- Understands that he/she can withdraw from the study:
  - Whenever he/she wants.
  - Without having to give explanations.
  - Without this having any effect on his/her medical care.

☐ I freely grant my consent to participate in the study.

☐ I wish to donate tumour tissue samples for the corresponding analysis.

☐ I wish to donate a blood sample for the corresponding analysis.

☐ I consent to my sample being used for research purposes in this and other lines of research.

Witness

(full name) (signature) (date)

Investigator (the person obtaining the consent must sign and date the form at the same time as the participant)

(full name) (signature) (date)

You will be given a signed and dated copy of this consent form. First copy or original for the investigator.