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

Sponsor:	GETNE (Grupo Español de Tumores Neuroendrocrinos)
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SIGNATURE PAGE FOR THE STATISTICAL ANALYSIS PLAN

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Sponsor, signature and date:	10/6/20
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1. Synopsis

Type of application	
Sponsor	**GETNE (Grupo Español de Tumores Neuroendrocrinos)** París 162, Pral. 1ª. 08036, Barcelona Phone:93 451 17 24; Fax: 93 451 43 66 Contact: getne@getne.org
Clinical trial title	**"TRIAL TO ASSESS THE EFFICACY OF LENVATINIB IN METASTATIC NEUROENDOCRINE TUMORS (TALENT STUDY)."**
Protocol number	GETNE1509 (TALENT)
Study Coordinator and Principal Investigator	Dr. Jaume Capdevila Medical Oncology Department. Gastrointestinal and Endocrine Tumor Unit Vall d'Hebron University Hospital Pg Vall d'Hebron, 119-129; 08035 Barcelona Tel. +34934894350; Fax. +34932746781 jacapdevila@vhebron.net; jcapdevila@onco.cat
Expected sites	Approximately 25 sites in several countries in Europe (planned sites in Spain, Italy, United Kingdom and Austria)
Central Ethics Committee/Institutional Review Board	• CEIC Hospital Universitari Vall d'Hebron • CEIC Área 4 – Hospital Universitario Ramón y Cajal • CEIC Área 5 – Hospital Universitario La Paz • CEIC Área 11 – Hospital 12 de Octubre • Comité Ético de Investigación Clínica de Asturias • Comité Ético de Investigación Clínica de Cantabria • CEIC Hospital Universitari de Bellvitge • CEIC Euskadi • CEIC de los Hospitales Universitarios Virgen Macarena – Virgen del Rocío de Sevilla
Name and qualification of the persons in charge of Monitoring	Experior, S.L. C/ Vicente Galmés, 1A; 46139 La Pobla de Farnals (Valencia)

	Tel.: 902.105.255; Fax: 96.145.21.91
Investigational drug	**Lenvatinib** Lenvatinib will be provided as 4-size hydroxypropyl methylcellulose (HPMC) capsules in 2 strengths differentiated by color: 4-mg capsule (yellowish-red cap and body) and 10-mg capsule (yellowish-red cap with yellow body). Dosing schedule of 24 mg once a day (two 10-mg capsules + one 4-mg capsule) has been selected for continued lenvatinib development.
Trial phase	II
Objectives	Primary objective To assess the efficacy of lenvatinib on tumor objective response rate in two independent cohorts of patients with advanced neuroendocrine tumors: patients with advanced/metastatic G1/G2 pancreatic neuroendocrine tumors after progression to a previous targeted agent (cohort A), and patients with advanced/metastatic G1/G2 neuroendocrine tumors of gastrointestinal tract after failure to somatostatin analogues therapy (cohort B). Secondary objectives To determine the safety and tolerability of lenvatinib. To estimate the early tumor shrinkage rate and the deepness of response of lenvatinib in each cohort of patients. To estimate progression-free survival in both cohorts of patients. Exploratory objectives To evaluate biochemical response (changes in CgA and NSE levels) and its association with response rate and progression-free survival. To assess whether baseline tumor and blood biomarkers may be predictive of response to lenvatinib. To explore additional hypotheses related to biomarkers and relationship to lenvatinib, neuroendocrine tumors, other

	endocrine disorders and/or cancer which may arise from internal or external research activities.
Design	Prospective, international, multi-center, open label, stratified, exploratory phase II study evaluating the efficacy and safety of lenvatinib.
Primary endpoint	The primary endpoint of the study is overall response rate (ORR) by RECIST v 1.1 upon central radiologic assessment.
Study population and total number of subjects	Patients with advanced/metastatic, histologically confirmed, grade 1/2 (G1/G2) of 2010 WHO classification neuroendocrine tumors of the pancreas after progression to a previous targeted agent (cohort A) or gastrointestinal tract after progression to somatostatin analogues (cohort B). **Number of patients:** 110 patients in total (55 per each cohort).
Approximate duration of subject participation	24 months
Calendar and estimated completion dates	Recruitment Start: September 2015 End of Recruitment Period: March 2017 3rd Tumor assessment of LP (Primary Analysis): July 2017 Database Lock for Interim Analysis: October 2017 End of Follow up Period: March 2019 FPFV: September 2015 LPLV: September 2018 Clinical Study Report: September 2019

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3. Abbreviations

AE:	Adverse Event
CgA:	Chromogranin A
CR:	Complete Response
DpR:	Deepness of Response
ECG:	Electrocardiogram
eCRF:	electronic Case Report Form
ETS:	Early Tumor Shrinkage
G1:	Grade 1
G2:	Grade 2
GETNE:	Grupo Español de Tumores Neuroendrocrinos
HPMC:	Hydroxypropyl Methylcellulose
NSE:	Neuron Specific Enolase
OOR:	Objective Response Rate
OS:	Overall Survival
PFS:	Progression-Free Survival
PI:	Principal Investigator
PR:	Partial Response
RECIST:	Response Evaluation Criteria In Solid Tumors
SAE:	Serious Adverse Event
WHO:	World Health Organization

4. Study objectives and variables

4.1 *Primary objective(s) and primary variable(s)*

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

The ORR is defined as the proportion of subjects who have best overall response of CR or PR (by RECIST criteria):

$$ORR = \frac{CR + PR}{Total\ of\ patients}$$

4.2 *Secondary objective(s) and secondary variables*

The secondary objectives are:

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

Secondary variables:

- To determine the safety and tolerability of lenvatinib. Safety will be assessed by adverse events (AEs) and serious adverse events (SAEs). Echocardiogram results (LVEF reductions) and QTc (using the QTcB and QTcF values) prolongations will be examined. QTc prolongation will be examined through the adverse events.
- To estimate the early tumor shrinkage (ETS) rate and the deepness of response (DpR) of lenvatinib in each cohort of patients:
    - ETS rate is defined as 20% reduction in target lesions after the first 6 weeks of treatment (first tumor assessment).
    - DpR is defined as percentage of maximum tumor shrinkage observed at the nadir (minimum value of total sum of diameters) compared with baseline.

  To assess ETS and DpR, total sum of diameters obtained in all tumor assessments will be considered.
- To estimate progression-free survival (PFS) in both cohorts of patients. PFS is defined as the time from the date of treatment start (C1D1) to the date of first documentation of disease progression or death (whichever occurs first) using RECIST 1.1.

To evaluate PFS, it will be considered:

- Start date of study drug
- Progression disease date or death date (whichever comes first)

PFS censoring rules will follow FDA guidance in 2007 [1]:

Table A. PFS 1 (includes documented progression only)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of measured lesions	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions	Censored

4.3 *Exploratory objective(s) and variables*

The exploratory objectives are:

- To evaluate biochemical response (changes in CgA, 5-HIAA and NSE levels) and its association with response rate and progression-free survival.
- To assess whether baseline tumor and blood biomarkers may be predictive of response to lenvatinib.
- To explore additional hypotheses related to biomarkers and relationship to lenvatinib, neuroendocrine tumors, other endocrine disorders and/or cancer which may arise from internal or external research activities.

Exploratory variables:

- The changes in tumor markers (CgA, 5-HIIAA and NSE) will be analysed by cohort and significant reductions defined as 50% reduction or more regarding the baseline values will be calculated.
- The relationship between reductions and PFS and radiological response will be assessed.

The second and third exploratory objectives will be assessed in the final analysis not in the interim analysis. According to the biomarkers that are available, the analysis of these objectives will be specified.

5. Study populations

The analysis sets will be defined as follows:

- Full Analysis Set will include all allocated subjects. This will be primary analysis set for the efficacy endpoints.
- Per Protocol Analysis Set will include those subjects who were allocated and received at least one dose of the assigned study drug and had no major protocol deviations. The subjects will complete both baseline and at least one post-baseline tumor assessments (week 6). Experior will send a list of major protocol deviations to establish the per-protocol set after the close out of data base. The PI (Dr. Capdevila) will decide which patients should be excluded to define the per protocol analysis set.
- Safety Analysis Set will include all subjects who were allocated and received at least one dose of the study drug and had at least one post-baseline safety evaluation (week 6). This will be the analysis set for all safety evaluations.

6. Statistical strategy

Below are detailed the statistical aspects of the data analysis.

6.1 *Primary analysis*

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

6.1.1 *Summary statistics*

The ORR will be calculated by RECIST v1.1 upon central radiologic assessment, independently for each cohort.

Waterfall plots (2D and 3D) will be calculated to examine the changes in tumor lesions from baseline.

6.1.2 *Statistical inference*

It is not planned statistical inference.

6.2 *Secondary analysis*

The secondary analysis will be based on the Full Analysis Set and the Safety Analysis Set.

6.2.1 *Summary statistics*

Secondary endpoints will be summarized with descriptive statistics. Continuous variables will be summarized with n, NA, mean, standard deviation, median and range. Frequency counts and percentage of subjects within each category will be provided for categorical data.

First secondary objective:

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized separately by cohort.

Adverse events will be classified into standardized medical terminology from the verbatim description (investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be presented by preferred term (PT) and by system organ class (SOC).

Echocardiogram results (LVEF), and their changes from baseline will be summarized using descriptive statistics. Prolongation of QTc will be analysed using descriptive statistics and frequency tables.

The degree of exposure (dose, duration of treatment, interruptions/reductions of dose) will be assessed to determine the degree to which study safety can be assessed. These results will be presented with descriptive statistics (n, NA, mean, standard deviation, median and range).

Second secondary objective:

The ETS and DpR will be calculated for each cohort. Both ratios will be calculated using the total sum of diameters provided in tumor assessments by central radiology review.

Third secondary objective:

PFS will be calculated using start date of study drug and progression disease or death date (whichever occurs first), based on the Full Analysis set and Per-protocol Analysis Set. PFS censoring rules will follow FDA guidance in 2007 (see Table A).

OS will be calculated using start date of study (C1D1).

A Kaplan Meier survival analysis will be carried out to analyse PFS, providing the median and the corresponding 95% CI of time to progression. Survival curves will be reported.

6.2.2 *Statistical inference*

Comparisons using log rank test or model of Cox proportional hazards multivariate analysis will be used if needed.

6.3 *Exploratory analysis*

First secondary objective:

Significant reductions of tumor markers (CgA, 5-HIAA and NSE), defined as reductions of 50% or more regard the baseline values, will be showed by frequency tables.

To examine the relationship of biochemical response with PFS and radiological response the Kaplan-Meier and Chi-square/Fisher methods will be used.

6.4 *Subgroup analysis*

Subgroup analysis for ORR, PFS, OS, biochemical response (tumor markers) will be performed outside the indications of the study protocol. The following variables will be part of this analysis to explore differences between subgroups of subjects:

- ORR:
  - Origin of gastrointestinal NET.
  - Functionality.
  - Tumor burden (this information will be extract from central radiologic assessment).
  - Number of previous lines (1, 2 or 3 lines) (only in pancreatic NET cohort).
  - Concomitant use of somatostatin analogues.
  - Previous treatment with everolimus or sunitinib (only in pancreatic NET cohort).
- PFS:
  - Origin of gastrointestinal NET.
  - Tumor burden.
  - Number of previous lines (1, 2 or 3 lines) (only in pancreatic NET cohort).
  - Concomitant use of somatostatin analogues.

- Previous treatment with everolimus or sunitinib (only in pancreatic NET cohort).
- ECOG.
- Prior surgery.
- Age (≤ 65 vs > 65 years).
- Differentiation grade (G1/G2).
- Radiological response (upon central radiologic assessment).

- OS:
  - Functionality.
  - Tumor burden.
  - Concomitant use of somatostatin analogues.

Survival curves will be calculated for OS

In addition to the subgroup analysis, it will be calculated:

- Duration of response will be assessed and represented graphically. It will be calculated as time since treatment initiation to progression disease.
- Time to follow-up will be described.

6.5 *Safety analysis*

The safety analysis has been included in secondary objective (see 6.2).

6.5.1 *Summary statistics*

Not applicable.

6.5.2 *Statistical inference*

Not applicable.

6.6 *Demographic and baseline characteristics*

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

Demographic and baseline characteristics variables are:

- Age
- Gender
- Menopausal status
- Race/ethnicity
- ECOG performance status
- TNM staging (tumor, nodules and metastasis)
- Time from diagnosis date to informed consent signature
- Time from metastatic diagnosis date to informed consent signature
- Histological characteristics: Differentiation grade, Ki67 expression, Miotic count, NYHA classification
- Medical and surgical history
- Previous anti-cancer treatments
- Functionality
- Origin of gastrointestinal NET

6.7 *Concomitant medications*

Concomitant medications associated with an AEs will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating anatomical main group and therapeutic subgroup.

6.8 *Statistical significance level*

A significance level of 5% will be considered.

6.9 *Statistical model assumptions*

The following assumptions will be verifying to guarantee t Student test (if applicable)

- Normality of data
- Variance homogeneity
- Independence in data

In case of applying a Cox regression model, proportional hazards assumption (graphically) will be checked.

6.10 *Transformation of expected variables*

- The ORR is defined as the proportion of subjects who have best overall response of CR or PR (by RECIST 1.1):

$$ORR= (CR+PR)/Total.$$

- The time to progression is defined as the difference between start of drug (C1D1) and the progression date or death (whichever occurs first) or the last tumor assessment documented.
- ETS rate is defined as 20% reduction in target lesions after the first 6 weeks of treatment.
- DpR is defined as percentage of maximum tumor shrinkage observed at the nadir (the minimum of total sum of diameters) compared with baseline.
- Overall survival is defined as the time from the start of drug (C1D1) to death.

6.11 *Handling of missing data*

No planned procedure of imputation of missing values. The analysis will be performed with the available data.

6.12 *Description of the softwares to be used for data analysis*

Statistical programming and analyses will be performed using R [2] statistical software.

6.13 *Interim analysis protocol*

The interim analysis will be performed when the last patient included in the corresponding cohort of the study will have at least two tumor assessments (12 weeks after the last patient recruited).

7. References

1. Guidance for Industry: Clinical Trail Endpoints the Approval of Cancer Drugs and Biologics (May 2007).
2. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL (http://www.R-project.org/).