EFFICACY AND SAFETY OF LANREOTIDE ATG 120 MG IN COMBINATION WITH TEMOZOLOMIDE IN SUBJECTS WITH PROGRESSIVE WELL DIFFERENTIATED THORACIC NEUROENDOCRINE TUMORS

A phase II, multicentre, SINGLE ARM, OPEN-LABEL trial

STUDY PROTOCOL

STUDY number: A-93-52030-325

Lanreotide ATG120 mg/52030

EudraCT number: 2014-005579-10

Final Version 3.0 (including Amendment No. 2 and 3) 16 November 2017

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol A-93-52030-325 entitled "Efficacy and safety of Lanreotide ATG 120 mg in combination with Temozolomide in subjects with progressive well differentiated thoracic neuroendocrine tumors".

I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: _____ SIGNATURE: _____

TITLE: PRINCIPAL INVESTIGATOR DATE: _____

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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol A-93-52030-325 entitled "Efficacy and safety of Lanreotide ATG 120 mg in combination with Temozolomide in subjects with progressive well differentiated thoracic neuroendocrine tumors".

I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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SUMMARY OF CHANGES

The current version of the protocol was released on 16 November 2017 and includes Amendments 1, 2 and 3. The amendment forms were prepared and is provided in Appendix 4 and Appendix 5 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	19 October 2016	Appendix 4
2 and 3	16 November 2017	Appendix 5

SYNOPSIS

Name of sponsor/company: Ipsen SpA

Name of finished product: Ipstyl ATG/ Temozo-cell

Name of active ingredient(s): Lanreotide Acetate/Temozolomide

Title of study: Efficacy and safety of Lanreotide ATG 120 mg in combination with Temozolomide in subjects with progressive well differentiated thoracic neuroendocrine tumors

Study number: A-93-52030-325

Number of planned centres: 14 sites in Italy

Planned study period:	**Phase of development**:
May 2016 – March 2019	Phase II pilot exploratory trial

Objectives:

Primary Objective:

To evaluate the efficacy of Lanreotide Autogel (ATG) 120 mg in combination with Temozolomide (TMZ) in subjects with unresectable advanced neuroendocrine tumours of the lung or thymus (typical and atypical carcinoids according to the WHO 2004 criteria) as Disease Control Rate (DCR) at 9 months, according to RECIST criteria v 1.1.

Secondary Objectives:

- To assess, according to RECIST criteria v 1.1:
  - Progression Free Survival (PFS)
  - Time to Response (TTR)
  - Duration of Response
  - Time to Progression (TTP)
  - Best Overall response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD)
  - Objective Response Rate (ORR): Complete Response (CR), Partial Response (PR)
  - Disease Control Rate (DCR): Complete Response (CR), Partial Response (PR) and Stable Disease (SD) at 12 months
  - The influence of typical carcinoids and atypical carcinoids on the Disease Control Rate (DCR) at 9 months.
- To assess the biochemical response [Chromogranin A (CgA) plasma levels]
- To assess neuron-specific enolase (NSE) and CgA biomarkers levels prognostic and predictive value
- To assess the prognostic value of biomarkers expression (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies) for PFS, Overall Response Rate (ORR), and DCR
- To assess the agreement of the central assessment of tumor radiological response and the local one on the DCR at 9 months

- To assess safety profile of Lanreotide ATG 120 mg in combination with TMZ in terms of AEs/SAEs, vital signs, physical examination, gallbladder evaluation, laboratory abnormalities and concomitant medications.

Methodology:

Multicenter, single arm, open label trial.
Lanreotide ATG 120 mg in combination with TMZ 250 mg for a treatment period of 52 weeks.

Number of subjects planned:

40 subjects with progressive well or moderately differentiated thoracic neuroendocrine tumors (lung and thymic carcinoids)

Diagnosis and criteria for inclusion:

Inclusion Criteria:

1) Provision of written Informed Consent prior to any study related procedures;
2) Adult subjects (male or female) ≥ 18 years old;
3) WHO Performance status ≤ 2;
4) Histological documented unresectable advanced (locally or metastatic) well or moderately differentiated neuroendocrine tumors of the lung or thymus (typical and atypical carcinoids according to the WHO 2004 criteria);
5) Imaging documented progression within 12 months before screening visit (V1), according to RECIST criteria v 1.1;
6) Measurable disease, as defined by RECIST criteria v 1.1, on a CT scan performed at screening visit (V1);
7) Octreoscan or Ga^{68}-DOTA-TATE/TOC/NOC-PET-TC within 12 months before screening visit (V1);
8) Adequate liver, renal and bone marrow function, as defined below:
   a. Adequate bone marrow function

      Absolute Neutrophil Count (ANC) ≥ 1.5×10^9/L

      Platelets ≥ 100×10^9/L

      Hemoglobin > 9 g/dL

   b. Adequate liver function

      Total serum bilirubin ≤ 2.0 × ULN (exception for Gilbert disease)

      International Normalized Ratio (INR) < 1.5

      ALT and AST ≤ 2.5 × ULN (≤ 5 × ULN, in subjects with liver metastases)

   c. Adequate renal function

      Serum creatinine ≤ 1.5 × ULN
9) Willing and able to comply with study restrictions and willing to return to the clinic for the required visits during the study period and for the follow up evaluation as specified in the protocol.
10) Female subjects of childbearing potential (not surgically sterile or 2 years

postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 6 months after participation in the study. Acceptable methods of contraception include double barrier method [i.e. condom and occlusive cap (diaphragm or cervical/vault caps)] with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

11) Male subjects with female partners of childbearing potential must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 6 months after participation in the study.

Exclusion Criteria:

1) History of hypersensitivity to the IMPs or drugs with a similar chemical structure or any excipient used in the formulation.
2) Any known contraindications to CT scan.
3) Poorly differentiated neuroendocrine carcinoma and mixed NET tumours, according to WHO 2004 criteria.
4) Neuroendocrine tumours other than lung or thymus.
5) Non-neuroendocrine thymic neoplasm.
6) Treated with systemic therapies (chemotherapy, interferon-alpha, somatostatin analogues, molecular target therapies) within 28 days prior to screening visit (V1).
7) Treated with a number of systemic therapy lines > 3 prior to screening visit (V1), and any of the following:
    a. for chemotherapy no more than 1 line prior to V1;
    b. for somatostatin analogue no more than 1 line therapy, considered as treatment lasting more than 6 months, prior to V1;
    c. no therapy with TMZ prior to V1.
8) Received a prior therapy with Peptide Receptor Radionuclide Therapy (PRRT) within 6 months prior to screening visit (V1).
9) Sign of recurrence of prior malignancies, or concomitant malignancies, or malignancies requiring active treatment within the last 3 years, other than the investigated disease, with the exception of previous basal cell skin cancer and previous cervical carcinoma in situ or neoplasm radically resected within 3 years prior to screening visit (V1).
10) Undergone major surgery/surgical therapy for any cause within 3 months prior to screening visit (V1).
11) Received external palliative radiotherapy within the last 28 days prior to screening visit (V1).
12) Received locoregional therapies (TAE, TACE, TARF) and SIRT within 3 months prior to screening visit (V1).
13) Presence of symptomatic brain metastasis.
14) Unstable angina pectoris, symptomatic congestive heart failure (NYHA Class III or IV), serious uncontrolled cardiac arrhythmia or a history of myocardial infarction ≤ 6 months prior to screening visit (V1).
15) Active or uncontrolled severe infection or known history of HIV seropositivity.
16) Previous Pneumocistis Carini Pneumonitis infection.
17) Liver cirrhosis, chronic active or persistent hepatitis, HCV and HBV positive test in presence of active disease clinical evidence.
18) Active bleeding diathesis, including abnormal coagulation (PT or APTT greater than

30% above ULN).
19) Uncontrolled diabetes mellitus as defined by HbA1c ≥ 8%, despite adequate therapy. Subjects with history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary.
20) Subjects with symptomatic cholelithiasis at screening visit (V1).
21) Any current or prior medical condition that may interfere with the conduct of the study.
22) Hypersensitivity to dacarbazine (DTIC).
23) Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
24) Treated with any other IMP within 28 days prior to screening visit (V1).
25) Likely to require treatment during the study with drugs that are not permitted by the study protocol.
26) Female subject pregnant or lactating. A pregnancy test will be performed at the start of the study for all female subjects of childbearing potential (i.e. not surgically sterile or 2 years postmenopausal).
27) Male subject who is planning a sperm donation during the entire study participation and at least 6 months after the last study drug administration.
28) History of, or known current, problems with substance or alcohol abuse.
29) Any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
30) Abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety.

Test product, dose, mode of administration:

Lanreotide ATG 120 mg every 28 days, deep subcutaneous injection
Temozolomide 250 mg, oral route, for 5 consecutive days every 28 days
Temozolomide 180 mg, oral route, for 5 consecutive days every 28 days, in case dose reduction required.

Duration of treatment: 52 weeks

Criteria for evaluation:

Efficacy:

Primary Endpoint(s) and Evaluation(s):

Response of subjects to the study combination therapy, 9–months after first treatment administration. Responders are subjects showing disease control rate (DCR) according to RECIST criteria v 1.1, defined as objective response or stability of the disease. They include: CR (complete response), PR (partial response) or SD (stable disease).

Secondary Endpoints(s) and Evaluation(s):

- Progression Free Survival (PFS), defined as the time from the first treatment administration until progression according to RECIST criteria v 1.1 or death from any cause
- Time to Response (TTR) defined as the time from the first treatment administration to the first objective tumor response (PR or CR) according to RECIST criteria v 1.1
- Duration of Response defined as the time from onset of the first objective

tumor response (PR or CR) to objective tumor progression (PD, according to RECIST criteria v 1.1) or death from any cause

- Time to Progression (TTP) defined as the time from the first treatment administration to the first objective tumor progression (PD) observed according to RECIST criteria v 1.1
- Best Overall response defined as the best response recorded from the time of the first treatment until disease progression/recurrence or the end of study, according to RECIST criteria v 1.1 (CR, PR, SD, PD)
- Objective Response Rate (ORR) according to RECIST criteria v 1.1 (CR, PR) at 9 and 12 months.
- Disease Control Rate (DCR) according to RECIST criteria v 1.1 (CR, PR, SD) at 12 months
- Biochemical Response according to decrease in CgA plasma level in subject with baseline CgA level greater than ULN. Biochemical objective response is defined as a decrease of CgA $\geq$ 50%, while stable disease as a decrease $\geq$ 25% and less than 50%, as their best response to study treatments
- Value of NSE and CgA biomarkers at visits 2, 4, 6, 9, 12, 16 (EOS)
- Biomarkers expression (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumor surgery specimens or biopsies) correlated to tumor response for PFS, ORR, and DCR at 9 and 12 months to assess their prognostic value
- Central and local assessments of tumor radiological response.

Safety:

- Occurrence of adverse events (AEs) by CTCAE v 4.03 (June 14, 2010) from informed consent and throughout the study.
- Standard haematology and biochemistry test results at each study visit.
- Vital signs (assessment of blood pressure (BP), heart rate (HR) and body weight in kg) measurements at each study visit.
- Physical examination at each study visit.
- Concomitant medication usage throughout the study.
- Electrocardiogram (ECG), Echocardiography at visits 1, 9 and 16.
- Gallbladder Echography at Visit 1, 9 and 16.

Statistical Methods:

Sample size

Sample size and statistical assumption were made according to a Fleming's Single Stage Design with the following assumptions:

- The proportion of responders should be equal or greater than 30% to be clinically relevant (π_1),
- a proportion of responders equal or lower than 10% is considered as not acceptable (π_0),
- the 1-sided error probability is set to $\alpha = 0.025$ and
- the power is 90% ($\beta = 0.10$).

Assuming a 10% of drop-out rate the total number of subjects to be included in the trial is N=40.

Efficacy Evaluations

The primary efficacy variable - disease control rate (DCR) according to RECIST criteria v 1.1 - will be analysed by an exact binomial proportion tests for one-way tables. The statistical test on the primary objective will be performed one sided with a type I error rate set at 2.5%.

Secondary endpoints to be evaluated are:

- Tumor response according to RECIST criteria v 1.1 assessed at Visit 1, Visit 6, Visit 9 and Visit 12, EOS analysed using frequency tables;
- Objective response rate according to RECIST criteria v 1.1 (CR, PR) assessed at Visit 1, Visit 6, Visit 9 and Visit 12, EOS analysed using frequency tables;
- Disease Control rate according to RECIST criteria v 1.1 (CR, PR, SD) analysed using frequency tables;
- CgA and NSE levels assessed at Visit 2, Visit 4, Visit 6, visit 9, visit 12 and EOS will be presented by mean values, standard deviations, minimum, maximum and 95%-confidence intervals of the mean at each timepoint and will be analysed by ANCOVA for repeated measures, using baseline values as covariates;
- Time to event data derived from tumor response for the endpoints Time to Response (TTR), Duration of Response, Time to progression (TTP) and, Progression Free Survival will be analysed using survival methods. The results will be presented both in summary tables and graphically using Kaplan-Meier plots;
- The influence of typical carcinoids and atypical carcinoid on the Disease control rate (DCR) at 9 months will be analysed using frequency tables;
- The prognostic value of NSE and CgA biomarkers at baseline on PFS will be analysed using a COX-proportional hazard model and the influence on ORR and DCR at Visit 12 and 16 will be analysed using a logistic model.
- The prognostic value of biomarkers expression (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies) for PFS will be analysed using a COX-proportional hazard model and the influence on DCR and ORR at Visits 12 and 16 will be analysed using a logistic model;
- The agreement of the central assessments of radiological response and the local one

will be analysed using Cohen's kappa.

Safety Evaluations

Summary statistics (mean, median, SD and range as appropriate) will be presented for vital signs, blood pressure, heart rate, ECG parameters, clinical laboratory tests etc. at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal exams.

Adverse events reported by investigators using the NCI-CTC classification (version 4.03) will be coded using MedDRA dictionary (version 20.0 or higher).

Summary incidence tables will be provided classified by body system, preferred term and associated NCI/CTC worst grade. In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) will be chosen. Dose delays, dose interruptions will be listed by cycle.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTC criteria. All haematology and biochemistry parameters by subject will be listed. For WBC, neutrophils, platelets and haemoglobin, with associated grade 3 or 4 toxicities, nadir and day to nadir will be calculated. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of study medication.

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LIST OF ABBREVIATIONS

βHCG	Beta human chorionic gonadotropin
AC	Atypical Carcinoids
AE	Adverse Event/Experience
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of covariance
aPTT	activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Autogel
BMI	Body mass index
bpm	Beats per minute
CA	Competent Authorities
CgA	Chromogranin A
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract research organisation
CSR	Clinical Study Report
CT	Computed tomography
CTSU	Clinical Trial Supplies Unit (relates to sponsor)
DCR	Disease Control Rate
DEA	Drug Enforcement Administration
ECG	Electrocardiogram
ED	Early death
EDC	Electronic data capture
eCRF	Electronic case report form
EOS	End of Study
ESMO	European Society for Medical Oncology
EU	European Union
EW	Early Withdrawal
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP_NET	GastroEnteroPancreatic Neuroendocrine Tumors
GH	Growth Hormone

GMP	Good Manufacturing Practice
HbA1c	Glycated Haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart Rate
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional review board
ITT	Intent to treat
IUD	Intrauterine device
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguanine-DNA methyltransferase
MRI	Magnetic resonance imaging
NANETS	North America Neuro Endocrine Tumors Society
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NSE	Neuron-Specific Enolase
ORR	Objective Response Rate
PCP	Pneumocystis jirovecii pneumonia
PD	Partial Disease
PDD	Protocol Deviation Document
PFS	Progression Free Survival
PI	Package Insert
PP	Per Protocol
PR	Partial Response
PRRT	Peptide Receptor Radionuclide Therapy
PT	Prothrombin Time
RBC	Red Blood Cell(s)
RT	Radio Therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®

s.c.	Subcutaneous
SCLC	Small cell lung carcinoma
SD	Stable Disease
Std	Standard deviation
SDV	Source document verification
SEER	Surveillance Epidemiology and End Results
SIRT	Selective internal radiotherapy
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	somatostatin analogues
SST	somatostatin
SSTR	human somatostatin receptors
T3	Triiodothyronine
T4	Thyroxine
TACE	Transcatheter arterial chemoembolization
TAE	Transcarterial emoembolization
TARF	thermo-ablation with radio-frequency
TC	Typical Carcinoids
TEAE	Treatment emergent adverse event
TFLs	Tables, Figures and Listings
TMF	Trial master file
TMZ	Temozolomide
TNM	Tumor Node Metastasis
T-NET	Thoracic Neuroendocrine Tumors
TSH	Thyroid Stimulating Hormone
TTP	Time To Progression
TTR	Time To Response
UDS	Urine drug screen
US	United States
VEGF	Vascular endothelial factor
WBC	White blood cell(s)
WHO	World Health Organisation

1 BACKGROUND INFORMATION

1.1 Introduction

In the Western World, thoracic neuroendocrine tumours are one of the most frequent type of neoplasm of neuroendocrine origin.

Well differentiated thoracic neuroendocrine (T-NET) tumours (bronchial and thymic carcinoid, according to the WHO 2004 Classification) represent the 25-30% of NETs, with the remaining part of 75% represented by NETs from the gastroenteropancreatic tract.

Furthermore according to all the published data [1, 2, 3], they constitute the subgroup of NETs with the most relevant increase of incidence in the last 2 decades.

NETs incidence and prevalence increase may be partly due to the improved understanding and recognition of these tumours, but maybe also to an actual rise in the number of cases.

Data from the US Surveillance Epidemiology and End Results (SEER) database, shows an estimated incidence of thoracic NETs of 1.37/100,000 inhabitants per year, where 1.35 is the contribute of bronchial NETs and 0.02 of thymic NETs, compared to about 2.5-5 cases per 100,000 reported for gastroenteropancreatic neuroendocrine tumors (GEP NETs) [4]. Among lung NETs, the epidemiology varies greatly between well-differentiated and poorly differentiated forms. The well differentiated forms, typical carcinoids (TC) and atypical carcinoids (AC), which represent a very small proportion of lung cancers, show a prevalence of about 1-2% and the atypical forms have a prevalence of 0.1-0.2% [5, 6]. Thymic NETs show an incidence < 1 case /100,000 inhabitants per year and represent 2-5% of all thymic tumors and 2% of mediastinic tumors [2, 7, 8].

Median age of subjects affected by bronchial NET and thymic NET is 64 and 59 years, respectively.

The increased incidence has not been matched by an improvement in outcome, in fact data from the US SEER database reported no substantial change in 5-year survival for the period 1973-2002. NETs Survival rates vary according to disease stages, and even grade 1 and grade 2 NETs have the potential to metastasize to distant sites, negatively impacting subject prognosis. Long term data from NCI SEER database (1973-2004) show that the median survival for subjects with well differentiated NETs with metastases is 33 months and 65% of these subjects die within 5 years [5].

The current classification of lung NET is based on WHO 2004 classification, with the distinction of four different histological subtypes: TC, AC, large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC). This classification is based on the morphological characteristics of the tumour combined with the mitotic rate and the presence or absence of necrosis [4]. Recently it has been proposed a grading of NETs based on the information given by Ki-67 and necrosis and mitotic counts with the identification of three different grades of disease (G1, G2, G3) with different prognosis, as a result of combining the WHO 2004, ENETS/WHO 2010 (GI NET) [9], ESMO 2012 [6] and ENETS 2015 [10] (**see Table 2**). According to WHO 2004, in Europe the current classification for thoracic NET differentiate three categories: well-differentiated and poorly differentiated (either low and intermediate grade or carcinoids tumours respectively TC and AC) and high grade NEC (LCNEC and SCLC).

In the latest review of Pelosi et al 2014 [11], the Ki-67 was detected as an interesting marker in lung NE tumours as prognostic criteria and the publication of Rindi et al 2013 [12] shows that the Ki-67 index has a prognostic significance and it is useful in grading of lung neuroendocrine tumours, in lung NETs, to be used in combination with mitotic count and

necrosis. To make the three-tiers grading system effective, they were identified site specific cut-offs of Ki-67 and mitotic count for lung NETs, since more large studies have to be conduct to validate it.

The staging of T-NETs follows the TNM (Tumor-Node-Metastasis) staging system and biochemical evaluation include Chromogranin A, plasma NSE and other biomarkers specific for symptoms of carcinoids syndrome.

Among the well differentiated T-NETs, the TCs show a good prognosis with a 5-years survival of 87-90%, but the ESMO guidelines recommend a follow up to 15 years, in fact it has been observed that distant metastases may develop from TCs many years after radical resection of primary tumour. ACs are associated with a poorer prognosis and the 5-year survival rate is of 44-78% [4].

Due to the aggressive behaviour of thymic NETs, which show a high incidence of recurrence after surgery, the prognosis for subjects affected by primary thymic NETs is poor: while low-grade thymic NETs present a 5-year survival of 50%, the high grade thymic NETs have a 5-years survival of about 0% [4].

NETs are tumours that develop from glands, islets or endocrine cells of various origin present in several districts of the organism. By their nature, NETs are sensitive to the action of somatostatin (SST) hormone present in all districts of the human body and which binds to specific receptors (SSTRs) present in the outer membrane of the endocrine cells. Its action is expressed by inhibiting some cellular functions, such as motility, proliferation and secretion of various hormones, including growth hormone and other hormones in the gastrointestinal tract. Somatostatin analogues (SSA) have a cytostatic and cytotoxic (pro-apoptotic) effect on tumour cells and they have been used in the treatment of NETs for many years, with the aim of inhibit tumour progression in advanced disease [13, 14].

Table 2 Histological classifications of NETs

Differentiation	Traditional Nomenclature	Grade	Mitotic Count[a]	Mitotic Count[b] (10 HPF)[c]	Necrosis[d]	Necrosis[b] (%)	Ki-67 index (%) (P-NET)[d]	Ki-67 index (%) T-NET[b]
Well differentiated	Typical Carcinoids	Low Grade (G1)	<2/10 HPF	2	Absent	Absent	≤2	<4
Moderately differentiated	Atypical Carcinoids	Intermediate Grade (G2)	2-9/10 HPF	>2-47	Present (focal)	Focal (<10% of sample)	3-20	4<25
Poorly differentiatied	SCLC LCNEC	High Grade (G3)	>9/10 HPF	>47	Present (extensive)	Diffuse (>10% of sample)	≥20	≥25

a ESMO Guidelines 2012

b Rindi et al 2013

c 10 HPF, ten high-power field=2 mm2, to be assessed in at least 50 fields at 40x I areas of highest mitotic density

d ENETS 2015

Lanreotide ATG, a somatostatin analogue (SSA), in Italy is currently approved for the treatment of symptoms associated with neuroendocrine tumours; recently it has been approved in the United States (US) for antitumor effect (for unresectable, well-or moderately-differentiated, locally advanced or metastatic GEP-NETs to improve progession-free survival, and submitted in European Union (EU) for the treatment of NETs including tumour control [for both grade 1 and grade 2 (Ki67 up to 10%) GEP-NETs in adult patients with unresectable locally advanced or metastatic disease], but the implementation of the indication at country

level in EU is ongoing. This new indication was approved in the US and EU based on the results from the CLARINET [15] study, a 96-week, randomised, double-blind, placebo-controlled, parallel group, multicountry study of Lanreotide ATG at a dose of 120 mg compared with placebo. The study demonstrated that Lanreotide ATG 120 mg produces a risk reduction of 53% for progression or death in 204 subjects with Ki-67 <10% and well- or moderately-differentiated GEP-NETs. Thus Lanreotide ATG has an anti-tumour effect in G1/low G2 GEP-NET, significantly prolonging progression-free survival (PFS) over 2 years months compared with placebo (HR 0.47; p=0.0002).

Despite CLARINET data and despite the most recent ENETS guidelines pointed out that the primary aims of the medical therapy of T-NET are the control of hormone related symptoms and the tumour growth, data currently available on the application of SSA in T-NETs comes from subgroup analysis of larger controlled randomized trials, such as RADIANT-2 [16], and from small groups of subjects evaluated in retrospective analysis and single centers experiences [17, 18, 19].

Temozolomide (TMZ) is an alkylating agent and by methylating DNA inhibites DNA and cellular replication. It's approved for use in the first-line treatment of glioblastoma multiforme. In Italy according to 648 law for the extension of the indication, TMZ can be used in endocrine advanced carcinoma.

The latest ENETS Guidelines indicated TMZ as palliative treatments in pulmonary carcinomas because the acceptable safety profile and as it is the most studied in the lung NET.

To date, only few retrospective studies evaluating the efficacy of therapy with TMZ in NETs have been published. TMZ in monotherapy has been proved to be efficacious in a series of 36 subjects leading to a tumor regression in 31% of bronchial carcinoid tumors and in 8% of pancreatic neuroendocrine tumors [20]. The association of TMZ with capecitabine seems to increase the percentage of responders in pancreatic NETs [21]. On the other hand, the combination of TMZ with thalidomide or bevacizumab seems to add significant toxicities, with some increase of response in pancreatic NETs, but not impacting in carcinoids [22, 23, 24].The overall response (stable disease plus partial response) ranged in the published series between 40 and 70%.

According to literature TMZ has been used alone or in combination with capecitabine or bevacizumab in well-differentiated neuroendocrine carcinoma, resulting in high response rates [20, 24]. In a previous paper a subject with poorly differentiated endocrine carcinoma (PDEC) has been described to be responder to TMZ treatment [25].

In a recent published study [26] the median of the progression free survival, in 31 subjects with bronchial carcinoid treated with TMZ, was 5.3 months.

A recent study evaluating the combination of TMZ with bevacizumab and octreotide demonstrated a good activity in advanced G2 NETs [27].

Some studies investigating SSAs treatment in T-NETs are currently ongoing: LUNA [28] and COOPERATE-II trials [29].

ESMO, NANETS and the most recent AIOM guidelines have underlined how the role of SSA and TMZ in T-NETs may be similar to GEP NET both in functioning and non-functioning carcinoids [4, 6, 7, 9].

Combining the properties of Lanreotide and of TMZ can be a rational treatment strategy to inhibit the tumour growth by multiple pathways. Furthermore the safety profile of both drugs is well known and the combination should not worsen the safety profile of the individual drugs.

The SONNET study is a German multicentre open-label study evaluating the efficacy of the combination of Lanreotide ATG 120 mg and TMZ in subjects with progressive GEP-NET G1/G2. It is on-going and no data are yet available [30].

To reinforce the SONNET objective and to investigate further Lanreotide ATG 120 mg plus TMZ combination, the ATLANT study will evaluate the efficacy of the combination of Lanreotide ATG 120 mg and TMZ in subjects with progressive thoracic neuroendocrine tumors, typical and atypical carcinoids and thymus, according to WHO 2004 classification.

The primary objective of the ATLANT study is the evaluation of efficacy of Lanreotide ATG 120 mg plus TMZ combination in patients with T-NETs (typical and atypical carcinoids and thymus) as DCR at 9 months, according to RECIST criteria vs 1.1. There is not enough data on both SSA and TMZ in monotherapy to estimate the time to progression (progression-free survival) for the combination treatment.

The only data for SSA in Midgut and Bronchopulmonary-NET comes from RADIANT-2 trial, where patients with advanced carcinoid tumor Received Octreotide Depot and Everolimus 10 mg/Day or Octreotide Depot and Placebo [16]. Limitation from this trial are the differences between central and local radiological review and the huge differences in the subgroups, thus not providing reliable PFS values (Total population: Central review 11 months, Local review 8.6 months; subgroup analysis: Midgut NET 14 months).

Available data on monotherapy with TMZ comes only from one retrospective trial in advanced neuroendocrine tumors (pNET n=12; CR=0, PR=8%, SD=67%, PD=25%) [20].

Other available data for TMZ comes from combination studies (TMZ + Thalidomide [22]: pNET ORR 45%, Carcinoids ORR 7%; TMZ + Bevacizumab [27]: pNET 33%, Carcinoids 0%; TMZ + Capecitabine [21]: pNET PR 70%, SD 27%).

The primary endpoint to assess the efficacy of the combination treatment is the Disease Control Rate (DCR), according to statistic methodology for a single arm phase II trial [31], such as ATLANT study.

According to those evidences it is suggested to choose “Disease Control Rate” (CR+PR+SD) as primary endpoint to evaluate the efficacy of the combination of Lanreotide ATG 120 mg and TMZ. Progression free survival and additional response parameters are addressed in this pilot exploratory study as secondary endpoints, and could be possible primary endpoints for a consecutive trial.

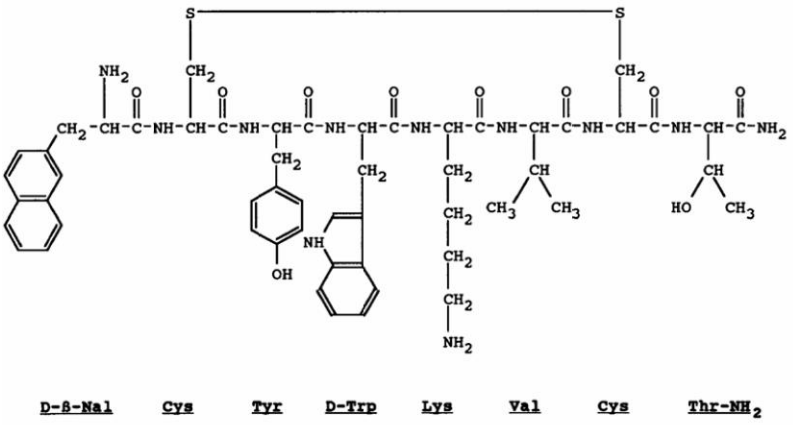
The sensitivity of tumor cells to alkylating agents, including TMZ, has been associated with decreased levels of the DNA repair enzyme, O6-methylguanine DNA methyltransferase (MGMT), which, through its ability to restore DNA to its normal form, can prevent chemotherapy-induced cell death. Among subjects with either advanced melanoma or glioblastoma treated with TMZ, loss of tumoral MGMT expression was associated with an improvement in survival. The correlation was not confirmed in all the tumor models, including pituitary aggressive tumors treated with TMZ [32, 33, 34, 35]. So since O6-methylguanine DNA methyltransferase (MGMT) expression in NETs could be helpful to select responders to TMZ treatment, in this study one of the secondary objectives is the assessment of the prognostic value of this biomarker expression.

1.2 Name and Description of Investigational Medicinal Product(s)

The Study Protocol foresees the combination of two Investigational Medicinal Product(s) (IMPs), Lanreotide ATG and Temozolomide.

Lanreotide is an octapeptide analogue of natural somatostatin. Its structural formula is shown in Figure 1.

Figure 1 Lanreotide structural formula



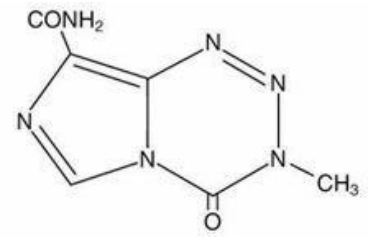
The mechanism of action of Lanreotide is believed to be similar to that of natural somatostatin. Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5 and a reduced binding affinity for human SSTR1, 3, and 4. Activity at human SSTR 2 and 5 is the primary mechanism believed responsible for GH (Growth Hormone) inhibition. Like somatostatin, Lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions.

Lanreotide is approved for the long term treatment of subjects with acromegaly when the circulating levels of GH and /or Insulin-like Growth Factor remain abnormal after surgery and/or radiotherapy, or in subjects who otherwise required medical treatment.

Lanreotide ATG in Italy is currently approved for the treatment of symptoms associated with neuroendocrine tumours; based on the results from CLARINET study [15] it has been recently approved in US and EU for the treatment of NETs including tumour control, but the implementation of the indication at a country level in EU is ongoing.

The chemical name of Temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide. The structural formula is shown in Figure 2.

Figure 2 Temozolomide structure



TMZ is not directly active but undergoes rapid non-enzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.

TMZ is indicated for the treatment of adult subjects with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment; children from the age of three years, adolescents and adult subjects with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

A more detailed description of the products is given in Section 3.4.

1.3 Findings from Nonclinical and Clinical Studies

NETs are highly vascularized tumours which overexpress angiogenic factors.

Angiogenesis is a topic mechanism on the tumour growth and its inhibition is a common anti-tumour process targeted by most of chemotherapeutic drugs, such as TMZ, methotrexate, paclitaxel, vinblastine, bevacizumab and doxorubicin, either directly or indirectly by the inhibition of cell proliferation, migration and blood vessel formation.

SST and SSA seem to inhibit the production and secretion of several angiogenic factors, such as the vascular endothelial growth factor (VEGF), with the result of tumours growth reduction [13].

Studies on TMZ, administered at metronomic doses, enhances the inhibition of angiogenesis accompanied by the down-regulation of MGMT expression in endothelial cells [36, 37].

Combine the properties of Lanreotide to decrease levels of angiogenic factors and enhanced apoptosis, and of TMZ, an alkylating agent, can be a rational treatment strategy to inhibit by multiple pathways, the angiogenesis [14].

It is estimated that the combination of these different mechanisms of anti-tumour activity could be supportive or even additive given the high expression of SSTR on NET.

A paper with the practical clinical recommendation from the principal European expert, collected during a meeting held in Perugia, recommended the association of TMZ or everolimus, according to the availability in the country, in subjects with T-NETs who develop progressive disease in the course of SSA [9]. The latest ENETS recommendations reinforce the use of SSA and TMZ in T-NETs [10, 38].

Current data available on the application of SSA in T-NETs comes from subgroup analysis of larger controlled randomized trials, such as RADIANT-2 [16], and from small groups of subjects evaluated in retrospective analysis and single centers experiences [17, 18, 19].

TMZ has been used alone or in combination with capecitabine or bevacizumab in well-differentiated neuroendocrine carcinoma, resulting in high response rates [20, 24]. In a

previous paper a subject with poorly differentiated endocrine carcinoma (PDEC) has been described to be responder to TMZ treatment [25].

The sensitivity of tumor cells to alkylating agents, including TMZ, has been associated with decreased levels of the DNA repair enzyme, O6-methylguanine DNA methyltransferase (MGMT), which, through its ability to restore DNA to its normal form, can prevent chemotherapy-induced cell death. Among subjects with either advanced melanoma or glioblastoma treated with TMZ, loss of tumoral MGMT expression was associated with an improvement in survival. The correlation was not confirmed in all the tumor models, including pituitary aggressive tumors treated with TMZ. These discrepancies ingenerated discussion on the ideal method to evaluate the activity of the enzyme, so at the moment appear more appropriate to evaluate the correlation with the enzymatic activity in "a posteriori" subgroup analysis [32, 33, 34, 35].

To date, only few retrospective studies evaluating the efficacy of therapy with TMZ in NETs have been published. TMZ in monotherapy has been proved to be efficacious in a series of 36 subjects leading to a tumor regression in 31% of bronchial carcinoid tumors and in 8% of pancreatic neuroendocrine tumors [20]. The association of TMZ with capecitabine seems to increase the percentage of responders in pancreatic NETs [21]. On the other hand, the association with thalidomide or bevacizumab seems to add significant toxicities, with some increase of response in pancreatic NETs, but not impacting in carcinoids [22, 23, 24].

The overall response (stable disease plus partial response) ranged in the published series between 40 and 70%.

To date, no studies have been published on the association with SSA alone. A recent study evaluating the combination of TMZ with bevacizumab and octreotide demonstrated a good activity in advanced G2 NETs [27].

In a recent published study [26] the median of the progression free survival, in 31 subjects with bronchial carcinoid treated with TMZ, was 5.3 months.

Other international studies investigating SSAs in thoracic NETs populations are ongoing.

LUNA trial is a prospective, multicenter, randomized, open-label, 3-arm, phase II study with a single-stage design in each arm. The purpose of this study is to test the effectiveness and safety of Everolimus or Pasireotide LAR alone or in combination in adult subjects with advanced (unresectable or metastatic) neuroendocrine carcinoma (typical and atypical) of the lung and thymus [28].

COOPERATE-1 is a phase I trial with the purpose to assess the safety and tolerability of pasireotide LAR in combination with everolimus in advanced metastatic gastroenteropancreatic or pulmonary neuroendocrine Tumors (NET). Two arms are planned with Pasireotide LAR followed by Pasireotide LAR + Everolimus versus Everolimus followed by Pasireotide LAR + Everolimus [29].

1.4 Known and potential risks and benefits to human subjects

During clinical studies in subjects affected by NET, Lanreotide ATG was well tolerated. Lanreotide ATG may reduce gallbladder motility and lead gallstone formation, therefore subjects may need to be monitored periodically.

Lanreotide, like somatostatin and other somatostatin analogues, inhibits secretion of insulin and glucagon. Hence, patients treated with Lanreotide may experience hypoglycaemia or hyperglycaemia. Blood glucose levels should be monitored when Lanreotide treatment is initiated, or when the dose is altered and any anti-diabetic treatment should be adjusted accordingly.

Slight decreases in thyroid function have been seen during treatment with Lanreotide in patients with acromegaly, although clinical hypothyroidism is rare (<1%). Tests of thyroid function should be done where clinically indicated.

In patients without underlying cardiac problems, Lanreotide may lead to a decrease of heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to Lanreotide treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with Lanreotide in patients with bradycardia.

The pharmacological gastrointestinal effects of Lanreotide ATG may reduce the intestinal absorption of co-administered drugs including ciclosporin and therefore may necessitate the adjustment of its dose to maintain therapeutic levels.

Interactions with highly plasma bound drugs are unlikely in view of the moderate binding of Lanreotide ATG to serum proteins. Limited published data indicate that concomitant administration of somatostatin analogues and bromocriptine may increase the availability of bromocriptine.

Concomitant administration of bradycardia-inducing drugs (e.g. beta blockers) may have an additive effect on the slight reduction of heart rate associated with Lanreotide ATG. Dose adjustments of such concomitant medications may be necessary.

The limited published data available indicate that somatostatin analogues may decrease the metabolic clearance of compounds known to be metabolised by Cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that Lanreotide ATG may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution.

The most commonly expected AE reactions following treatment with Lanreotide are: gastrointestinal disorders (most commonly reported are diarrhoea and abdominal pain, usually mild or moderate and transient), cholelitiasis (often asymptomatic) and injection site reactions (pain, nodules and indurations).

The following adverse reactions occurred in subjects suffering from acromegaly and treated in clinical trials with Lanreotide are listed in (see Table 3).

Safety profile is similar for other indication.

Post-marketing Adverse Drug Reactions include pancreatitis and allergic reactions (including angioedema, anaphylaxis, hypersensitivity).

Additional information regarding risks and benefits to human subjects may be found in the SmPC (version updated on February 2015).

Table 3 Summary of undesirable effects reported by subjects treated with Lanreotide

Blood system disorders	
Common (> 1/100-> 1/10)	ALAT increased/abnormal, ASAT abnormal, blood bilirubin increased, blood glucose increased, Glycosylated Haemoglobin increased, weight decreased
Uncommon (> 1/1000-> 1/100)	ASAT increased, Blood alkaline phosphatase increased, blood bilirubin abnormal, blood sodium decreased
Cardiac Disorders	
Common (> 1/100-> 1/10)	Sinus Bradycardia
Nervous System Disorders	
Common (> 1/100-> 1/10)	Dizziness, headache
Gastrointestinal disorders	
Very Common (> 1/10)	Diarrhoea, loose stools, abdominal pain
Common (> 1/100-> 1/10)	Nausea, vomiting, constipation, flatulence, abdominal distension, abdominal discomfort, dyspepsia
Uncommon (> 1/1000-> 1/100)	Faeces discoloured
Skin and subcutaneous tissue disorders	
Common (> 1/100-> 1/10)	Alopecia, hypotrichosis
Metabolism and nutrition disorders	
Common (> 1/100-> 1/10)	Hypoglycaemia
Uncommon (> 1/1000-> 1/100)	Diabetes Mellitus, hyperglycaemia
Vascular disorders	
Uncommon (> 1/1000-> 1/100)	Hot flush
General disorders and administration site conditions	
Common (> 1/100-> 1/10)	Fatigue, injection site reactions (pain, mass, induration, nodule, pruritus)
Uncommon (> 1/1000-> 1/100)	Asthenia
Hepatobiliary system disorders	
Very Common (> 1/10)	Cholelithiasis
Common (> 1/100-> 1/10)	Biliary dilatation
Psychiatric disorders	
Uncommon (> 1/1000-> 1/100)	Insomnia

Regarding TMZ, when is administered during a longer dosing regimen there may be a higher occurrence of *Pneumocystis jirovecii pneumonia* (PCP). However, all subjects receiving TMZ, particularly subjects receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in subjects using TMZ, in particular in combination with dexamethasone or other steroids.

Hepatic injury, including fatal hepatic failure, has been reported in subjects treated with TMZ. Baseline liver function tests should be performed prior to treatment initiation. For all subjects, liver function tests should be checked after each treatment cycle. For subjects with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with TMZ.

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely.

Nausea and vomiting are very commonly associated with TMZ. Anti-emetic therapy may be administered prior to or following administration of TMZ.

Subjects treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2 receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.

Use of TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

In patients treated with TMZ in a clinical study setting, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving TMZ concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions (including neutropenia, lymphopenia, thrombocytopenia, leucopenia, anaemia) were reported commonly or very commonly in both indications.

Additional serious adverse reactions, that have been identified during post-marketing exposure, are reported in Table 4.

Additional information regarding risks and benefits to human subjects may be found in the SmPC (version updated on February 2015).

Table 4 Summary of events reported with Temozolomide in the post-marketing setting

Blood and lymphatic system disorders	
Very rare:	prolonged pancytopenia, aplastic anaemia[a]
Neoplasm benign, malignant and unspecified	
Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
Respiratory, thoracic and mediastinal disorders	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure[a]
Hepatobiliary disorders[b]	
Common:	liver enzymes elevations
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure†
Skin and subcutaneous tissue disorders	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

[a] Including cases with fatal outcome

[b] Frequencies estimated based on relevant clinical trials

The safety profile of Lanreotide ATG and TMZ is well established; an increase in AEs due to the combination of both substances is not expected. Combining the properties of Lanreotide and of TMZ can be a rational treatment strategy to inhibit the tumour growth by multiple pathways.

For this reason, ATLANT study will evaluate the efficacy of the combination of Lanreotide ATG 120 mg and TMZ in subjects with progressive thoracic neuroendocrine tumors, typical and atypical carcinoids and thymus, according to WHO 2004 classification.

1.5 Selection of Investigational Medicinal Products and Dosages

The Study will evaluate the combination of two IMPs, Lanreotide ATG and TMZ.

Lanreotide dosage to be evaluated in this open label study was selected on the basis of the usual dosage in NET treatment: the usual clinical dosing regimen of Lanreotide ATG in NETs is 120 mg, deep s.c. injection every 28 days. In the recently published CLARINET clinical trial [15], it has been demonstrated the safety and efficacy of this dosing regimen in the control of tumour growth in gastroenteropancreatic NETs.

Lanreotide ATG is a controlled release preparation of Lanreotide acetate and water for injection which together form supersaturated solution of the peptide. Prolonged release of the peptide occurs by the physical nature of the supersaturated solution. The formulation enables active serum levels to be maintained for 1 to 2 months.

For what regards TMZ, according to the monotherapy administration of the drug as described in the SmPC, starting dose should be 150 mg/m^2/day for 5 consecutive days followed by 23 days free of treatment. At the beginning of the second cycle of therapy, dosage can be increased to 200 mg/m^2/day, if non-haematological toxicity in the first cycle of therapy was Grade ≤ 2 (with the exception for alopecia, nausea and vomiting), ANC $\geq 1.5 \times 10^9$/L and thrombocyte count is $\geq 100 \times 10^9$/L. Dosage after second cycle remains fix apart for toxicity which can require dose reduction to 100 mg/m^2/day (same schedule) due to Grade 3 non-haematological toxicity or ANC $< 1.0 \times 10^9$/L and/or platelets count $< 50 \times 10^9$/L. TMZ administration should stop if persistent haematological toxicity, or Grade 4 non-haematological, is registered.

In our protocol, based on clinical trials and experts clinical experience [20, 26] a starting dose of 250 mg x day for 5 consecutive days followed by 23 days free of treatment (corresponding to SmPC starting dosage of 150 mg/m^2, but considering a total adult body surface of 1.73 m^2, man of about 70 kg weight) is considered well tolerated and efficacious. The first intake will start the same day of the administration of Lanreotide ATG 120 mg and will continue for the next 4 days (5 days of treatment in total). This treatment schedule will be administered for a maximum of 12 months. This initial dose can be continued until disease progression/death or toxicity. In case of toxicity TMZ dose reduction must be considered, when ANC falls to < 1.0 x 10^9/L or platelet count is < 50 x 10^9/L during any cycle. In this case TMZ dose will be reduced to 180 mg per day, equivalent to 100 mg/m^2, considering the total standard adult body surface of 1.73 m^2 (man of about 70 kg of weight). If dose is reduced subject should remain on the reduced dose level for the rest of the study. Up titration dose is not allowed. If at any study visit, at dosing before treatment cycle administration, haematology results 1.0 < ANC < 1.5 x 10^9/L and/or 50<platelet count<100 x 10^9/L therapy must be postponed by 1 week and haematological test repeated. If the repeated test show ANC ≥ 1.5 x 10^9/L and platelets count ≥ 100 x 10^9/L therapy may recommends, if not weekly testing must be performed up to the third week after last TMZ administration. If haematological levels remain low, the subject must be withdrawn.

There are no dietary restrictions with TMZ. To reduce nausea and vomiting, TMZ should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered prior to and/or following administration of TMZ. Capsules should not be opened or chewed. They should be swallowed whole with a glass of water. If capsules are accidentally opened or damaged, precautions should be taken to avoid inhalation or contact with the skin or mucous membranes.

A more detailed description of administration procedures is given in Section 6.1.

1.6 Compliance Statement

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines [39]. Any episode of noncompliance will be documented.

Considering that Electronic Data Capture (EDC) will be used, the study will be in compliance with the following regulations: Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials requirements [40, 41].

In addition, the study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

1.7 Population to be Studied

The study will enrol 40 adult subjects, males or females afferent to 14 Italian clinical sites, diagnosed with progressive well or moderately differentiated thoracic NETs (typical and atypical carcinoids and thymus) and with at least one measurable tumour lesion.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

The aim of this study is to explore the efficacy and safety of the combination of Lanreotide ATG 120 mg and TMZ in progressive T-NETs.

2.2 Study Objectives

The primary objective of the study is to evaluate the efficacy of Lanreotide ATG 120 mg in combination with TMZ in subjects with unresectable advanced neuroendocrine tumours of the lung or thymus (typical and atypical carcinoids according to the WHO 2004 criteria), as disease control rate (DCR) at 9 months, according to RECIST criteria v 1.1.

The secondary objectives of the study are:

- To assess, according to RECIST criteria v 1.1:
  - Progression Free Survival (PFS)
  - Time to Response (TTR)
  - Duration of Response
  - Time to Progression (TTP)
  - Best Overall Response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD)
  - Objective Response Rate (ORR): Complete Response (CR), Partial Response (PR) at 9 and 12 months
  - Disease Control Rate (DCR): Complete Response (CR), Partial Response (PR) and Stable Disease (SD) at 12 months
  - The influence of typical carcinoids and atypical carcinoid on the Disease Control Rate (DCR) at 9 months
- To assess the Biochemical Response (CgA plasma levels)
- To assess NSE and CgA biomarkers levels prognostic and predictive value
- To assess the prognostic value of biomarkers expression (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies) for PFS, ORR and DCR
- To assess the agreement of the central assessment of tumor radiological response and the local one, on the DCR at 9 months
- To evaluate the safety of study treatments as assessed by the following:
  - occurrence of adverse events (AEs) throughout the study
  - clinical laboratory test results (haematology, biochemistry at each study visit, and urinalysis at visits 1, 6, 9, 12, End of Study (EOS)
  - vital signs (blood pressure, heart rate and body weight) measurements at each study visit
  - electrocardiogram (ECG), echocardiography at visits 1, 9 and EOS
  - physical examination at each study visit
  - concomitant medication usage throughout the study
  - Gallbladder echography at visits 1, 9 and EOS.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a phase II, open label, single arm, prospective, multicenter, non-comparative, pilot study to evaluate the efficacy and safety of Lanreotide ATG 120 mg /28 days in combination with TMZ 250 mg/day for 5 consecutive days/28 days on Disease Control Rate (DCR), in adult subjects with a histologically documented unresectable advanced (locally or metastatic) well or moderately differentiated neuroendocrine tumor of the lung or thymus (typical and atypical carcinoids), according to the WHO 2004 criteria. The study consists of a screening period (maximum 4 weeks), followed by a 52 week open label phase.

At Screening visit (V1), after informed consent for the study has been obtained, an eligibility CT scan must be performed.

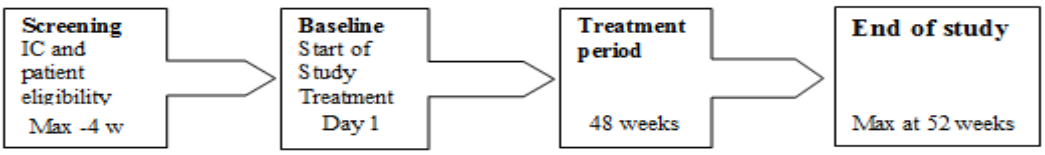
At Baseline visit (V2), performed after a maximum of 4 weeks after V1, subjects fulfilling the inclusion and exclusion criteria will be treated with Lanreotide ATG 120 mg every 28 days and TMZ 250 mg daily for 5 consecutive days every 28th days (in case of bone marrow toxicity the dose may subsequently be reduced to 180 mg daily for 5 consecutive days of each month) for a maximum treatment period of 52 weeks (about 12 months) or until disease progression, death or unacceptable toxicity, subject/physician decision, whichever comes first. Specific details of the dosage groups are given in Section 6.

Subjects who complete all scheduled visits will be considered to have completed the study. Subjects who progress or die are considered to have completed the study. Subjects who complete all scheduled visits until Visit 12 (36 weeks of treatment) will be considered to be evaluable for primary objective of the study.

Subjects who complete the study will have final procedures and assessments performed at the final visit (EOS – Visit 16). Subjects who withdraw from the study before the completion of the evaluation period will have an Early Withdrawal Visit within 4 weeks after last IMP intake either one has been administered (i.e. lanreotide ATG or TMZ) and should perform all assessments provided at final visit (EOS).

At their last study visit (EOS- V16-Week52), subjects still benefiting from treatment (according to the investigator judgment) will have the option, to continue to receive the combination of Lanreotide ATG 120 mg and TMZ 250 mg. In such a situation, Lanreotide 120 mg and TMZ 250 mg will be provided free of charge by the Sponsor to the investigational sites under its commercial packaging, for a maximum of 12 months. During this post-trial treatment, the Investigator will report immediately to Ipsen Pharmacovigilance Contact any safety concerns arising from the use of the product.

Figure 3 Study Design



3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Efficacy Endpoint and Evaluation

The primary endpoint is the percentage of responders (DCR according to RECIST criteria v 1.1) at 9 months (V12) after first treatment administration, defined as objective response or stability of the disease. They include: CR (complete response), PR (partial response) or SD (stable disease).

3.2.2 Secondary Efficacy Endpoints and Evaluations

Secondary endpoints are:

- Progression Free Survival (PFS) from first treatment administration; Progression, according to RECIST criteria v 1.1
- Time to Response (TTR) defined as the time from first treatment administration to the first objective tumor response (PR or CR according to RECIST criteria v 1.1)
- Duration of Response defined as the time from onset of the first objective tumor response (PR or CR) to objective tumor progression (PD, according to RECIST criteria v 1.1) or death from any cause
- Time to Progression (TTP) defined as the time from first treatment administration to the first objective tumor progression (PD) observed according to RECIST criteria v 1.1
- Best Overall Response defined as the best response recorded from the time from the first treatment until disease progression/recurrence or the end of study, according to RECIST criteria v 1.1 (CR, PR, SD, PD) Objective Response Rate (ORR): Complete Response (CR), Partial Response (PR) at 9 and 12 months
- Disease Control Rate (DCR): Complete Response (CR), Partial Response (PR) and Stable Disease (SD) at 12 months
- The influence of typical carcinoids and atypical carcinoid on the Disease control rate (DCR) at 9 months
- Biochemical Response according to decrease in CgA plasma level in subjects with baseline CgA level greater than ULN. Biochemical objective response is defined as a decrease of CgA $\geq$ 50%, while stable disease as a decrease $\geq$ 25% and less than 50%, as their best response to study treatment
- Value of NSE and CgA biomarkers levels (Centrally assessed) at baseline (V2), 1 month (V4), 3 months (V6), 6 months (V9), 9 months (V12) and End of study (V16), to assess their predictive and prognostic value
- Biomarkers expression (Centrally assessed) (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies) correlated to tumor response for PFS, ORR, DCR at 9 (V12) and 12 months (V15), to assess their prognostic value
- Agreement between central and local assessment of tumor radiological response.

3.2.3 Safety Endpoints and Evaluations

The safety and tolerability of Lanreotide in combination with TMZ will be assessed throughout the study by evaluating AEs/SAEs, changes from baseline in physical examination, vital signs (blood pressure, heart rate and body weight), laboratory tests (haematology, biochemistry, urinalysis), diagnostic tests (ECG, Echocardiography, Gallbladder Echography) and concomitant medication usage.

Assessments of adverse events will be evaluated for timing, seriousness and relatedness and graded for type, incidence and severity according to the National Cancer Institute (NIC) using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03-14 June 2010 (refer to Appendix 3).

3.3 Randomisation and Blinding

This is a non-randomised, open label study.

3.4 Study Treatments and Dosage

Each subject eligible and enrolled in the Study will be treated with the combination of Lanreotide ATG 120 mg and TMZ 250 mg, as specified in the following paragraphs.

Lanreotide ATG 120 mg, will be administered, at study site, to the subjects at baseline and every 28 days until 48 weeks of treatment (12 injections) through deep subcutaneous injection.

Lanreotide will be packaged and delivered to investigational sites by CREAPHARM, ZA Air Space, Av de Magudas CS2007, 33187 Le Haillan, France.

The treatment will be provided in a pre-filled syringe, sealed in a laminated bag.

A more detailed description of administration procedures is given in Section 6.1.1.

TMZ will be administered at starting dose of 250 mg per day for 5 consecutive days of each month for a maximum of 48 weeks (5 hard capsules dispensed at 12 visits). In case of bone marrow toxicity the dose may subsequently be reduced to 180 mg per day for 5 consecutive days of each month. The first intake will start the same day of the administration of Lanreotide ATG 120 mg and will continue for the next 4 days (5 days of treatment in total).

TMZ will be provided in glass bottles or blisters containing 5 hard capsules of Temozolomide, at two different dosages: 250 mg and 180 mg, to allow a dose reduction in case of bone marrow toxicity.

TMZ will be packaged and delivered to investigational sites by CREAPHARM, ZA Air Space, Av de Magudas CS2007, 33187 Le Haillan, France.

A more detailed description of administration procedures is given in Section 6.1.2.

A sufficient quantity of IMP will be supplied as well as an acknowledgement of receipt form. The sponsor's representative will receive a Certificate of Analysis for which batch of IMP has been used under their study, Material Data Safety Sheet for both active IMPs, Packaging Order which reflects the product release statement.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements [Good Manufacturing Practice (GMP) Annex 13 [42], national laws in force and in accordance with the local languages. A description of the core text of the IMP labels is displayed below:

- Study Number,
- Pharmaceutical dosage form,
- Route of administration,
- Quantity of dose units,
- Batch number,
- "Keep out of reach of children",
- a treatment number
- a specific blank space to enter the subject ID

- "For clinical study use only"
- Name, address and telephone number of the sponsor (the main contact for information on the product and clinical study)
- Name of Investigator
- Storage conditions
- Expiry date

The investigator, or designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP carrying his/her number. The dispensing for each subject will be documented in the eCRF.

3.5 Study Duration

Subjects are expected to participate in this study for a minimum of 53 weeks and up to 56 weeks, considering that the study will consist of a four week (maximum) screening period, and a 52 week open label phase.

The subject's participation in the study will be considered to have ended at the time of the last visit (EOS – V16), 4 weeks after last IMP intake, either one has been administered (i.e. lanreotide ATG or TMZ).

For subjects who prematurely withdraw from the study, every effort should be done to perform Early Withdrawal Visit within 4 weeks after last IMP intake, either one has been administered (i.e. lanreotide ATG or TMZ). Subjects enrolment will last 20 months and the overall duration of the study will be approximately 3 years. The study will be considered to have started when the first subject has provided his/her signed informed consent.

The study will be considered to have ended after the last subject last visit has been performed.

At their last study visit (EOS- V16-Week52), subjects still benefiting from treatment (according to the investigator judgment) will have the option, to continue to receive the combination of Lanreotide ATG 120 mg and TMZ 250 mg. In such a situation, Lanreotide 120 mg and TMZ 250 mg will be provided free of charge by the Sponsor to the investigational sites under its commercial packaging, for a maximum of 12 months. During this post-trial treatment, the Investigator will report immediately to Ipsen Pharmacovigilance Contact any safety concerns arising from the use of the product.

3.6 Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events (SAEs) will be reviewed (see Section 8.1.4) as they are reported from the study centre to identify safety concerns.

A subject may discontinue participation in the study at any time for any reason (e.g. lack of efficacy, withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g. protocol violation or deviation as defined in Section 12.1.2, non-compliance with the protocol conditions or AE).

The Sponsor may terminate this study at any time. Reasons for termination may include but are not limited to the following:

- The incidence or severity of adverse events (AEs) in this or other studies points to a potential health hazard for trial subjects.
- Insufficient subject enrolment.
- Any information becoming available during the study that substantially changes the expected benefit risk profile of the study treatments.

- Investigator's decision according to clinical judgment.

3.7 Investigational Medicinal Product Preparation Storage and Accountability

3.7.1 Investigational Medicinal Product Storage and Security

The investigator, or an approved representative (e.g. pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

- Lanreotide ATG 120 mg will be stored under the recommended temperature (between +2°C and +8°C) and will be administered to the subjects through deep subcutaneous injection, at study sites.
- TMZ capsules should not be stored above 30°C. Procedures for drug administration are provided in the drug instructions leaflet and more details provided in the study manual.

3.7.2 Investigational Medicinal Product Preparation

The investigator, or an approved representative (e.g. pharmacist), will ensure that all IMP is dispensed by qualified staff members.

3.7.3 Investigational Medicinal Product Accountability

All IMP and any other study related material is to be accounted for on the IMP accountability log provided by the sponsor. It is essential that all used and unused supplies are retained for verification (by the sponsor or sponsor's representative). The investigator should ensure adequate records are maintained in the IMP accountability log.

The procedure for either return of unused clinical study supplies to the sponsor or destruction of these unused clinical study supplies at site are detailed in the Study Manual.

3.8 Maintenance of Randomisation and Blinding

Not applicable.

3.9 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 CFR Part 11. As required by GCP, the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), IMP administration, and any AEs and associated concomitant medication.

As required by ICH GCP Section 6.4.9, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

Definition for source data and source documents are given below:

- **Source Data**: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source Documents**: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies,

microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel, and by local, and possibly foreign, CAs. This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

All subjects must fulfil all of the following criteria to be included in the study:

(1) Provision of written Informed Consent prior to any study related procedures;

(2) Adult subjects (male or female) ≥ 18 years old;

(3) WHO Performance status ≤ 2;

(4) Histological documented unresectable advanced (locally or metastatic) well or moderately differentiated neuroendocrine tumors of the lung or thymus (typical and atypical carcinoids according to the WHO 2004 criteria);

(5) Imaging documented progression within 12 months before screening visit (V1), according to RECIST criteria v.1.1;

(6) Measurable disease, as defined by RECIST criteria v 1.1, on a CT scan performed at screening visit (V1);

(7) Octreoscan or Ga^{68}-DOTA-TATE/TOC/NOC-PET-TC within 12 months before screening visit (V1);

(8) Adequate liver, renal and bone marrow function, as defined below:

- Adequate bone marrow function
  - ANC ≥ 1.5×10^9/L
  - Platelets ≥ 100×10^9/L
  - Hemoglobin > 9 g/dL
- Adequate liver function
  - Total serum bilirubin ≤ 2.0 × ULN (exception for Gilbert disease)
  - INR < 1.5
  - ALT and AST ≤ 2.5 × ULN (≤ 5 × ULN, in subjects with liver metastases)
- Adequate renal function
  - Serum creatinine ≤ 1.5 × ULN

(9) Willing and able to comply with study restrictions and willing to return at the clinic for the required visits during the study period and for the follow up evaluations as specified in the protocol.

(10) Female subjects of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 6 months after participation in the study. Acceptable methods of contraception include double barrier method [i.e. condom and occlusive cap (diaphragm or cervical/vault caps)] spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

(11) Male subjects with female partners of childbearing potential must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 6 months after participation in the study.

4.2 Exclusion Criteria

Subject will not be included in the study if:

(1) History of hypersensitivity to the IMP or drugs with a similar chemical structure or any excipient used in the formulation.

(2) Any known contraindications to CT scan.

(3) Poorly differentiated neuroendocrine carcinoma and mixed NET tumours, according to WHO 2004 criteria.

(4) Neuroendocrine tumours other than lung or thymus.

(5) Non-neuroendocrine thymic neoplasm.

(6) Treated with Systemic therapies (chemotherapy, interferon-alpha, somatostatin analogues, molecular target therapies) within 28 days prior to screening visit (V1).

(7) Treated with a Number of systemic therapy lines > 3 prior to screening visit (V1), and any of the following:
   (a) for chemotherapy no more than 1 line prior to V1;
   (b) for somatostatin analogues no more than 1 line therapy, considered as treatment lasting more than 6 months, prior to V1;
   (c) no therapy with TMZ prior to V1.

(8) Received a prior therapy with Peptide Receptor Radionuclide Therapy (PRRT) within 6 months prior to screening visit (V1).

(9) Sign of recurrence of prior malignancies, or concomitant malignancies, or malignancies requiring active treatment within the last 3 years, other than the investigated disease, with the exception of previous basal cell skin cancer and previous cervical carcinoma in situ or neoplasm radically resected within 3 years prior to screening visit (V1).

(10) Undergone major surgery/surgical therapy for any cause within 3 month prior to screening visit (V1).

(11) Received external palliative radiotherapy within the last 28 days prior to screening visit (V1).

(12) Received locoregional therapies (TAE, TACE, TARF) and SIRT within 3 months prior to screening visit (V1).

(13) Presence symptomatic brain metastasis.

(14) Unstable angina pectoris, symptomatic congestive heart failure (NYHA Class III or IV), serious uncontrolled cardiac arrhythmia or a history of myocardial infarction ≤ 6 months prior to screening visit (V1).

(15) Active or uncontrolled severe infection or known history of HIV seropositivity.

(16) Previous Pneumocistis Carini Pneumonitis infection.

(17) Liver cirrhosis, chronic active or persistent hepatitis, HCV and HBV positive test in presence of active disease clinical evidence.

(18) Active bleeding diathesis, including abnormal coagulation (PT or APTT greater than 30% above ULN).

(19) Uncontrolled diabetes mellitus as defined by HbA1c ≥ 8%, despite adequate therapy. Subject with known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary.

(20) Subjects with symptomatic cholelithiasis at screening visit (V1).
(21) Any current or prior medical condition that may interfere with the conduct of the study.
(22) Hypersensitivity to dacarbazine (DTIC).
(23) Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
(24) Treated with any other IMP within 28 days prior to screening visit (V1).
(25) Likely to require treatment during the study with drugs that are not permitted by the study protocol.
(26) Female subject pregnant or lactating. A pregnancy test will be performed at the start of the study for all female subjects of childbearing potential (i.e. not surgically sterile or 2 years postmenopausal).
(27) Male subject who is planning a sperm donation during the entire study participation and at least 6 months after the last study drug administration.
(28) History of, or known current, problems with substance or alcohol abuse.
(29) Any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
(30) Abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety.

4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, pregnancy (see section 8.1.5), or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.6, 5.2.5.1, 6.2 and 8.1.7.

If one or more of the following occurs, the subject will be discontinued from study medication:

- In case of disease progression as defined in the RECIST criteria version 1.1 (refer to Appendix 1);
- In case of AEs, SAEs, serious and unexpected worsening of clinical conditions, or any other reasons that, in the Investigator's judgement, may jeopardize the subject safety;

If one or more of the following occurs the subject will be withdrawn from the study:

(1) Informed consent withdrawal / Subject's request;
(2) Occurrence of disease(s) which can interfere with subject's final evaluation;
(3) Administration of prohibited drugs;
(4) If TMZ is not tolerated and unacceptable toxicity persists even after TMZ dose reduction or delay (see Table 7 Dose Adaptation of TMZ);
(5) According to clinical judgement of the investigator or to their own request;
(6) Substantial non-compliance with the requirements of the study;
(7) Development of a situation which would, in the Judgment of the investigator, affect clinical study endpoint measurements with a significant degree;
(8) Subjects lost to follow- up;
(9) Subject death.

Discontinued subjects will not be replaced.

Should a subject decide to withdraw from the study after administration of IMP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2.5.1) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the CRF. The Investigator will provide or arrange for appropriate follow-up (if required) for subjects withdrawing from the study, and will document the course of the subject's condition.

If a subject withdraws consent, every attempt will be made to determine the reason.

If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made. The specific AE or test result(s) must be recorded on the CRF. All evaluations should be performed, according to the protocol, on the last day the subject receives IMP, or as soon as possible thereafter.

In case of subject discontinuation due to SAE or AE, the evolution of the SAE or AE will be followed up and recorded by the Investigator till the outcome definition. If possible, subjects removed from the Study should perform the Early withdraw visit (see Section 5.2.5.1.) concomitantly with the Study Drug discontinuation decision, and in any case within 4 weeks after last dose of drug administered (i.e. lanreotide ATG or TMZ).

CCI [redacted] If a subject wishes to withdraw his consent, the investigator must inform the study monitor in writing of the subject's decision. Within the sponsor, the request for sample withdrawal will be forwarded to the repository leader. If the samples are in the sponsor's repository (or at the central laboratory prior to shipping to the repository), the repository leader will ensure destruction of the samples and all corresponding aliquots and issue confirmation of the withdrawal, which will be forwarded to the investigator. If the samples are still at the investigator site at the time the subject withdraws his consent, the investigator must inform the study monitor and destroy the samples. The study monitor will forward confirmation of the destruction to the repository leader.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 6.

The total volume of blood drawn for all evaluations throughout this study is approximately 286 mL for each subject.

CCI [redacted]

Table 5 Blood Volume Calculation

Description	Number of Samples	Volume (mL)	Total Volume (mL)
Haematology	17	8	136
Blood Biochemistry	16	5	80
CgA and NSE	6	10	60
Serology	1	10	10
CCI [redacted]	[redacted]	[redacted]	[redacted]
Total Volume (mL)/subject			**301**

Table 6 Study Procedures and Assessments

	Pretreatment		Treatment period														End of Study (or Early Withdrawal)
	V1	V2	V3	V3 bis[a]	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Allowed visit schedule deviation (days)		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Procedures and assessments	Screening Maximum -4W	Baseline Day 1	W2	W 3	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W52
Informed consent	X																
Demography	X																
Medical/Surgical history	X																
Prior Therapies for T-NETs	X																
Octreoscan or Ga^{68}-DOTA/TATE/TOC/NOC-PET	X																
Disease History	X																
Inclusion and exclusion criteria	X	X															
Clinical and Physical examination	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
WHO performance score	X						X			X			X				X
Prior / concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample tissue for centralized SSTR2, MGMT, Ki-67 evaluation	X																
Gallbladder echography	X									X							X

	V1	V2	V3	V3 bis[a]	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Allowed visit schedule deviation (days)		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
Procedures and assessments	**Screening Maximum -4W**	**Baseline Day 1**	**W2**	**W 3**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**
Urinalysis	X				X	X	X			X			X				X
Blood sample collection to assess Haematology	X[b]	X[b]	X	X[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X
Blood sample collection to assess Biochemistry	X[c]	X[c]	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Blood sample collection to assess Serology (HCV, HBV)	X																
Pregnancy test (Serum)	X																
CCI																	
Blood sample collection for CgA and NSE dosage		X			X		X			X			X				X
ECG and Echocardiography	X									X							X
CT scan [e]	X						X			X			X				X
LAN ATG 120 mg		X			X	X	X	X	X	X	X	X	X	X	X	X	
TMZ 250 mg (or 180 mg if dose down titrated) x 5days		X			X	X	X	X	X	X	X	X	X	X	X	X	

a Haematology will be reconfirmed at day 21, to assess the TMZ bone marrow tardive toxicity (only WBC, ANC, Hemoglobin, Platelets).

b Please refer to section 5.2 for completed list of parameters to be assessed at each visit. Tests to be assessed BEFORE STUDY INTAKE.

c Please refer to section 5.2 for completed list of parameters to be assessed at each visit. Tests to be assessed BEFORE STUDY INTAKE.

CCI

e The CT scan report must be available at the time of scheduled visits; the exam could be performed within maximum 10 days before the visit

5.2 Study Visits

5.2.1 Procedures for Screening and Enrolment (Visit 1)

A signed and dated **Informed Consent Form** will be obtained before screening procedures. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.

CCI [redacted]

[redacted] Subjects who agree to participate will be requested to sign a separate informed consent. After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required. The screening visit (Visit 1) will take place between Day –28 and Day -1 of the study. The following assessments will be performed:

5.2.2 Screening Visit (V1) / max -4W

- Demography (sex, age, ethnic origin)
- Medical/surgical history in the past year
- Documented histology of typical/atypical carcinoid of lung or thymus according to WHO 2004 criteria
- Disease history (date of diagnosis, tumour localization and tumour staging according to UICC/AJCC 7th Edition TNM System
- WHO performance score
- Prior and concomitant medications/therapies
- Prior Chemotherapy, Radiotherapy, Target Therapies, Locoregional Therapies (TAE, TACE, TARF, SIRT), PRRT for T-NETs in the past year
- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate, height and body weight (kg)
- Blood sample collection to assess Haematology: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c), coagulation indexes: aPTT, PT and INR.
- Blood sample collection to assess Biochemistry: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4.
- Blood sample collection to assess serology: hepatitis C virus (HCV) and hepatitis B virus (HBV)
- Urinalysis
- Serum pregnancy test
- Tissue sample for SSTR2, MGMT, Ki-67: check if available
- CT scan (chest, abdomen and pelvis). If a CT scan was already performed in the last 28 days it would be considered suitable for the screening tumour evaluation.

- ECG, Echocardiography
- Gallbladder Echography
- Octreoscan or GA^{68}-DOTA/TATE/TOC/NOC-PET (within 12 months)
- Eligibility check (starting verify inclusion/exclusion criteria)

Each Investigator has to check the patient safety (AE reporting) starting from the signature of Informed Consent. The subjects under no circumstances will be screened more than once. Following confirmation of eligibility for the study, subjects will start the study treatments, specified in Section 6.1. Each investigator will also maintain a record of all subjects screened into the study (i.e. who signed the informed consent form). Records up to the time of premature termination should be completed. In the event that the subject was not receiving IMP, the primary reason will be recorded.

5.2.3 Procedures Before Study Treatment - Baseline (V2) / Day 1

The following procedures will be performed at Baseline on Day 1 of the study, prior to the administration of study treatments:

- Eligibility check (final evaluation of inclusion/exclusion criteria)
- Review of pre-treatment AEs
- New or changed concomitant medications
- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (kg)
- Blood sample collection to assess Haematology: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c), aPTT, PT and INR. Do not repeat if V1 haematology has been performed less than 7 days before.
- Blood sample collection to assess Biochemistry: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4. Do not repeat if V1 biochemistry has been performed less than 7 days before.
- Blood sample collection for centralized dosage of CgA and NSE
- CCI [redacted]

After above check performed,

- Lanreotide ATG 120 mg
- TMZ 250 mg for the first consecutive 5 days

5.2.4 Procedures During Study Treatment

The following procedures will be performed at Visit 3 (W2 ± 2 days):

- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (kg)
- Blood sample collection to assess bone marrow, liver and renal function: WBC count, ANC, Haemoglobin, Platelets, total serum bilirubin (direct bilirubin only if total serum

bilirubin is out of range), γGT, ALT, AST, serum Cr, Urea, LDH, aPTT, PT, INR, electrolytes (chloride, sodium, potassium, calcium, phosphate)

- Review of AEs
- New or changed concomitant medications

The following procedures will be performed at Visit 3 bis (W3 ± 2 days):

- Blood sample collection to assess TMZ tardive bone marrow toxicity: WBC count, ANC, Haemoglobin, Platelets
- Review of AEs
- New or changed concomitant medications

The following procedures will be performed at Visit 4 (W4 ± 2 days)

- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (kg)
- Blood sample collection to assess Haematology: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c), aPTT, PT and INR.
- Blood sample collection to assess Biochemistry: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4
- Urinalysis
- Blood sample collection for centralized dosage of CgA and NSE
- Review of AEs
- New or changed concomitant medications

After above check performed,

- Lanreotide ATG 120 mg
- TMZ 250 mg for the first consecutive 5 days, or dose reduction if appropriate– see Section 6.1.2.

The following procedures will be performed at Visit 5 (W8 ± 2 days)

- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (kg)
- Blood sample collection to assess Haematology: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c), aPTT, PT and INR.
- Blood sample collection to assess Biochemistry: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4)
- Urinalysis
- Review of AEs

- New or changed concomitant medications

After above check performed,

- Lanreotide ATG 120 mg
- TMZ 250 mg for the first consecutive 5 days, or dose reduction if appropriate– see Section 6.1.2.

The following procedures will be performed at Visit 6 (W12 ± 2 days) and Visit 12 (W36 ± 2 days):

- Clinical and physical examination
- WHO performance score
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (kg)
- Blood sample collection to assess Haematology: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c), aPTT, PT and INR.
- Blood sample collection to assess Biochemistry: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4)
- CT scan (chest, abdomen and pelvis)
- Review of AEs
- New or changed concomitant medications
- CCI [redacted]
-

After above check performed,

- Lanreotide ATG 120 mg
- TMZ 250 mg for consecutive 5 days, or dose adjustment if appropriate – see Section 6.1.2.

The following procedures will be performed at Visit 7 (W16 ± 2 days), Visit 8 (W20 ± 2 days), Visit 10 (W28 ± 2 days), Visit 11 (W32 ± 2 days), Visit 13 (W40 ± 2 days), and Visit 14 (W44 ± 2 days):

- Blood sample collection to assess bone marrow, liver and renal function: WBC count ANC, Haemoglobin, Platelets, total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), γGT, ALT, AST, serum Cr, Urea, LDH, aPTT, PT, INR electrolytes (chloride, sodium, potassium, calcium, phosphate)
- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (Kg)
- Review of AEs
- New or changed concomitant medications

After above check performed,

- Lanreotide ATG 120 mg at monthly schedule

- TMZ 250 mg for consecutive 5 days, or dose adjustment if appropriate – see Section 6.1.2.

The following procedures will be performed at Visit 9 (W24 ± 2 days):

- Clinical and physical examination
- WHO performance score
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (kg)
- Blood sample collection to assess Haematology: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c), aPTT, PT and INR.
- Blood sample collection to assess Biochemistry: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4
- Urinalysis
- Blood sample collection for Centralized dosage of CgA and NSE
- CT scan (chest, abdomen and pelvis)
- ECG and Echocardiography
- Gallbladder Echography
- Review of AEs
- New or changed concomitant medications

After above check performed,

- Lanreotide ATG 120 mg
- TMZ 250 mg for consecutive 5 days every 28 days, or dose adjustment if appropriate – see Section 6.1.2.

The following procedures will be performed at Visit 15 (W48 ± 2 days):

- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (Kg)
- Blood sample collection to assess bone marrow, liver and renal function: WBC count, ANC, Haemoglobin, Platelets, total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), γGT, ALT, AST, serum Cr, Urea, LDH, aPTT, PT, INR, electrolytes (chloride, sodium, potassium, calcium, phosphate)
- Review of AEs
- New or changed concomitant medications

After above check performed,

- Lanreotide ATG 120 mg at monthly schedule
- TMZ 250 mg for consecutive 5 days, or dose adjustment if appropriate – see Section 6.1.2

5.2.5 Procedures After Study Treatment

5.2.5.1 End of Study Visit or Early Withdrawal Visit

Subjects who participate in the study in compliance with the protocol for at least 48 weeks of IMP administration will be considered to have completed the study and will be evaluated at 52 weeks (Visit 16 – EOS).

For subjects who withdraw prematurely from the study, final evaluations should be performed concomitantly with the Study Drug discontinuation decision, and in any case within 4 weeks after last dose of drug administered, either one has been administered (i.e. lanreotide ATG or TMZ).

Data from any efficacy evaluations performed after this time will not be collected on the CRF. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2.4, respectively.

The following procedures will be performed at the End of Study Visit (Visit 16, W52 ± 2 days), or Early Withdrawal visit:

- Clinical and physical examination
- Vital signs: assessment of blood pressure (BP), heart rate and body weight (kg)
- WHO performance score
- Blood sample collection to assess Haematology: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c), aPTT, PT and INR.
- Blood sample collection to assess Biochemistry: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range), electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4
- Urinalysis
- Blood sample collection for Centralized dosage of CgA and NSE
- CCI [redacted]
- CT scan (chest, abdomen and pelvis)
- ECG and Echocardiography
- Gallbladder Echography
- Review of AEs
- New or changed concomitant medications

At their last study visit (EOS- V16-Week52), subjects still benefiting from treatment (according to the investigator judgment) will have the option, to continue to receive the combination of Lanreotide ATG 120 mg and TMZ 250 mg. In such a situation, Lanreotide 120 mg and TMZ 250 mg will be provided free of charge by the Sponsor to the investigational sites under its commercial packaging, for a maximum of 12 months. During

this post-trial treatment, the Investigator will report immediately to Ipsen Pharmacovigilance Contact any safety concerns arising from the use of the product.

6 TREATMENT OF SUBJECTS

6.1 Study Drugs Administered

At Screening, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be treated as follow:

- Lanreotide ATG 120 mg every 28 days, deep subcutaneous injection for a maximum of 48 weeks, for a total number of 13 injections.
- TMZ 250 mg hard capsules, for 5 consecutive days every 28 days, oral route, for a maximum of 48 weeks.

6.1.1 Lanreotide ATG

Lanreotide ATG will be provided in a pre-filled syringe, and will be administered to the subjects at baseline and every 28 days, for 48 weeks of treatment through deep subcutaneous injection (total number of 13 injections), at the investigational site.

If strictly required and after discussion with Sponsor, a maximum delay of four weeks in lanreotide administration is allowed.

6.1.2 Other Investigation Medicinal Products

TMZ will be provided in glass bottles or blisters containing 5 hard capsules of TMZ. Capsules are presented as dose strength 180 mg or 250 mg.

Starting dose of TMZ will be 250 mg /day. The first cycle intake will start the same day of the administration of Lanreotide ATG 120 mg and will continue for the next 4 days (5 days of treatment in total). A cycle treatment includes the first 5 days of each month. 250 mg of TMZ are equivalent to 150 mg/m^2, considering the total standard adult body surface of 1.73 m^2 (man of about 70 kg of weight); this treatment schedule will be administered for a maximum of 48 weeks (about 12 months) or until progression/death or toxicity.

TMZ hard capsules should be administered in the fasting state. Capsules must be swallowed whole with a glass of water and must not be opened or chewed. Anti-emetic therapy may be administered prior to or following administration of TMZ.

Prior to dosing the following laboratory parameters must be met: ANC ≥ 1.5 x 10^9/L and platelet count ≥ 100 x 10^9/L.

If at any study visit, at dosing before treatment cycle administration, haematology results 1.0 < ANC < 1.5 x 10^9/L and/or 50<platelet count<100 x 10^9/L therapy must be postponed by 1 week and haematological test repeated. If next dosing is ANC ≥ 1.5 x 10^9/L and platelets count ≥ 100 x 10^9/L therapy is assigned; if not, weekly re-dosing must be performed up to the third week after last TMZ administration. If haematological levels remain low, subject must be withdrawn.

A TMZ dose reduction must be considered if ANC falls to < 1.0 x 10^9/L or platelet count is < 50 x 10^9/L during any cycle (see Table 7). In this case therapy must be postponed by 1 week and haematological test repeated weekly until recovery (ANC ≥ 1.5 x 10^9/L and platelet count ≥ 100 x 10^9/L), up to the fourth week after last TMZ administration. After recovery, TMZ dose will be reduced to 180 mg / day. This cycle treatment reduction is equivalent to

100 mg/m^2, considering the total standard adult body surface of 1.73 m^2 (man of about 70 kg of weight).

If no recovery occurred within four weeks after last TMZ administration, subject should be discontinued from the study.

If dose is reduced subject should remain on the reduced dose level for the rest of the study. Up titration dose is not allowed.

Table 7 Dose adaptation of TMZ

TMZ (TMZ) dose levels		
Dose level	TMZ dose (mg/day)	Remarks
0	250	Initiation dose
-1	180	Reduction for prior toxicity
TMZ dose reduction or discontinuation during monotherapy treatment		
Toxicity	Reduced TMZ by 1 dose level (a)	Discontinue TMZ
Absolute neutrophil count (ANC)	< 1.0 x 10^9/L	See footnote (b)
Thrombocyte count	<50x10^9/L	See footnote (b)
CTC non-haematological toxicity	CTC Grade 3	CTC Grade 4 (b)
a – TMZ dose levels are listed above b – TMZ is to be discontinued if • Dose level -1 (180 mg/day) still results in unacceptable toxicity • The same Grade 3 non-haematological toxicity recurs after dose reduction		

6.1.3 Other Study Drugs

Anti-emetic therapy may be administered prior to or following administration of TMZ.

6.2 Concomitant Medication/Therapy

Any prior or concomitant medication given to a subject during the course of the study will be indicated on the CRF.

Dose and generic name or trade name will be indicated.

The following concomitant medications are not permitted during this study:

- Cytotoxic therapies
- Immunotherapies
- Herbal medicine for anticancer treatment
- Other Anti-cancer chemotherapy
- Molecular target therapy
- PRRT
- Locoregional Therapies (TAE, TACE, SIRT, TARF)
- Tumor Surgery
- Radiotherapy (with the exception of external radiotherapy for bone metastasis)
- Other Investigational therapies
- Any somatostatin analogues other than study drug
- Cyclosporin
- GH (Growth Hormone) antagonist
- Dacarbazine

6.3 Procedures for Monitoring Subject Compliance

The investigator will be responsible for monitoring subject compliance.

Subjects can be withdrawn from the study at any time if the investigator or the sponsor decides that the subject is not in compliance with the study protocol.

Compliance will be assessed only for TMZ by returned capsule count, because Lanreotide ATG will be administered as deep subcutaneous injection at the investigational site, so its compliance is ensured. Appropriate number of TMZ capsules will be given to the subject during visits. Deviations of 80 % of the scheduled amount of TMZ intake will be regarded as a major protocol violation

Where a subject is consistently noncompliant with IMP intake they should be discontinued from IMP/withdrawn from the study. Please refer to Section 4.3 for the criteria for discontinuing the subject from IMP.

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 6.

7.1 Primary Efficacy Endpoint and Evaluation

The primary efficacy endpoint is the response of subjects to the study combination therapy, 9 months (Visit 12) after first treatment administration. Responders are subjects showing disease control according to RECIST criteria v 1.1, defined as objective response or stability of the disease. They include: CR (complete response), PR (partial response) or SD (stable disease).

7.2 Secondary Efficacy Endpoints and Evaluations

Secondary endpoints are:

- Progression Free Survival (PFS), defined as the time from first treatment administration to disease progression according to RECIST criteria v 1.1 or death
- Time to Response (TTR), defined as the time from first treatment administration to the first objective tumor response (PR or CR) according to RECIST criteria v 1.1
- Duration of Response, defined as the time from onset of the first objective tumor response (PR or CR) to objective tumor progression (PD, according to RECIST criteria v 1.1) or death from any cause
- Time to Progression (TTP) defined as the time from first treatment administration to the first objective tumor progression (PD) observed according to RECIST criteria v 1.1
- Best Overall Response defined as the best response recorded from the time of the first treatment until disease progression/recurrence, or the end of study, according to RECIST criteria v 1.1 (CR, PR, SD, PD)
- Objective Response Rate (ORR): Complete Response (CR), Partial Response (PR) at 9 and 12 months
- Disease Control Rate (DCR): Complete Response (CR), Partial Response (PR) and Stable Disease (SD) at 12 months
- The influence of typical carcinoids and atypical carcinoid on the Disease control rate (DCR) at 9 months
- Biochemical Response according to decrease in CgA plasma level in subject with baseline CgA level greater than ULN. Biochemical objective response is defined as a decreases of CgA $\geq$ 50%, while stable disease as a decrease $\geq$ 25% and less than 50%, as their best response to study treatment
- Value of NSE and CgA biomarkers levels at visits 2, 4, 6, 9, 12, 16 to assess their prognostic and predictive value
- Biomarkers expression (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies) correlated to tumor response (PFS and ORR and DCR) at 9 months and 12 months (V 12 and V 16), to assess their prognostic value
- The agreement of the central assessments of tumor radiological response and the local one, on the DCR at 9 months

Secondary efficacy endpoints and evaluations are summarised in Table 8.

Table 8 Secondary Efficacy Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Tumor response according to RECIST criteria v 1.1	At (visits 1, 6, 9, 12, 16)	Tumor response (CR, PR, SD or PD)	• Objective response rate (ORR) according to RECIST data presentation model • Disease Control Rate (DCR) at 12 months • Influence of typical/atypical carcinoids on DCR at 9 months • Time to Response (TTR) • Duration of Response • Time to progression (TTP) • Progression free survival (PFS) • Agreement between the central assessment of tumor radiological response and the local one • Best overall response •
NSE and CgA plasma level	each visit (visits 2, 4, 6, 9, 12, 16)	CgA and NSE	• Biochemical Response • Prognostic and predictive value of CgA and NSE on PFS, ORR and DCR
Biomarkers expression	visits 1 (availability of tissue sample)	SSTR2, Ki67, MGMT	• Prognostic value of biomarkers expression for PFS, ORR and DCR at 9 and 12 months

7.3 Methods and Timing of Assessing, Recording, and Analysing Efficacy Data

Methods for assessing efficacy data are described below. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 14.1, and methods of analyses are discussed in Section 10.4.5.

7.3.1 Responder Subjects

Responders are subjects showing disease control at 9 months (Visit 12) according to RECIST criteria v 1.1 (see Appendix 1) defined as objective response or stability of the disease. They include: CR (complete response), PR (partial response) or SD (stable disease).

Measurable disease lesions must be accurately measured in at least one dimension with longest diameter ≥ 10 mm with CT scan (with minimum lesion size no less than double the slice thickness).

Tumor Evaluation with CT scan

Tumor evaluation (chest, abdomen and pelvis) will be assessed at screening visit (V1) by means of triphasic CT scan. Measurable lesions, i.e., target lesions and the non-target lesions, by which subsequent response assessments will be judged, must be identified during tumor assessment at baseline (based on CT scan performed at screening visit).

A CT scan or MRI, for imaging progression disease evaluation, done within 12 months prior to screening visit must be available and will be considered for subjects selection.

Confirmation of a measurable tumour lesion presence will be done through a CT scan at screening visit, (V1).

A triphasic CT scan (chest, abdomen and pelvis) has to be repeated every 3 months and at End of Study (EOS) or at Early Withdrawal. The CT scan report must be available at the time of scheduled visits; the exam could be performed within maximum 10 days before the visit.

All CT scans must be performed at the investigational site; each site must have a designated radiologist or other physician responsible for the interpretation of CT scans, to evaluate CT scan report according to RECIST v 1.1 criteria. The same radiologist/physician should perform the evaluation for the entire duration of the study.

Clinical decisions and evaluation assessments according to the endpoints will be done locally by the investigator with the local radiologist consultation.

A second set of all original images are required for independent review to be performed by a centralized independent radiologist. The independent review will be performed at the end of the study and in addition to the local radiologist assessment. Treatment decisions during the study will be based on Investigator assessment. The primary analysis will be performed on the local RECIST v 1.1 assessment; a sensitivity analysis will be performed on the independent review. Agreement between the local and the independent review will be assessed.

Baseline requirement

All subjects should have at least one measurable target lesion. Measurable target lesions must be accurately measured in at least one dimension with longest diameter ≥ 10 mm with CT scan (with minimum lesion size no less than double the slice thickness), according to RECIST criteria v 1.1.

Target lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at screening visit (V1). Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements. A sum of the longest diameters for all target lesions will be calculated and reported as the baseline sum of the longest diameters. The baseline sum of the longest diameters will be used as reference by which to characterize the objective tumour response.

Response assessment

Disease control rate is defined as SD, PR or CR according to RECIST criteria v 1.1.

Partial response (PR) requires at least a 30% decrease in the sum of the longest diameters of all target lesions, taking as reference the baseline sum of the longest diameters. Complete response (CR) requires disappearance of all target and non-target lesions.

Progression is either a 20% or more increase in the sum of the longest diameters of all target lesions taking as reference the smallest sum on study, or the appearance of a new lesion, or the unequivocal progression of non-target lesions.

Best Overall Response

The best overall response to study treatment is the highest objective response achieved by the subject until the End of study/Early Withdrawal visit (V16), and will be rated according to RECIST v 1.1 criteria for reporting of results and include the following categories:

- complete response (CR),
- partial response (PR),
- stable disease (SD),
- progressive disease (PD)

For Subjects with Measurable Disease the definition is as follows (Table 9):

Table 9 Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

7.3.2 WHO performance score

The WHO or Zubrod score (after C. Gordon Zubrod) will be collected at V1, V6, V9, V12 and EOS, also known as Eastern Cooperative Oncology Group (ECOG) score, runs from 0 to 5, with 0 denoting perfect health and 5 death (See Appendix 2).

7.3.3 Biomarkers

NSE and CgA biomarkers (centralized evaluation)

To detect biochemical response (CgA) and to evaluate the prognostic and predictive value of NSE and CgA, CCI [redacted]

SSTR2, Ki-67 and MGMT (centralized evaluation)

In order to evaluate the prognostic value of SSTR2, Ki67 and MGMT biomarkers expression, centralised immunohistochemistry assays, using appropriate specific antibodies, will be performed on tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies: every effort should be done by the site staff to make them available. Biomarkers predictive value will be evaluated in terms of PFS, ORR and DCR at V12 and V16.

Tumour tissue samples must be prepared and shipped by each centre to the central laboratory, according to procedures and time frame specified in the Study Manual.

7.3.4 CCI [redacted]

[redacted]

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study (see Section 3.5 for a definition of the study duration) and will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

The safety of combination therapy will be monitored monthly through haematology renal, and biochemistry evaluations and TMZ dosage adjusted accordingly.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5).

Natural progression or deterioration of the disease under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE.

Death due to disease progression will be recorded as part of the efficacy evaluation and will not be subject to expedited reporting to regulatory authorities.

Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the baseline disease.

These signs and symptoms should only be reported as AEs/SAEs (depending on the investigator's judgement) if they are:

- Judged by the investigator to be unusually severe or accelerated disease or
- If the investigator considers the deterioration of disease signs and symptoms to be caused directly by the IMP.

If there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE/SAE as appropriate.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

Adverse events will be recorded and graded according to the current version of the NCI-CTCAE version 4.03-14 June 2010. In view of meta-analyses, and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild,
- NCI-CTCAE Grade 2 corresponds to moderate,
- NCI-CTCAE Grade 3 corresponds to severe,
- NCI-CTCAE Grade 4 corresponds to life threatening/disabling,
- NCI-CTCAE Grade 5 corresponds to death (related to AE).

Where:

- **Mild**: symptoms do not alter the subject's normal functioning
- **Moderate**: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject
- **Severe**: symptoms definitely hazardous to wellbeing, significant impairment of function or incapacitation.
- **Life threatening**: any event that places the subject at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death (also see Section 8.1.4).

8.1.2.2 Causality Classification

The relationship of an AE to IMP administration will be classified according to the following:

- **Related**: reports including good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

8.1.2.3 Assessment of Expectedness

The expectedness of an AE shall be determined by the sponsor according to the summary of product characteristics (SmPC) or package insert (PI) for an authorised medicinal product that is being used according to the terms and conditions of the marketing authorisation. If the IMP has marketing authorisations in several countries with different SmPCs or PIs, one will be selected as the reference document for assessing expectedness.

The reference document for assessing expectedness of AEs/event in this study will be the current SmPCs.

8.1.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the investigator.

8.1.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the investigator, in physical examination findings (abnormalities) will be recorded as AEs.

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings as judged by the investigator as clinically significant (e.g. electrocardiogram changes) that result in a change in IMP dosage or administration schedule, or in discontinuation of the IMP, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.3 Recording and Follow up of Adverse Events

At each visit, the subject should be asked a non-leading question such as: "How have you felt since starting the new treatment/last dose/the last assessment?"

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the CRF/eCRF, including all AEs occurred within 4 weeks after the last dose of IMP, either one has been administered (i.e. lanreotide ATG or TMZ). Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbation's of pre-existing illnesses should be recorded according to the National Cancer Institute (NCI) terminology. Any AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IMP or other illness). The investigator is required to assess causality and record that assessment on the CRF/eCRF. Follow up of the AE, after the date of IMP discontinuation, is required if the AE or its sequelae persist. Follow up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

8.1.4 Reporting of Serious Adverse Events

All SAEs (as defined below) regardless of treatment group or suspected relationship to IMP must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

A SAE is any AE that:

(1) Results in death,

(2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death,

(3) Results in in-subject hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further),

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP,

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-subject hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any in-subject admission (even if less than 24 hours). For chronic or long term in-subjects, in-subject admission also includes transfer within the hospital to an acute/intensive care in-subject unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-subject hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.
- Pre-planned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to IMP administration occurring at any other time after completion of the study must be promptly reported.

The following information is the minimum that must be provided to the sponsor pharmacovigilance contact (pharmacovigilance.italy@ipsen.com) within 24 hours for each SAE:

- Study number
- Centre number
- Subject number
- AE/SAE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

8.1.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected post-study and it may be necessary to discontinue administration of the IMP.

Information regarding pregnancies must be collected on the AE page of the CRF/eCRF and reported to the sponsor as an SAE. The sponsor will request further information from the

investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all female subjects to inform them immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow up after the subject's involvement in the study has ended.

Pregnancies with a conception date within 90 days after subject's last dose of IMP must also be reported to the investigator for onward reporting to the sponsor.

If the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, this should be reported to the sponsor. After the partner has given written consent, she should be counselled and followed as described above. Monitoring of the partner should continue until conclusion of the pregnancy.

8.1.6 Deaths

All AEs resulting in death either during the study period or within 4 weeks after the last dose of IMP either one has been administered (i.e. lanreotide ATG or TMZ), must be reported as an SAE within 24 hours of the investigator's knowledge of the event.

For AEs leading to death, NCI CTCAE Grade 5 is the only appropriate grade (see Section 9.1.1). Deaths that cannot be attributed to an NCI CTCAE term associated with Grade 5 or that cannot be reported within an NCI CTCAE category as 'Other' have to be reported as one of these four AE options:

- Death NOS,
- Disease progression NOS,
- Multi-organ failure,
- Sudden death.

8.1.7 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IMP (see Section 4.3).

If the IMP is discontinued due to a SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.4).

In all cases, the investigator must ensure the subject receives appropriate medical follow up (see Section 8.1.3).

8.1.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CA), IECs and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements.

8.2 Clinical Laboratory Tests

Blood samples will be collected at each visit (see Table 6 and Section 5.2) for the evaluation of haematology and biochemistry; urine samples will be collected at Visits 1, 2, 4, 5, 6, 9, 12, 16 for urinalysis.

The investigator will review the safety laboratory test results, document the review, and record any clinically relevant changes occurring or observed during the study in the AE

section of the CRF/eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to Baseline (V2) values or to a level deemed acceptable by the investigator and the sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

8.2.1 Haematology

Blood samples (about 5 mL, according to Local Laboratory Procedures) will be collected in a potassium ethylene-diamine-tetra-acetic acid (EDTA) tube to assess the following parameters: RBC count, haemoglobin, haematocrit, MCV, MCH, MCHC, WBC count, ANC, Platelets, Glycated Haemoglobin (HbA1c).

Blood samples (about 3 mL according to Local Laboratory Procedures) will be collected in a citrated tube to assess the following coagulation parameters: activated partial thromboplastin time (aPTT), prothrombin time (PT) and and international normalised ratio (INR).

8.2.2 Blood Biochemistry

Blood samples (about 5 mL, according to Local Laboratory Procedures) will be collected in an activator gel tube to assess the following parameters: urea, serum creatinine (Cr), total serum bilirubin (direct bilirubin only if total serum bilirubin is out of range) , electrolytes (chloride, sodium, potassium, calcium, phosphate), lactate dehydrogenase (LDH), ALT, AST, gamma glutamyl transferase (γGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, vitamin B12, TSH, FT3, FT4.

Blood samples (about 10 mL) will be collected at screening visit (V1) to perform Serology assessments (hepatitis B surface antigen, hepatitis C antibody), according to Local Laboratory Procedures.

CrCl will be calculated using Cockcroft-Gault Equation (Figure 4).

Figure 4 Cockcroft-Gault Equation

Women

$$GFR[ml/\min] = 0{,}85 \cdot \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

Men

$$GFR[ml/\min] = \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

8.2.3 Urinalysis

Fresh urine samples (at least 10 mL) will be collected to assess the following parameters: pH, protein, ketones, total bilirubin, blood, WBC, urobilinogen, glucose, nitrite and specific gravity and microscopy if necessary. Analysis by dipstick is allowed.

Microscopy will be performed, if indicated, but results will not be collected in the eCRF. If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE in the eCRF.

8.2.4 Pregnancy Test

A human chorionic gonadotrophin (βHCG) serum test will be performed for all female subjects of childbearing potential at Screening (V1) and if clinically indicated thereafter. Any subject becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.5.

8.2.5 Other Clinical Laboratory Tests

If necessary, additional clinical laboratory tests will be performed to ensure the safety of the subjects, but will not be an assessment of the safety of the study drug.

8.3 Physical Examination

Physical examinations will be conducted at each visit.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4 Vital Signs

Blood pressure (Systolic and Diastolic) and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded in supine, sitting or standing position according to clinical practice. Absolute values and change from Baseline (V2) will be analysed.

8.5 Electrocardiography

An ECG analysis will be included as a safety evaluation/endpoint in this study.

The ECGs will be recorded at screening (V1), V9 and EOS.

Twelve lead ECGs will be recorded so that the different ECG intervals (RR, PR, QRS, QT) can be measured QTc will be measured automatically according the Bazett formula [Corrected QT (QTC) = Bazett's Formula = QT Interval / √ (RR interval) RR Interval = 60/HR]. The ECG will be recorded with the subject in supine position after five minutes of rest until four regular consecutive complexes are available. Automated ECG intervals estimates taken from the ECG recorder will be used in this study.

Any clinically significant abnormalities will be recorded as AEs.

8.6 Echocardiography

M- and B-mode echocardiography will be performed at screening (V1), V9 and EOS. The following assessments, as recommended by ENETS Consensus Guidelines [44] will be performed:

- Valves function and morphology
- Left and Right Ventricular size and function
- Patency of the foramen ovale
- Wall thickness

8.7 Gallbladder echography

Within 4 weeks prior to first study treatment intake, ultrasound examination of the gallbladder will be performed on each subject by Gallbladder echography. The measurement will be repeated at V9 and EOS. It is highly recommended to use the technique used at the screening visit for the following assessments of gallbladder function for each subject.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics are not assessed in this study.

10 STATISTICS

10.1 Analyses Populations

The following population will be used during statistical analyses:

- **Screened population**: All subjects screened (i.e. who signed the informed consent).
- **Intention to treat (ITT)/Safety population**: All subjects who received at least one dose of study medication (either LAN ATG 120 mg or TMZ).
- **Per protocol (PP) population**: All subjects in the ITT population for whom no major protocol violations/deviations occurred.

10.1.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint(s) will be performed on the ITT/Safety population. In addition, PP analysis may be performed as a supportive analysis.

The analyses of safety data will be performed based on the ITT/safety population.

10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation will be described in the Protocol Deviation Specification Document and its impact on inclusion in each analysis population (ITT/safety and PP populations) for any subject will be specified. The final list of protocol deviations impacting the PP population will be reviewed during the data review meeting held prior to database lock. The list of major protocol deviations impacting inclusion in the populations will be reviewed during the data review meeting held prior to database lock. The list will be updated to include any additional major protocol deviations impacting inclusion in all populations.

10.2 Sample Size Determination

Sample size and statistical assumption were made according to a Fleming's Single Stage Design.

To demonstrate the efficacy of TMZ associated to Lanreotide, we consider the proportion of responders as subjects with DCR after 9 months of therapy.

The following assumptions are made:

- The proportion of responders should be equal or greater than 30% to be clinically relevant (π_1),
- a proportion of responders equal or lower than 10% is considered as not acceptable (π_0),
- the 1-sided error probability is set to $\alpha = 0.025$ and
- the power is set to 90% ($\beta = 0.10$).

The 1-sided hypotheses to be tested are:

$\pi \leq \pi_0$ and $\pi \geq \pi_1$;

35 evaluable subjects are needed.

Estimating a 10% of drop-out rate the total number of subjects to be treated is set to N=40.

Calculations were made using "Statistical Tables for the Design of Clinical Trials" [43].

10.3 Significance Testing and Estimations

The statistical test on the primary objective will be performed one sided with a type I error rate set at 2.5%.

All other statistical tests will be performed two sided with a type I error set at 5 %.

10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO), managed by the sponsor's Specialty Franchise Clinical Operations Department.

A Statistical Analysis plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 8 or higher).

CCI [redacted]

10.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease (predosing AEs and ongoing medical history, prior medications and therapies, baseline symptoms, etc) will be presented for the ITT/safety population.

10.4.2 Homogeneity of Treatment Groups

Not applicable.

10.4.3 Subject Disposition and Withdrawals

The numbers and percentages of subjects screened and included in each of the populations will be tabulated. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were treated, discontinued and completed will be tabulated. Primary reasons for discontinuation of study treatment will be tabulated.

10.4.4 Pharmacokinetic Data

Not applicable.

10.4.5 Efficacy Evaluation

As indicated in Section 7.1, the primary efficacy variable is response of subjects to the study combination therapy, 9 months (V 12) after first treatment administration. Responders are subjects showing disease control according to RECIST criteria v 1.1, defined as objective response or stability of the disease. They include: CR (complete response), PR (partial response) or SD (stable disease). The response rate will be analysed by an exact binomial proportion test for one-way tables in the ITT/safety population. A supportive analysis will be performed on the PP population. In addition a sensitivity analysis will be performed on both populations based on the independent assessment performed at the end of the study by the central reading committee.

As indicated in Section 7.2, the secondary efficacy endpoints are:

- Best Overall Response defined as the best response recorded from the time of the first treatment until disease progression/recurrence or the end of study, according to RECIST criteria v 1.1 (CR, PR, SD, PD
- analysed using frequency tables;
- Chromogranin A (CgA) levels will be detected at baseline and during treatment period every 3 months as a surrogate efficacy endpoint (biochemical response). Subjects will be considered to have an objective biochemical response if there is a ≥50% reduction in plasma CgA from baseline level, while stable disease is defined as decrease ≥25% and less than 50%, as the best response to study treatment.

- Chromogranin A (CgA) and NSE levels assessed at Visit 2, Visit 4, Visit 6, visit 9, visit 12 and EOS will be presented by mean values, standard deviations, minimum, maximum and 95%-confidence intervals of the mean at each timepoint (for raw values and changes from baseline). In addition, both of these parameters will be analysed by ANCOVA for repeated measures, using baseline values as covariates.
- Progression Free Survival (PFS) is defined as the time from 1st treatment administration until progression according to RECIST criteria vs 1.1.

PFS of subjects who are lost to follow-up and those who have not progressed at EOS will be censored at the date of the last disease assessment subject to rules summarised in Table 10.

Table 10 Censoring Rules for PFS

Situation	Date of Censoring
No baseline evaluable assessment	Date of 1st treatment administration
Two or more not evaluable (NE) assessments before PD or death	Date of last evaluable disease assessment before the second NE assessment
No PD	Date of last evaluable disease assessment
Treatment discontinuation for undocumented progression	Date of last evaluable disease assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable disease assessment
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last evaluable disease assessment prior to the initiation of not permitted medication or therapies.

The distribution of PFS times will be estimated using the Kaplan-Meier method. The median PFS and its associated 95 % CI will be estimated.

- Time to response (TTR) is defined as the time from 1st treatment administration to the first objective tumor response (PR or CR) according to RECIST criteria vs 1.1.

  TTR of subjects who are lost to follow-up or die prior to any objective tumor response will be censored at the date of the last disease assessment subject to rules summarised in Table 11.

Table 11 Censoring Rules for TTR

Situation	Date of Censoring
No baseline evaluable assessment	Date of 1st treatment administration
PD or death	Date of last evaluable disease assessment before PD or death.
No PR nor CR	Date of last evaluable disease assessment
Treatment discontinuation	Date of last evaluable disease assessment

- The distribution of TTR will be estimated using the Kaplan-Meier method. The median TTR and its associated 95 % CI will be estimated.

  Duration of response is defined as the time from onset of the first objective tumor response (PR or CR) to objective tumor progressions (PD) according to RECIST criteria vs 1.1.

  Subjects without any PR or CR will not be taken into account in this analysis. Duration of response of subjects who are lost to follow or do not progress following the first objective tumor response will be censored at the date of the last disease assessment.

The distribution of duration of response will be estimated using the Kaplan-Meier method. The median duration of response and its associated 95 % CI will be estimated.

- Time to progression (TTP) is defined as the time from first treatment administration to the first objective tumor progression (PD) according to RECIST criteria vs 1.1.

  TTP of subjects who are lost to follow-up, and those who have not progressed at EOS will be censored at the date of the last disease assessment subject to rules summarised in Table 12.

Table 12 Censoring Rules for TTP

Situation	Date of Censoring
No baseline evaluable assessment	Date of 1st treatment administration
Two or more not evaluable (NE) assessments before PD or death	Date of last evaluable disease assessment before the second NE assessment
No PD	Date of last evaluable disease assessment
Treatment discontinuation for undocumented progression	Date of last evaluable disease assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable disease assessment
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last evaluable disease assessment prior to the initiation of not permitted medication or therapies.

The distribution of TTP times will be estimated using the Kaplan-Meier method. The median TTP and its associated 95 % CI will be estimated.

- Best overall response according to RECIST criteria v 1.1 (CR, PR, SD, PD)
- Objective Response Rate (ORR): Complete Response (CR), Partial Response (PR) at 12 months
- Disease Control Rate (DCR): Complete Response (CR), Partial Response (PR) and Stable Disease (SD) at 9 and 12 months
- The influence of typical carcinoids and atypical carcinoid on the Disease control rate (DCR) at 9 months (V 12) will be analysed using frequency tables.
- The prognostic and predictive value of NSE and CgA biomarkers levels on PFS will be analysed using a Cox-proportional hazard model and the influence on DCR at 9 and 12 months (V 12 and V 16) will be analysed using a logistic model.
- The prognostic value of biomarkers expression (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies) for PFS will be analysed using a Cox-proportional hazard model and the influence on ORR and DCR at 9 and 12 months (V 12 and V 16) will be analysed using a logistic model.
- The agreement of the central assessments of radiological response and the local one will be analysed using Cohen's kappa.

10.4.6 Adjustment for Country/Centre Effect

No adjustment per centre will be performed.

10.4.7 Safety Evaluation

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.

Adverse events reported by investigators using the NCI-CTC classification (version 4.03) will be coded using MedDRA dictionary (version 20.0 or higher).

Summary incidence tables will be provided, classified by body system, preferred term and associated NCI/CTC worst grade. In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) will be chosen. Dose delays, dose interruptions will be listed by cycle.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTC criteria. All haematology and biochemistry parameters by subject will be listed. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of study medication.

A TEAE is defined as any AE that occurs during the active phase of the study if:

- it was not present prior to receiving the first dose of IMP, or
- it was present prior to receiving the first dose of IMP but the intensity increased during the active phase of the study, or
- it was present prior to receiving the first dose of IMP, the intensity is the same but the drug relationship became related during the active phase of the study.

All TEAEs will be flagged in the AEs listings.

Concomitant medication will be coded by using WHO Drug Dictionary (version 2009) and will be summarised with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, SD and range as appropriate) by overall will be presented for vital signs, blood pressure, heart rate, ECG parameters, clinical laboratory tests at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal exams.

10.5 Subgroup Analyses

Subgroup analyses will be performed according to the typical/atypical classification.

10.6 Interim Analyses

No interim analysis will be performed.

11 ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external CAs and sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 12.4, and to any other locations used for the purpose of the study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor's representative as soon as possible, to assist with preparations for the inspection.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

12.1.2 Protocol Deviations, Violations, and Exceptions

A protocol deviation is nonadherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study centre personnel, on the CRF.

As a matter of policy, the sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the subject will be allowed to enter the study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP.

12.2 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

12.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring this data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.

Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs according to the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

A Steering Committee will be composed of investigator and sponsor representatives to govern the overall scientific and operational management of the study. A specific charter may be developed to define roles and responsibilities.

12.4 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 11).

12.5 Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

12.6 Steering Committee

Since September 2016 a Study Steering Committee has been designated. The role of the Study Steering Committee (SSC) is to provide overall supervision for the ATLANT Study in collaboration with the Trial Sponsor (Ipsen).

The ATLANT Steering Committee member's responsibilities are the following:

- To leverage external and internal expertise in the planning and execution of the study
- To identify and resolve study obstacles and issues
- To provide advice and support to the Sponsor on medical and safety aspects of the trial.
- To analyze and comment the study results
- To facilitate the communication with the participating sites
- To collaborate with the Trial Sponsor in the Scientific Communications & Publications of study results
- To agree to proposals for substantial protocol amendments

The ATLANT Study Steering Committee will consist of 3 external members experts in treatment of lung NETs. The SSC will consist of the following KOLs:

- Alfredo Berruti – U.O.Oncologia A.O. Spedali Civili (Brescia)
- Nicola Fazio – Unità Oncologia Medica Gastrointestinale e Tumori Neuroendocrini IEO (Milano)
- Piero Ferolla – SC Oncologia Medica A.O. U. di Perugia Ospedale "Santa Maria della Misericordia (Perugia)

The formal designation of SSC members, their activities as well as the confidentiality of all information/study document/data are described and regulated by the specific contract properly signed by parties.

13 ETHICS

13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1 or 1.6).

In addition, this study will adhere to all local regulatory requirements and Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

13.2 Informed Consent

Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IMP). Sufficient time will be allowed to discuss any questions raised by the subject.

The sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the sponsor, and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

13.4 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, subjects will not be identified by their names, but by an identification code (e.g. initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the CRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc, should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF.

The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

14.2 Data Management

Electronic Data Capture (EDC) will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO, directed by the sponsor's Specialty Franchise Clinical Operation department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Monitoring Procedures). Any data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history and concomitant medication terms will be performed by the sponsor's Coding Group. Concomitant medications will be coded using WHODRUG and AEs/Surgical procedures/Non drug Therapies/Medical history terms will be coded using MedDRA.

14.3 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Trial documents must be retained according to current and applicable regulatory requirements and national laws. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

15 FINANCING AND INSURANCE

15.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

Financial Disclosure Statements will need to be completed, as requested by Local legislation (AIFA, D.M. 51, 21-Dec 2007).

15.2 Insurance, Indemnity and Compensation

The sponsor will provide Product Liability insurance for all subjects included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

16 REPORTING AND PUBLICATIONS OF RESULTS

16.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

16.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

CCI [redacted]

17 REFERENCES

1. Yao JC et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35825 cases in the United States. J Clin Oncol. 2008;26(18): 3063.
2. Faggiano-Ferolla et al. Natural history of gastroenteropancreatic and thoracic neuroendocrine tumors. Data from a large prospective and retrospective Italian epidemiology study. J Endocrinol Invest. 2012;35(9): 817-23.
3. Ferolla et al. Epidemiology of non-gastroenteropancreatic (neuro)endocrine tumors. Clin EndoClin Endocrinol (Oxf). 2007;66(1): 1-6.
4. NANETS consensus guidelines for the diagnosis and management of neuroendocrine tumors. Phan AT et al. Pancreas 2010; 39(6): 784-798.
5. De Herder WW, Mazzaferro V, Tavecchio L and Wiedenmann B. Multidisciplinary approach for the treatment of neuroendocrine tumors. Tumori. 2010;96: 833-46.
6. Oberg K et al. Neuroendocrine bronchial and thymic tumors: esmo clinical practice guidelines for diagnosis treatment and follow-up. Annals of Oncology. 2012;23(7):vii120-vii123.
7. AIOM GUIDELINES 2014" Linee Guida Neoplasie Neuroendocrine Gastroenteropancreatiche.
8. Ferolla P. Medical Treatment of Advanced Thoracic Neuroendocrine Tumors. , Thoracic Surgery Clinics. 2014 Aug;24(3):351–355. DOI: 10.1016/j.thorsurg 2014.05.006
9. ENETS Guidelines 2014.
10. Pulmonary Neuroendocrine (Carcinoid) Tumors: European Neuroendocrine Tumor Society Expert Consensus and Recommendations for Best Practice for Typical and Atypical Pulmonary Carcinoid –Feb 2015.
11. Pelosi GL, Rindi G, Travis WD, Papotti M. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. J Thorac Oncol. 2014 Mar;9(3):273-8.
12. Rindi et Al. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. Endocr Relat Cancer. 2013 Dec;16;21(1):1-16.
13. Grozinsky-Glasberg S et al. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer. 2008 Sep;15(3):701-20.
14. DeVita, Hellman, and Rosenberg's. Cancer: Principles & Practice of Oncology, 9th edition. DeVita V.T. et al. – Cap 29 – Edited by Wolters Kluwer Health, Lippincot Williams and Wilkins.
15. CLARINET NEJM Jul 2014
16. Pavel ME et al. Everolimus plus Octreotide Long-acting repeatable for the treatment of advanced neuroendocrine tumors associated with carcinoid syndrome (RADIANT-2): a randomized, placebo-controlled, phase-III study. LANCET 2011;378: 2005-12.
17. Bianchi A et al. The treatment of neuroendocrine tumors with long-acting somtostatin analogues: a single center experience with Lanreotide autogel. J Endocrinol Invest 2011;34 (9):692.
18. Srirajaskanthan R. et al. Surgical management and palliative treatment in bronchial neuroendocrine tumors: a clinical study of 45 subjects. Lung Cancer 2009;65:68–73.

19. Filosso P.L. et al. Long-term survival of atypical bronchial carcinoids with liver metastasis, treated with octreotide. European Journal of Cardio-thoracic Surgery 2002;21:913–917.
20. Ekeblad S et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. Clin Cancer Res. 2007;13(10):2986-91.
21. Strosberg J et al. First-line chemotherapy with capecitabine and Temozolomide in subjects with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117(2):268-75.
22. Kulke MH et al. Phase II study of Temozolomide and thalidomide in subjects with metastatic neuroendocrine tumors. J Clin Oncol. 2006;24(3):401-6.
23. Walter T et al. New treatment strategies in advanced neuroendocrine tumours. Dig Liver Dis 2012;44(2):95-105.
24. Chan JA and Kulke MH. New treatment options for subjects with advanced neuroendocrine tumors. Curr Treat Options Oncol. 2011;12(2):136-48.
25. Welin S et al. Clinical effect of Temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. Cancer. 2011; doi: 10.1002/cncr.26124
26. Crona et al. Effect of Temozolomide in subjects with metastatic bronchial carcinoids. Neuroendocrinology 2013; 98(2): 151-5.
27. Koumarianou A et al. Combination treatment with metronomic Temozolomide, bevacizumab and long-acting octreotide for malignant neuroendocrine tumours. Endocr Relat Cancer. 2012; 19(1): L1-L4.
28. 3-arm Trial to Evaluate Pasireotide LAR/Everolimus Alone/in Combination in Patients With Lung/Thymus NET - LUNA Trial, http://www.clinicaltrial.gov/ct2/show/NCT01563354?term-luna&rank=1
29. Safety and Tolerability of Pasireotide LAR in Combination With Everolimus in Advanced Metastatic NETs (COOPERATE-1), http://clinicaltrials.gov/show/NCT01263353
30. Combination of Lanreotide Autogel 120mg and Temozolomide in Progressive GEP-NET (SONNET) https://clinicaltrials.gov/ct2/show/NCT02231762
31. Handbook of Statistics in Clinical Oncology, Third Edition, John Crowley, Antje Hoering - 2012 - Mathematics-par 9.1 pg 140.
32. Hassel JC et al. MGMT gene promoter methylation correlates with tolerance of Temozolomide treatment in melanoma but not with clinical outcome. Br J Cancer 2010;103(6): 820-6.
33. Neyns B et al. Dose-dense Temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects. Cancer. 2010; 116(12):2868-77.
34. Eriksson B. New drugs in neuroendocrine tumors: rising of new therapeutic philosophies? Curr Opin Oncol 2010;22(4):381-6.
35. Kulke MH et al. O6-methylguanine DNA methyltransferase deficiency and response to Temozolomide-based therapy in subjects with neuroendocrine tumors. Clin Cancer Res. 2009; 15(1): 338-45.
36. Perry JR1 et Al. Phase II trial of continuous dose-intense Temozolomide in recurrent malignant glioma: RESCUE study. J Clin Oncol. 2010 Apr 20;28(12): Erratum in J Clin Oncol. 2010 Jul 20;28(21):3543

37. Kyung-Ko et Al. Metronomic treatment of Temozolomide increases anti-angiogenicity accompanied by down-regulated O(6)-methylguanine-DNA methyltransferase expression in endothelial cells. Exp Ther Med. 2011 Mar;2(2):343-348
38. Caplin M., Baudin E., Ferolla P. et al. in submission to Annals of Oncology 2014
39. International Conference on Harmonisation (ICH) E9 and Federal register Vol 63, No. 179 (September 1998).
40. Food and Drug Administration (FDA) 21 CFR Part 11, Electronic Records, Electronic Signatures
41. FDA Guidance for Industry: Computerized Systems Used in Clinical Trials
42. GMP Annex 13
43. Machin,D. and Campbell,M: Statistical tables for the Design of Clinical Trials, Blackwell, London 1987
44. Plokinger U et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Ehocardiography. Neuroendocrinology. 2009;90:190-193

18 LIST OF APPENDICES

Appendix 1 RECIST Criteria version 1.1

RECIST Criteria version 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Changes in the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- **Chest x-ray** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
- **Use of MRI** remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- **PET-CT** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **Ultrasound** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
- Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Appendix 2 WHO Performance status

WHO Performance status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 3 Common Terminology Criteria for Adverse Events (CTCAE)

Common Terminology Criteria for Adverse Events (CTCAE)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf