Name of Sponsor/Company: *Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)*	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	***(For National Authority Use Only)***
Name of Finished Product: *Sunitinib*		
Name of Active Ingredient: *TH-302*		

Title of Study:	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. EudraCT: 2014-004072-30
Investigators:	1. Enrique Grande /Teresa Alonso 2. Rocío García Carbonero 3. Marta Benavent 4. Jaume Capdevila 5. Alexandre Teulé Vega 6. Ana Custodio 7. Carlos López 8. Isabel Sevilla 9. Encarnación González 10. Javier Munarriz Ferrandis
Study centre(s):	1. Hospital Universitario Ramón y Cajal 2. Hospital Universitario 12 de Octubre 3. Hospital Universitario Virgen del Rocio 4. Hospital Universitari Vall d'Hebron 5. ICO L'Hospitalet 6. Hospital Universitario La Paz 7. Hospital Universitario Marqués de Valdecilla 8. Hospital Universitario Virgen de la Victoria 9. Hospital Virgen de las Nieves 10. Hospital Provincial de Castellón
Publication (reference):	*Interim analysis:* ● Grande E, Castellano DE, Custodio AB, García-Carbonero R, González E, López-López C, Munarriz J, Sevilla I, Teulé A, Benavent-Viñuales M, Alonso-Gordoa T, Gajate-Borau P, Palacios J, Capdevila J. ***A phase II trial to assess the activity and safety of the hypoxia-activated prodrug evofosfamide (TH302) in combination with sunitinib in patients with disseminated Grade 1 and 2 pancreatic neuroendocrine tumors (pNET) as a first-line approach: The GETNE-1408 Trial.*** J Clin Oncol. 2016;34(suppl_4):479.

	● Grande E, López C, Alonso-Gordoa T, Benavent M, Capdevila J, Teulé A, Custorio A, Sevilla I, Gajate P, Molina-Cerrillo J, Hernando J, García-Carbonero R. ***The SUNEVO (GETNE-1408) trial to evaluate the activity and safety of the combination of SUNitinib with EVOfosfamide (TH-302) in patients with G1/G2 metastatic pancreatic neuroendocrine tumours (pNETs) naïve for systemic treatment. A Phase II study of the Spanish Task Force Group for Neuroendocrine and Endocrine Tumours (GETNE).*** J Clin Oncol. 2019; 37(suppl_15):4105-4105. ● Grande E, López C, Alonso-Gordoa T, Benavent M, Capdevila J, Teulé A, custorio A, Sevilla I, Gajate P, Molina-Cerrillo J, Hernando Cubero J, García-Carbonero R. ***SUNitinib with EVOfosfamide (TH-302) for G1/G2 metastatic pancreatic neuroendocrine tumours (pNETs) naïve for systemic treatment. The SUNEVO phase II trial of the Spanish task force group for neuroendocrine and endocrine tumours (GETNE).*** Ann Oncol. 2019;30:566. ● Santos M, Lanillos J, López C, Alonso-Gordoa T, Benavent M, Capdevila J, Teulé A, Custodio A, Sevilla I, García-Carbonero R, Rodríguez-Antona C, Grande E. ***Molecular correlation of the activity of evofosfamide (EVO) in combination with sunitinib (SUN) in pancreatic Neuroendocrine Tumors (pNETs) in the SUNEVO GETNE Trial.*** Poster accepted for presentation at the 17th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease. 2020. *Final results:* Pending for publication	
Studied period (years):	5 years	***Phase of development:*** Therapeutic exploratory (II)
Date of first enrolment:	11-may-2015	

Date of last completed:	10-jan.-2020	
Objectives:	*Primary:* 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). *Secondaries:* ● 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.	
Methodology:	This was a prospective, single-arm, open-label phase II study led by the Spanish Group for Neuroendocrine and Endocrine Tumours (GETNE), that has been conducted in 10 centers across Spain, aimed to evaluate the efficacy and safety of EVO plus SUN in patients with well- and moderately-differentiated metastatic pNETs who were naïve to systemic treatment other than somatostatin analogues. The study also included a serological biomarker analysis to investigate its clinically beneficial prognostic and predictive role. A Simon two-stage optimal design was used, considering a minimum of 3 responses in the first 18 pts in order to start with the second stage (power =0.80, alpha= 0.05). Evofosfamide was initially administered at doses of 340 mg/m^2 by intravenous infusion on days 8, 15 and 22, while sunitinib was concomitantly given orally at 37.5 mg per day continuously from day 1 through to day 28 (28-days treatment cycle). Continuous safety monitoring by the study experts scientific committee led to modifications on the treatment scheme after a high number of treatment	

	related-adverse events, with recommendation of administering evofosfamide only in days 8 and 22. As per protocol, the study treatment was intended to continue until evidence of confirmed radiological progression by to RECIST 1.1 criteria. Treatment discontinuation was considered when patients best interests could not be guaranteed or at the discretion of the investigator (these decisions balance the maximum benefit with acceptable tolerability). In all cases, patients would continue taking the study treatment only when they experience clinical benefit. The trial was primarily aimed to assess the ORR based on the disease evaluation performed every 8 weeks, as the cumulative percentage of patients with confirmed complete response (CR) or partial response (PR), based on radiological imaging, according to RECIST 1.1 criteria throughout the study. Confirmed response is defined as that persisting in a repeated imagining test performed at ≥ 4 weeks after the initial documentation of response. Other efficacy variables included PFS, TTP (time between the start of treatment and PD), DoR (time between the best overall response and PD and or death and OS (time between the start of treatment and death). Safety was evaluated based on type, frequency, and intensity of overall adverse events and those related to the combination treatment. Safety-related incidents on treatment compliance were also analyzed. Biomarkers study was developed through analyses of tumor DNA from 10 FFPE tumor samples were successfully sequenced with an enrichment panel (Nimblegen, Roche) including 42 cancer-related genes and TERT promoter region. Median coverage was 793x. Coding non-synonymous and loss-of-function variants were considered for the analysis. Final analysis included tumor samples from the 10 patients with NGS results. Target next generation sequencing of tumor DNA was used to sequence the full coding region plus the splice sites of 42

	genes plus TERT promoter region using Nimblegen, SeqCap EZ HyperCap Target Enrichment (Roche) for library production and sequencing in a 100bpx2 output mode in a HiSeq (Illumina). Somatic variant calling was done using Mutect2 from GATK (v.4.0.5.1). The variants present in gnomAD with an allele frequency >0.0001 were not considered further, as they were potentially germline. Coding non-synonymous and loss-of-function variants allele frequency≥0.15 were considered for the analysis. Results presented here are calculated based on the intention-to-treat sample (for efficacy outcomes); safety, on the other hand, has been analysed considering all patients with at least one dose of the investigational product. Data has been considered from first patient's inclusion to database close-out (March 15, 2019).
Number of patients	
● Planned:	43
● Analysed:	17
Diagnosis:	Metastatic pancreatic neuroendocrine tumours
Main criteria for inclusion:	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.
Test product	

• **Dose:**	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.
• **Mode of administration:**	Orally and intravenous
• **Batch number:**	Not applicable
• **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.
Reference therapy	*Not applicable*
• Dose:	-
• Mode of administration:	-
• Batch number:	-
Criteria for evaluation	
• Efficacy	• Objective response rate (ORR) • Progression-free survival (PFS) • Time to progression (TTP) • Duration of response (DoR) • Overall survival (OS)
• Safety	• Safety Analysis • Adverse Events
• Biomarkers	Somatic mutations
Statistical methods:	All results are presented using intention-to-treat analysis. For continuous variables, mean, standard error (for efficacy variables), standard deviation (for other measurements), median, minimum and maximum (range), were considered. Categorical variables are presented using frequencies and percentages along with confidence

	intervals at 95% (CI 95%s), if applicable. Survival was assessed with two-sided confidence CI 95%s Kaplan–Meier curves. Safety data were analysed throughout the entire study and is presented as number and proportion of each event.
SUMMARY CONCLUSIONS	
EFFICACY RESULTS	Between May/2015 and May/2018, 21 patients were screened and finally 17 were included: 64.7% male, mean (SD) age 60.8 (10.8) years; 64.7% with an ECOG performance status = 0; 64.7% with an Abbreviated Charlson comorbidity index = 2; 88.2% with histological grade 2; 47.1%, 29.4% and 23.5% with Ki-67 index >10%, >2% - 5%, and >5% - 10%, respectively). Most patients had a stage IV disease (76.5%), all 17 however with non functioning tumors and mitosis 10 HPF <2 in 35.3% and between 2 and 20 in 29.4% of patients (35.3% unknown). Median follow up was 15.74 months (m). All patients received at least one cycle of the study treatment. Dose reductions were reported in 35.3% and 100 % of patients (sunitinib and evofosfamide, respectively). The study treatment (any) was discontinued in 15 patients at data cut-off, currently 3 patients remain on treatment (one patient with sunitinib monotherapy). Further information on reasons for treatment discontinuation are reported in the safety results section of this report. The most common finding was disease stabilization (n=11; 64.6%, CI95% 42.0% - 87.4%). ORR corresponded to 17.6% (CI95% 0% - 35.8%; 1 and 2 patients with confirmed CR and PR, respectively). Median duration of response was 18.5 (range: 4.2 - 38.3) months. One of the patients with confirmed PR response after medical surgery in one of the target lesions, while one more patient who was reported as PR in the first tumor assessment died due to a diagnostic procedure, therefore was not able to confirm this outcome as per protocol specifications. Time to progression of disease (n=11) corresponded to a median of 5.3 (1.7 - 13.6) months. Estimated median PFS

	was 10.4 (CI95% 2.7-18.0) months and median OS was not reached (mean, CI95% = 32.3 months, 25.1 - 39.5).
SAFETY RESULTS	Simultaneous end of treatment was reported in 10 patients and a half of these were associated with progression for disease; toxicity was the main cause for other 4 cases, while the remaining patient died without completing the treatment as intede. Discontinuation of both treatments on different dates was observed in 4 patients, all of them caused by toxicity. Sunitinib premature end of treatment was also reported for 2 patients (because of PD) and 1 with toxicity. Safety analysis was performed considering all patients that have received at least one dose of the study treatment, until the end of study. Treatment-related adverse events were reported in 16 patients (94.1%), with fatigue as the most common finding (82.4%) considering overall toxicities, followed by oral mucositis (58.8%), neutropenia (afebrile) and diarrhea both in 52.9% and anorexia for 41.2%. When ≥ G3 adverse reactions were summarized, neutropenia (35.3%) and fatigue (17.6%) were the most frequently reported. Other frequent adverse reactions with at least a grade 3 severity were platelet count decreased, hypertension and ALT increased (all three in 11.8% of patients).
BIOMARKER RESULTS	Somatic mutations were found in MEN1 (70%), DAXX (30%), ATRX (20%), SETD2 (20%) and PTEN (10%). Mutations in the telomere maintenance genes DAXX and ATRX were concordant with mutual exclusivity. The loss of MEN1 was associated with a greater number of mutations (p=0.019). Patients with complete and partial response showed heterogeneous genetic profiles.

CONCLUSION	Sunitinib-induced hypoxia might increase the cytotoxic activity of evofosfamide in patients with metastatic G1 and G2 pNETS and naïve for systemic treatment other than somatostatin analogues (SSA), as this combination seems to have additive effect in terms of objective responses (17.6%) in patients with advanced pNETs. Responses observed were durable (median 18.5 months), however, feasibility of the combination is not possible in real conditions as concerns over toxicity arose, affecting tolerability and, so, treatment compliance. Molecular alterations of the patients in the SUNEVO trial were consistent with those previously described for metastatic pNETs. No clinical nor molecular predictors of response were observed.
Date of report	24 - march - 2020