Document Name: a9352030325-stat-plan

Clinical	PPD 3:35:44 GMT+0000
Clinical	PPD 7:33 GMT+0000
Managerial	PPD 4:38:10 GMT+0000
Managerial	PPD 10:58 GMT+0000

Approved

STATISTICAL AND ANALYSIS PLAN

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

PROTOCOL VERSION AND DATE:
FINAL 3.0: 16 NOVEMBER 2017

SAP Version	Date
Final, Version 2.0	04 May 2020

STUDY NUMBER:	A-93-52030-325
EUDRACT NUMBER	2014-005579-10
PROTOCOL TITLE:	EFFICACY AND SAFETY OF LANREOTIDE ATG 120 MG IN COMBINATION WITH TEMOZOLOMIDE IN SUBJECTS WITH PROGRESSIVE WELL DIFFERENTIATED THORACIC NEUROENDOCRINE TUMORS
SAP VERSION:	Final version 2.0
SAP DATE:	04 May 2020

Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

Responsibility	Name, title & Office	Signature	Date
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IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical and Analysis Plan version became the Final Statistical and Analysis Plan

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
11	1.2	16SEP2019	04MAY2020	Delete sentence stating that the primary endpoint will be based on subjects who completed all scheduled visit until V12, since disease control rate will also be assessed according to subjects withdrawn before 9 months.
21 21 25 26 41 41 44 45	3.1.1 3.1.2 3.2.1.1.1 3.2.1..1.2 3.2.1.2.7 3.2.1.2.8 3.2.1.2.13 3.2.1.2.14	16SEP2019	04MAY2020	Deletion of reference to visits 12 and 16 after the mentions of the 9 and 12 months assessments since subjects withdrawn earlier will also be considered.
22	3.2.1	16SEP2019	04MAY2020	Update of the summary of efficacy analyses to describe the amended analyses.
25	3.2.1.1.1	16SEP2019	04MAY2020	Update of the primary endpoint definition to include subjects withdrawn before 9 months in the assessment of DCR at 9 months. Addition of the threshold 10 % for the statistical test of the proportion of responders.
26	3.2.1..1.2	16SEP2019	04MAY2020	Update of the sensitivity analyses to include subjects withdrawn before 9 months in the assessment of DCR at 9 months.
41	3.2.1.2.7	16SEP2019	04MAY2020	Update of the objective rate definition to include subjects withdrawn before 9 and 12 months in the assessments at 9 and 12 months.
41	3.2.1.2.8	16SEP2019	04MAY2020	Update of the DCR at 12 months definition to include subjects withdrawn before 12 months in the assessment.
45 57 61	3.2.1.2.14 6 7.2	16SEP2019	04MAY2020	Update of publications references.

56	5	16SEP2019	04MAY2020	Modification of the primary endpoint reported as a change from the protocol.
66	7.3	16SEP2019	04MAY2020	Update of the list of TFLs according to modifications done in the body of the document

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADaM:	Analysis Data Model
AE:	Adverse Event/Experience
ANC:	Absolute Neutrophils Count
aPTT:	activated Partial Thromboplastin Time
ATG:	Autogel
ALT:	Alanine aminotransferase
AST:	Aspartate aminotransferase
ATC:	Anatomic Therapeutic Class
ANCOVA:	Analysis of Covariance
BMI:	Body Mass Index
BOR:	Best Overall Response
ßHCG:	Human Chorionic Gonadotrophin
CgA:	Chromogranin A
CI:	Confidence Interval
Cr:	Serum creatinine
CR:	Complete Response
CS:	Clinically Significant
CT:	Computed Tomography
CTC:	Common Toxicity Criteria
CTCAE:	Common Terminology Criteria for Adverse Events
DCR:	Disease Control Rate
DOR:	Duration Of Response
DMC:	Data Monitoring Committee
ECG:	ElectroCardioGram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	Electronic Case Report Form
EOS:	End Of Study
EW:	Early Withdrawal
FDA:	Food and Drug Administration
FT3:	Free Triiodothyronine
FT4:	Free Thyroxine
γ-GT:	Gamma glutamyl transferase
HbA1c:	Glycated haemoglobin

HBV:	Hepatitis B surface antigen
HCV:	Hepatitis C antibody
IC:	Informed consent
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
INR:	International Normalised Ratio
ITT:	Intention-To-Treat
KM:	Kaplan-Meier
LDH:	Lactate Dehydrogenase
LLN:	Lower Limit of Normal range
LOCF:	Last Observation Carried Forward
MCH:	Mean Cell Haemoglobin
MCHC:	Mean Cell Haemoglobin Concentration
MCV:	Mean Corpuscular Volume
MedDRA:	Medical Dictionary for Regulatory Activities
MGMT:	O6-methylguanine-DNA methyltransferase
MRI:	Magnetic Resonance Imaging
NCI:	National Cancer Institute
NCI–CTCAE:	National Cancer Institute – Common Toxicity Criteria for Adverse Events
NCR:	Non-Complete Response
NCS:	Not Clinically Significant
NE:	Not Evaluable
NET:	NeuroEndocrine Tumor
NPD:	Non-Progressive Disease
NSE:	Neuron-Specific Enolase
NYHA:	New York Heart Association
ORR:	Objective Response Rate
PD:	Progressive Disease
PFS:	Progression-Free Survival
PP:	Per-Protocol
PR:	Partial Response
PRRT:	Peptide Receptor Radionuclide Therapy
PT:	Prothrombin Time
QC:	Quality control

QRS:	QRS interval duration
QT:	Time interval for ventricular depolarisation and repolarisation
QTc:	Corrected QT interval
RBC:	Red Blood Cells
RECIST:	Response Evaluation Criteria In Solid Tumours
SAP:	Statistical and Analysis Plan
SAE:	Serious Adverse Event/Experience
SAS®:	Statistical Analysis System®
SD:	Stable Disease
SI:	Standard International
SIRT:	Selective Internal Radiotherapy
SSTR2:	Somatostatin Receptor type 2
TACE:	Transcatheter Arterial Chemoembolization
TAE:	Transcarterial Emoembolization
TARF	Thermo-Ablation with Radio-Frequency
TEAE:	Treatment Emergent Adverse Event/Experience
TFLs:	Tables, Figures and Listings
TMZ:	Temozolomide
TNM:	Tumor Node Metastasis
T-NET:	Thoracic NeuroEndocrine Tumor
TPR:	Time Point Response
TSH:	Thyroid-Stimulating Hormone
TTP:	Time To Progression
TTR:	Time To Response
ULN:	Upper Limit of Normal range
v:	Version
V:	Visit
W:	Week
WBC:	White Blood Cell
WHO:	World Health Organization
WHO-DD:	World Health Organization – Drug Dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

To evaluate the efficacy of Lanreotide Autogel (ATG) 120 mg in combination with Temozolomide (TMZ) in subjects with unresectable advanced neuroendocrine tumour of the lung or thymus (typical and atypical carcinoids according to the World Health Organization (WHO) 2004 criteria) as Disease Control Rate (DCR) at 9 months (i.e. Complete Response (CR), Partial Response (PR) or Stable Disease (SD)), according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1.

1.1.2 Secondary objectives

- To assess, according to RECIST criteria v 1.1:
  - Progression-Free Survival (PFS),
  - Time to Response (TTR),
  - Duration of Response (DOR),
  - Time to Progression (TTP),
  - Best Overall Response (BOR) defined as the best response recorded from the time of first treatment until disease progression/recurrence or the end of study (CR, PR, SD, Progressive Disease (PD)),
  - Objective Response Rate (ORR) at 9 and 12 months: CR, PR,
  - DCR at 12 months: CR, PR and SD,
  - The influence of typical carcinoids and atypical carcinoids on the 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 Somatostatin receptor type 2 (SSTR2), Ki67 and O6-methylguanine-DNA methyltransferase (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 (V1 - screening), V6, V9, V12 and V16 (End of Study (EOS)) or early withdrawal (EW)),
  - vital signs (blood pressure, heart rate and body weight) measurements at each study visit,
  - electrocardiogram (ECG), electrocardiography at V1, V9 and V16 (EOS) or EW,
  - physical examination at each study visit,
  - concomitant medications usage throughout the study,
  - gallbladder echography at V1, V9 and V16 (EOS) or EW.

1.2 Study design

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 DCR, in adult subjects with a histologically documented unresectable advanced (locally or metastatic) well or moderately differentiated neuroendocrine tumor (NET) 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 (IC) for the study has been obtained, an eligibility Computed Tomography (CT) scan (total body) must be performed, unless a CT scan was already performed in the last 28 days, then it would be considered suitable for the screening tumour evaluation.

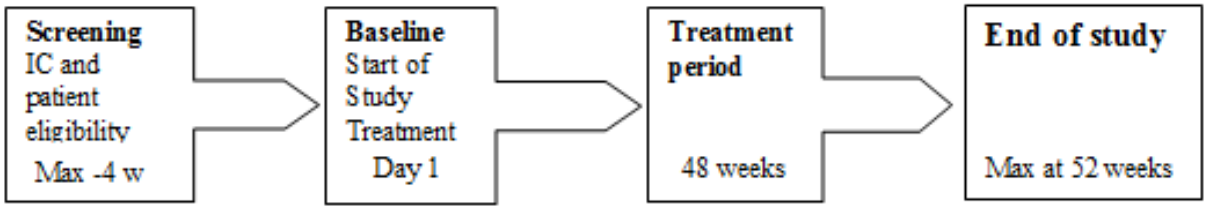
At baseline visit (V2), performed after a maximum of 4 weeks after V1, subjects fulfilling the inclusion and exclusion criteria will be treated with Lanreotide ATG 120 mg every 28 days and TMZ 250 mg daily for 5 consecutive days every 28th days (in case of bone marrow toxicity the dose may subsequently 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.

Subjects who complete all scheduled visits or who progress or die before the end of the study will be considered to have completed the study.

Subjects who complete the study will have final procedures and assessments performed at the final visit (V16, i.e. EOS). Subjects who withdraw from the study before the completion of the evaluation period will have an early withdrawal (EW) visit and should perform all assessments provided at final visit (V16 EOS).

At their last study visit (EOS V16 W52), subjects still benefiting from treatment (according to the investigator judgement) will have the option to continue to receive the combination of Lanreotide ATG 120 mg and TMZ 250 mg. In such a situation, Lanreotide ATG 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 1 Study design



1.2.1 Study population

40 subjects with progressive well or moderately differentiated thoracic neuroendocrine tumor (T-NET) (lung and thymic carcinoids) are planned to be enrolled in this study.

1.2.2 Study exposure

Subjects' enrolment will last approximately 20 months and the overall duration of the study will be approximately 3 years.

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 4-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 (V16 - EOS), 4 weeks after the last IMP intake.

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.

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

After IC 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.

Following confirmation of eligibility for the study, subjects will be treated as follows:

- 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.

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

- Tumor assessment according to RECIST criteria v 1.1 will be assessed at V1 (screening), V6, V9, V12 and V16 (EOS) or EW locally (by the investigator with the local radiologist consultation). Central review will be performed at the end of the study by a centralized independent radiologist (according to Biotrial Core Lab Image Review Charter).
- NSE and CgA plasma levels will be collected at V2, V4, V6, V9, V12 and V16 (EOS) or EW.
- WHO performance status (ECOG) at V1 (screening), V6, V9, V12 and V16 (EOS) or EW.

1.3.2.2 Safety assessments

- AEs:

AEs will be monitored from the time that the subject gives IC and throughout the study and will be elicited by direct, non-leading questioning or by spontaneous reports.

- Clinical laboratory test:

Blood samples will be collected at each visit for the evaluation of haematology and biochemistry, excepted for haematology and biochemistry at V2 if V1 haematology and biochemistry blood sample has been performed less than 7 days before, and at V3 bis only some haematological parameters were required. Urine samples will be collected at V1

(screening), V4, V5, V6, V9, V12 and V16 (EOS) or EW for urinalysis. 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.

- For haematology, the following parameters will be collected: red blood cells (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), white blood cell (WBC) count, absolute neutrophils count (ANC), platelets and glycated haemoglobin (HbA1c), as well as coagulation indexes: activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalised ratio (INR).
- For blood biochemistry, the following parameters will be collected: urea, serum creatinine (Cr), total serum bilirubin, direct bilirubin (only when total serum bilirubin is out of ranges), chloride, sodium, potassium, calcium, phosphate, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (γ-GT), albumin, total protein, total cholesterol, triglycerides, fasting glucose, insulin, C-peptide, Vitamin B12, Thyroid-Stimulating Hormone (TSH), Free Triiodothyronine (FT3) and Free Thyroxine (FT4).
- For serology, the following parameters will be collected at V1 (screening) only: hepatitis B surface antigen (HBV) and hepatitis C antibody (HCV).
- For urinalysis, the following parameters will be collected: pH, protein, ketones, total bilirubin, blood, WBC, urobilinogen, glucose, nitrite and specific gravity by dipstick and microscopy if necessary. Microscopy will be performed, if indicated, but results will not be collected in the electronic case report form (eCRF). If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE.

• Physical examinations will be conducted at each visit. Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs.

• Vital signs will be collected at each visit: blood pressure (systolic and diastolic) and heart rate (excepted at V1, V9 and V16 when it will be measured during the ECG) will be assessed with an automated device. Blood pressure and heart rate will be recorded in supine, sitting or standing position according to clinical practice.

• Electrocardiogram (ECGs) will be recorded at V1 (screening), V9 and V16 (EOS) or EW. Twelve-lead ECGs will be recorded so that the different ECG intervals (RR duration, PR duration), QRS interval duration (QRS), time interval for ventricular depolarisation and repolarisation (QT)) can be measured, as well as heart rate. Corrected QT interval (QTc) will be measured automatically according to the Bazett's formula. Any clinically significant abnormalities will be recorded as AEs.

• Echocardiography: M- and B-mode echocardiography will be performed at V1 (screening), V9 and V16 (EOS) or EW. The following assessments will be performed:

- valves function (with cardiac valvular regurgitation severity and cardiac valve stenosis severity) and morphology for mitral, aortic and tricuspid valves,
- left and right ventricular morphology and function,
- left atrium, aorta, pericardium and pericardial effusion morphology,
- patency of the foramen ovale,

- interpretation of clinical significance.

- Gallbladder echography: at V1 (screening), ultrasound examination of the gallbladder will be performed on each subject by gallbladder echography. The measurement will be repeated at V9 and V16 (EOS) or EW.

1.3.2.3 Other assessments

The following assessments will be collected at the screening visit (V1):

- Demography (sex, age, race),
- New York Heart Association (NYHA) functional classification evaluation of cardiac disease,
- A human chorionic gonadotrophin (ßHCG) serum test (i.e. pregnancy test) performed for all female subjects of childbearing potential at screening (V1) and if clinically indicated thereafter,
- Medical/surgical history (including documented histology of typical/atypical carcinoid of lung or thymus according to WHO 2004 criteria),
- Disease history (date of diagnosis, tumor localization, mitotic count, foci of necrosis, metastasis, Tumor Node Metastasis (TNM) staging according to UICC/AJCC 7th Edition TNM System),
- Prior medications and non-drug therapies (others than for T-NETs),
- Prior medications for T-NETs,
- Prior chemotherapy, radiotherapy, locoregional therapies (TAE, TACE, TARF, SIRT), prior therapy with Peptide Receptor Radionuclide Therapy (PRRT) for T-NETs, prior targeted therapy and prior surgical procedure in the past year,
- Octreoscan or GA-DOTA/TATE/TOC-PET within 12 months (overall and by method of imaging),,
- Eligibility checks (inclusion/exclusion criteria).
- Biomarkers expression (immunohistochemistry assay SSTR2, Ki67 and MGMT status in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies) if tissue samples are available at screening.

CCI [redacted]

Concomitant medications for T-NETs, concomitant medications/non-drug therapies/surgical procedures other than for T-NETs as well as treatment administrations will also be collected throughout the study.

1.3.2.4 Withdrawal/discontinuation

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, 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 protocol sections 3.6, 4.3, 5.2.5.1 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 v 1.1 (refer to protocol appendix 1);
- In case of AEs, serious 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) IC 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 (see section 1.3.3 with the schedule of assessments for 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 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 eCRF. 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 eCRF. 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 concomitantly with the study drug interruption, a final physical examination, an ECG recording, a check of the concomitant medications, a blood sampling for chemistry and haematology, a recording of the clinic (office) blood pressure and heart rate.

CCI [redacted] If a subject wishes to withdraw his/her 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/her 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.

1.3.3 Schedule of assessments

The schedule of procedures and assessments during the study is summarised in Table 1.

Table 1 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 [redacted]																	
Blood sample collection for CgA and NSE dosage		X			X		X			X			X				X
ECG and Echocardiography	X									X							X
CT scan	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 [redacted]

1.3.4 Planned sample size

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

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

The following assumptions were 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 % was considered as not acceptable (π_0),
- the 1-sided error probability was set to $\alpha = 0.025$ and
- the power should be 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".

2 SUBJECT POPULATIONS (ANALYSIS SETS)

The following populations will be used during the statistical analyses: the Screened population i.e. all subjects screened (i.e. who signed the informed consent), the intention-to-treat (ITT)/safety population and the per-protocol (PP) population, as described below.

2.1 Efficacy

2.1.1 Intention-to-treat (ITT)/safety population

The ITT/Safety population is all subjects who received at least one dose of study medication (either Lanreotide ATG 120 mg or TMZ).

2.1.2 Per-protocol population (PP)

The PP population is all subjects in the ITT/Safety population for whom no major protocol violations/deviations occurred.

Criteria for exclusion from the PP population will be provided in the deviations specifications document. Listings of subjects regarding inclusion in each population and satisfying the population definition and associated data will be reviewed by the study team.

Reasons for exclusion from PP population will be presented in a summary table.

2.2 Safety

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

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with International Conference on Harmonisation (ICH) E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated.

Statistical analyses described in this document will be performed by Biotrial Biometrics, Rennes, France, using the Statistical Analysis System (SAS®) software 9.4 release or higher (SAS Institute Inc. Cary NC USA).

3.1.1 Primary efficacy endpoint

The primary endpoint is the percentage of responders (DCR according to RECIST criteria v 1.1 assessed locally by the investigator, after tumor evaluation (by CT scan or MRI) identifying measurable lesions (i.e. target, non-target and new lesions) by which subsequent response assessment is judged) at 9 months after first treatment administration, defined as objective response (including CR and PR) or stability of the disease (i.e. SD).

3.1.2 Secondary efficacy endpoints

Secondary endpoints are:

- DCR at 9 months assessed centrally by the independent radiologist, after review of collected tumor evaluation (i.e. CT scan or MRI images) identifying measurable lesions (i.e. target, non-target and new lesions) by which subsequent response reassessment is done,
- PFS from first treatment administration until progression, according to RECIST criteria v 1.1 locally and centrally,
- 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 locally and centrally),
- DOR 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 locally and centrally) or death from any cause,
- TTP defined as the time from first treatment administration to the first objective tumor progression (PD) observed according to RECIST criteria v 1.1 locally and centrally,
- BOR according to RECIST criteria v 1.1 locally and centrally defined as the best response recorded from the time of first treatment until disease progression/recurrence or the end of study (CR > PR > Non-CR/Non-PD (NCR/NPD) > SD > PD > ND > NE),
- ORR locally and centrally at 9 and 12 months: CR or PR,
- DCR locally and centrally at 12 months: CR, PR and SD,
- The influence of type of carcinoid (typical, atypical, carcinoid neuroendocrine tumor) on the DCR at 9 months locally and centrally,
- Biochemical response according to decrease in CgA plasma level in subjects with baseline CgA level greater than upper limit of normal range (ULN) throughout the study (at V2, V4, V6, V9, V12 and V16). Biochemical objective response is defined as a decrease of CgA ≥ 50 %, while stable disease as a decrease ≥ 25 % and less than 50 %, as their best response to study treatment,

- Value of NSE and CgA levels at baseline and at 1, 3, 6, 9 and 12 months (EOS) or EW (i.e. at V4, V6, V9, V12 and V16), to assess their predictive and prognostic value,
- Biomarkers expression (immunohistochemistry assay centrally assessed 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 locally and centrally at 9 and 12 months, to assess their prognostic value.
- Agreement between central and local assessment of tumor radiological response.
- Blood MGMT methylation centralized assessment done at V2, V12 and EOS described in a separate SAP.

3.1.3 Safety endpoints

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, blood chemistry, urinalysis), diagnostic tests (ECG, echocardiography, gallbladder echography) and concomitant medication usage.

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

3.1.4 Multiplicity

No multiple testing will be performed in this study.

3.1.5 Significance testing and estimation

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 %.

3.2 Analysis methods

3.2.1 Efficacy

The efficacy analyses will be described below, but here is a summary:

Table 2 Summary of all efficacy analyses

Time	Assessment	Population	Additional information	TFL Number
Disease control rate				
At 9 months	Local	ITT/Safety	Considering: - all subjects attending 9 months, - subjects with PD prior or at 9 months and, - other subjects withdrawn for reason other than PD or missing reason before 9 months as failures.	14.2.1.1.1

Time	Assessment	Population	Additional information	TFL Number
			Disease control rate	
At 9 months	Local	ITT/Safety	Considering all treated subjects except subjects withdrawn before 9 months for reason other than PD or missing assessment.	14.2.1.1.3
			Considering: - subjects with assessments between 7.5 and 10.5 months as 9-month assessment - subjects with PD prior or at 9 months and, - subjects withdrawn for reason other than PD or missing reason before 9 months as failures.	14.2.1.1.4
			Influence of typical and atypical carcinoids	14.2.1.6.1
			Influence of NSE and CgA - Logistic regression	14.2.8.6.1
			Influence of biomarkers expression - Logistic regression	14.2.9.4.1
		PP	Considering: - all subjects attending 9 months, - subjects with PD prior or at 9 months and, - other subjects withdrawn for reason other than PD or missing reason before 9 months as failures.	14.2.1.1.2
	Central	ITT/Safety	Considering: - all subjects attending 9 months, - subjects with PD prior or at 9 months and, - other subjects withdrawn for reason other than PD or missing reason before 9 months as failures.	14.2.1.2.1
			Influence of typical and atypical carcinoids	14.2.1.6.2
			Influence of NSE and CgA - Logistic regression	14.2.8.6.2
			Influence of biomarkers expression – Logistic regression	14.2.9.4.2
		PP	Considering: - all subjects attending 9 months, - subjects with PD prior or at 9 months and, - other subjects withdrawn for reason other than PD or missing reason before 9 months as failures.	14.2.1.2.2

Time	Assessment	Population	Additional information	TFL Number
			Disease control rate	
At 9 months	NA	ITT/Safety	Agreement of the central assessment of tumor radiological response and the local one	14.2.10.1
At 12 months	Local	ITT/Safety	Considering: - all subjects attending 12 months, - subjects with PD prior or at 12 months and, - other subjects withdrawn for reason other than PD or missing reason before 12 months as failures.	14.2.1.3.1
			Influence of NSE and CgA - Logistic regression	14.2.8.6.3
			Influence of biomarkers expression - Logistic regression	14.2.9.4.3
	Central	ITT/Safety	Considering: - all subjects attending 12 months, - subjects with PD prior or at 12 months and, - other subjects withdrawn for reason other than PD or missing reason before 12 months as failures.	14.2.1.3.2
			Influence of NSE and CgA - Logistic regression	14.2.8.6.4
			Influence of biomarkers expression - Logistic regression	14.2.9.4.4
			Time point response	
Per time point	Local	ITT/Safety	NA	14.2.1.4.1.1
		PP	NA	14.2.1.4.1.2
	Central	ITT/Safety	NA	14.2.1.4.2.1
		PP	NA	14.2.1.4.2.2
			Diameters of target tumor lesions	
Per time point	Local	ITT/Safety	NA	14.2.1.5.1
	Central	ITT/Safety	NA	14.2.1.5.2
			Progression-free survival	
NA	Local	ITT/Safety	NA	14.2.2.1.1
			Figure	14.2.2.2.1
			Influence of NSE and CgA - Cox proportional hazard model	14.2.8.4.1
			Influence of biomarkers expression - Cox proportional hazard model	14.2.9.2.1
NA	Central	ITT/Safety	NA	14.2.2.1.2
			Figure	14.2.2.2.2
			Influence of NSE and CgA - Cox proportional hazard model	14.2.8.4.2

Time	Assessment	Population	Additional information	TFL Number
		Progression-free survival		
NA	Central	ITT/Safety	Influence of biomarkers expression - Cox proportional hazard model	14.2.9.2.2
		Time to response		
NA	Local	ITT/Safety	NA	14.2.3.1.1
			Figure	14.2.3.2.1
	Central	ITT/Safety	NA	14.2.3.1.2
			Figure	14.2.3.2.2
		Duration of response		
NA	Local	ITT/Safety	NA	14.2.4.1.1
			Figure	14.2.4.2.1
NA	Central	ITT/Safety	NA	14.2.4.1.2
			Figure	14.2.4.2.2
		Time to progression		
NA	Local	ITT/Safety	NA	14.2.5.1.1
			Figure	14.2.5.2.1
NA	Central	ITT/Safety	NA	14.2.5.1.2
			Figure	14.2.5.2.2
		Best overall response		
NA	Local	ITT/Safety	NA	14.2.6.1
NA	Central	ITT/Safety	NA	14.2.6.2
		Objective response rate		
At 9 months	Local	ITT/Safety	Considering: - all subjects attending 9 months, - subjects with PD prior or at 9 months and, - other subjects withdrawn for reason other than PD or missing reason before 9 months as failures.	14.2.7.1.1
			Influence of NSE and CgA - Logistic regression	14.2.8.5.1
			Influence of biomarkers expression - Logistic regression	14.2.9.3.1
	Central	ITT/Safety	Considering: - all subjects attending 9 months, - subjects with PD prior or at 9 months and, - other subjects withdrawn for reason other than PD or missing reason before 9 months as failures.	14.2.7.1.2
			Influence of NSE and CgA - Logistic regression	14.2.8.5.2
			Influence of biomarkers expression - Logistic regression	14.2.9.3.2

Time	Assessment	Population	Additional information	TFL Number
			Objective response rate	
At 12 months	Local	ITT/Safety	Considering: - all subjects attending 12 months, - subjects with PD prior or at 12 months and, - other subjects withdrawn for reason other than PD or missing reason before 12 months as failures.	14.2.7.2.1
			Influence of NSE and CgA - Logistic regression	14.2.8.5.3
			Influence of biomarkers expression - Logistic regression	14.2.9.3.3
	Central	ITT/Safety	Considering: - all subjects attending 12 months, - subjects with PD prior or at 12 months and, - other subjects withdrawn for reason other than PD or missing reason before 12 months as failures.	14.2.7.2.2
			Influence of NSE and CgA - Logistic regression	14.2.8.5.4
			Influence of biomarkers expression - Logistic regression	14.2.9.3.4
			CgA	
Per time point	Central	ITT/Safety	CgA (µg/L and in x ULN) - Summary statistics on raw data and changes from baseline	14.2.8.1.1
			CgA (in x ULN) - Summary statistics by class	14.2.8.1.2
			CgA (in x ULN) - Shift tables	14.2.8.1.3
Global	Central	ITT/Safety	ANCOVA on the change from baseline of CgA in x ULN - Full model	14.2.8.1.4
			ANCOVA on the change from baseline of CgA in x ULN - Additive model	14.2.8.1.5
			NSE	
Per time point	Central	ITT/Safety	NSE (µg/L and in x ULN) - Summary statistics on raw data and changes from baseline	14.2.8.2.1
			NSE (in x ULN) - Summary statistics by class	14.2.8.2.2
			NSE (in x ULN) - Shift tables	14.2.8.2.3
Global	Central	ITT/Safety	ANCOVA on the change from baseline of NSE in x ULN - Full model	14.2.8.2.4
			ANCOVA on the change from baseline of NSE in x ULN- Additive model	14.2.8.2.5

Time	Assessment	Population	Additional information	TFL Number
Biochemical response				
Per time point	NA	ITT/Safety	NA	14.2.8.3
WHO performance status scale (ECOG)				
Per time point	NA	ITT/Safety	Frequency table	14.2.11.1
			Shift table	14.2.11.2
Biomarkers expression				
Per time point	NA	ITT/Safety	Summary statistics	14.2.9.1
Should an analysis be performed on the PP population (if there is a difference of at least 10 % between ITT/Safety and PP populations), the tables on efficacy parameters (from 14.2.13.1 to 14.2.11.2) will be repeated and numbered adding one level in the numbering (i.e. 1 for ITT/Safety population and 2 for Per Protocol Population).				

3.2.1.1 Primary efficacy analysis

3.2.1.1.1 Disease control rate (DCR) at 9 months as per investigator

The primary efficacy variable is the response of subjects to the study combination therapy, 9 months after first treatment administration. Responders are subjects showing DCR according to RECIST criteria v 1.1 assessed locally, defined as objective response (i.e. CR and PR) or stability of the disease (SD).

Primary efficacy analyses will be performed on the ITT/Safety population.

The number of assessed subjects at 9 months according to their response status (CR / PR / SD / NE / NCR NPD / Missing), with the number of subjects in PD prior or at 9 months, and the number of withdrawn subjects before 9 months with reason other than PD will be displayed. The DCR will be based on all subjects in the ITT/Safety population with subjects with PD prior or at 9 months as well as subjects with missing assessment and withdrawn subjects from any reason considered as failures.

The DCR will be analysed by an exact binomial proportion test for one-way tables in the ITT/Safety population and will then be compared to the thresholds of 30 % and of 10 % using the following SAS Freq procedure:

CCI [redacted];

The proportion of responders will be displayed along with the 95 % Clopper-Pearson Confidence Intervals (CI), a one sided test with an α of 0.025 should be used. The one-sided p-values from the exact binomial test comparing the proportion of responders to 0.3 (i.e. 30 %) and to 0.1 (i.e. 10 %) will be displayed.

3.2.1.1.2 Disease control rate (DCR) rate at 9 months - sensitivity analyses

A supportive analysis of the primary analysis of local DCR at 9 months, using the same methodology, will be performed on the PP population.

A sensitivity analysis of local DCR at 9 months will be performed on the ITT/Safety population excluding the subjects withdrawn before 9 months with reason other than PD or missing assessment and considering subjects with PD prior or at 9 months as failures.

In addition, a sensitivity analysis will be performed in order to consider assessments done between 7.5 and 10.5 months as 9 months assessments when 9-month assessment is missing using the same methodology as the primary analysis, i.e. considering PD prior or at 9 months and subjects withdrawn with other or missing reasons as failures.

The analyses of DCR at 9 months will also be repeated based on the central tumour response assessment on the ITT/Safety and PP populations considering subjects with PD prior or at 9 months and subjects withdrawn for other or missing reason as failures.

3.2.1.2 Secondary efficacy analyses

All secondary efficacy analyses will be performed on the ITT/Safety population and all RECIST based secondary analyses will be performed both on the local and the central assessments.

Time point response (TPR) at each visit will be analysed on the ITT/Safety population as well as on the PP population. All other secondary efficacy analyses will also be performed on the PP population if there is a difference of at least 10 % between ITT/Safety and PP populations.

3.2.1.2.1 Time point response and sum of the largest diameters of target tumor lesions

The TPR to study treatment which is the observed response for each subject at each visit from the time of first treatment until disease progression/recurrence or the end of study, and classified as CR, PR, SD, PD, Non-Complete Response (NCR)/Non-Progressive Disease (NPD) and not evaluable (NE) per RECIST criteria v 1.1 will be presented using 2 separate descriptive summaries, one using local review and the second one using central review.

The sum of the largest diameters of target tumor lesions will be summarized at each visit as well as the change and the percentage change from screening and the change and percentage change from nadir. Two separate descriptive summaries of the largest diameters will be presented, one using local review and the second using central review.

3.2.1.2.2 Progression-free survival

3.2.1.2.2.1 Local assessment

The secondary efficacy endpoint of PFS according to local review will include investigator assessed PD and deaths. Other data will be censored.

Clinical progression (i.e. locally assessed documented progression where the subject is withdrawn from the study due to clinical judgement of progression, however the progression is not confirmed by independent centralized review) is considered as a progression endpoint in this analysis.

In case of locally assessed PD followed by death, the first event will be considered in the analysis.

Definition of progression date:

The PD date is assigned to the first time at which PD can be declared.

- For PD based on a new lesion, the PD date is the date of the first radiological assessment when the new lesion was detected.
- For PD based on an increase in the sum of the target lesion measurements, the PD date is the date of the last radiological assessment of target lesions that shows the predefined increase in the sum of the target lesion measurements.

Definition of censoring date:

- Censoring dates are defined in subjects with no PD or death before end of study or withdrawal. In these subjects, the censoring date is defined as the last date on which progression status was 'adequately' assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by local investigator review.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.
- PDs occurring after more than one missed visit will be censored in the analysis at the last adequate assessment before the missing assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the investigator.

Definition of PFS time:

The PFS time will be calculated as the time from first treatment administration to either locally assessed PD or death.

PFS time = [(Date of event – date of first treatment administration) + 1] / 7 (weeks)

Table 3 specifies the event and censoring dates to be used in the analysis of PFS via local review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 3 PFS analysis assessed locally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Date of first treatment administration	Censored
PD documented locally (either based on new lesion or increase in the sum of the target lesion measurements during the study)	Date of radiological assessment showing PD	Event
Two or more NE assessments before PD or death	Date of last radiological assessment before the second NE assessment	Censored
No PD	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored
Death (due to any cause) before first PD assessment	Date of death	Event
Death (due to any cause) between adequate assessment visits	Date of death	Event
Death or progression after more than one missed visit	Date of last radiological assessment	Censored

Table 4 displays the event status for various scenarios with missing data.

Table 4 Event status for various scenarios with missing data

Scan Time	Week 12	Week 24	Week 36	Week 52	Event Status
Scenario 1	Missing	PD			Event at week 24
Scenario 2	Missing	Missing	PD		Censoring at screening
Scenario 3	Missing	SD	PD		Event at week 36
Scenario 4	Missing	Missing	SD	PD	Event at week 52
Scenario 5	SD	SD	Missing	PD	Event at week 52
Scenario 6	SD	Missing	SD	PD	Event at week 52

The distribution of PFS times will be estimated using the Kaplan-Meier (KM) product limit method. The 25th percentile, median and 75th percentile PFS times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median time to progression or death due to any cause as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with local progression or death due to any cause, the numbers and percentages of observed and censored subjects. The summaries will also include the median time to local progression or death due to any cause as well as the 25th and 75th percentiles, the percentage of subjects who had progressed or had died at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16), and the associated 95 % CIs for each of these outcomes. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16).

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3.2.1.2.2.2 Central assessment

The secondary efficacy endpoint of PFS according to central review will include centrally assessed PD and deaths. Other data will be censored including investigator assessed PD occurring before centrally assessed PD and deaths.

Clinical progression (i.e. centrally assessed documented progression even though the progression is not assessed by the investigator) is considered as a progression endpoint in this analysis.

In case of centrally assessed PD followed by death, the first event will be considered in the analysis unless an investigator assessed PD occurred before then the data would be censored.

Definition of progression date:

The PD date is assigned to the first time at which PD can be declared.

- For PD based on a new lesion, the PD date is the date of the first radiological assessment when the new lesion was detected.
- For PD based on an increase in the sum of the target lesion measurements, the PD date is the date of the last radiological assessment of target lesions that shows the predefined increase in the sum of the target lesion measurements.

Definition of censoring date:

- Censoring dates are defined in subjects with no PD or death before end of study or withdrawal. In these subjects, the censoring date is defined as the last date on which progression status was 'adequately' assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by central review.
- In the case of locally declared PD, not confirmed by the central independent radiologist, the subject will be censored at the date of local PD.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.
- PDs occurring after more than one missed visit will be censored in the analysis at the last adequate assessment before the missing assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the central review.

Definition of PFS time:

The PFS time will be calculated as the time from first treatment administration to either centrally assessed PD or death.

PFS time = [(Date of event – date of first treatment administration) + 1] / 7 (weeks)

Table 5 specifies the event and censoring dates to be used in the analysis of PFS via central review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 5 PFS analysis assessed centrally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Date of first treatment administration	Censored
PD documented centrally (either based on new lesion or increase in the sum of the target lesion measurements during the study)	Date of radiological assessment showing PD	Event
PD documented locally only (either based on new lesion or increase in the sum of the target lesion measurements during the study)	Date of radiological assessment showing PD	Censored
Two or more NE assessments before PD or death	Date of last radiological assessment before the second NE assessment	Censored
No PD	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored
Death (due to any cause) before first PD assessment	Date of death	Event
Death (due to any cause) between adequate assessment visits	Date of death	Event
Death or progression after more than one missed visit	Date of last radiological assessment	Censored

The distribution of PFS times will be estimated using the KM product limit method. The 25th percentile, median and 75th percentile PFS times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median time to progression or death due to any cause as well as the 25th and 75th percentile CIs will be calculated using the method of

Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with central progression or death due to any cause, the numbers and percentages of observed and censored subjects. The summaries will also include the median time to central progression or death due to any cause as well as the 25th and 75th percentiles, the percentage of subjects who had progressed or had died at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16), and the associated 95 % CIs for each of these outcomes. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16).

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3.2.1.2.3 Time to response

Time to response (TTR) is defined as the time from first treatment administration to the first objective tumor response (PR or CR) according to RECIST criteria v 1.1. TTR will be analysed separately using the local and central assessments.

3.2.1.2.3.1 Local assessment

Objective tumor response (PR or CR) will be assessed locally by the investigator.

Definition of response date:

The response date is assigned to the date of the first radiological assessment when PR or CR can be declared locally.

Definition of censoring date:

- Censoring dates are defined in subjects with no PR or CR assessed locally before end of study, withdrawal, lost to follow-up or death as the last date on which response was 'adequately' assessed i.e. the date of the last radiological assessment.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.
- Response occurring after more than one missed visit will be censored in the analysis at the last adequate assessment before the missing assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the investigator.

Definition of TTR time:

The TTR time will be calculated as the time from first treatment administration to the first PR or CR declared locally.

TTR time = [(Date of event – date of first treatment administration) + 1] / 7 (weeks)

Table 6 specifies the event and censoring dates to be used in the analysis of TTR via local review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 6 TTR analysis assessed locally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Date of first treatment administration	Censored
CR or PR documented locally	Date of radiological assessment showing response	Event
Two or more NE assessments before CR or PR documented locally	Date of last radiological assessment before the second NE assessment	Censored
No CR or PR documented locally	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored

The distribution of TTR times will be estimated using the KM product limit method. The 25th percentile, median and 75th percentile TTR times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median TTR as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with response, the numbers and percentages of observed and censored subjects. The summaries will also include the median TTR as well as the 25th and 75th percentiles, the percentage of subjects who had a response at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16), and the associated 95 % CIs for each of these outcomes. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16).

The SAS Lifetest procedure will be used as follows:

CCI [redacted]

3.2.1.2.3.2 Central assessment

Objective tumor response (PR or CR) will be assessed centrally by the independent radiologist.

Definition of response date:

The response date is assigned to the date of the first central radiological assessment when PR or CR can be declared by the independent radiologist.

Definition of censoring date:

- Censoring dates are defined in subjects with no PR or CR assessed centrally before end of study, withdrawal, lost to follow-up or death as the last date on which response was ‘adequately’ assessed i.e. the date of the last radiological assessment.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.

- Response occurring after more than one missed visit will be censored in the analysis at the last adequate central assessment before the missing central assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the independent radiologist.

Definition of TTR time:

The TTR time will be calculated as the time from first treatment administration to the first PR or CR declared centrally.

TTR time = [(Date of event – date of first treatment administration) + 1] / 7 (weeks)

Table 7 specifies the event and censoring dates to be used in the analysis of TTR via central review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 7 TTR analysis assessed centrally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Date of first treatment administration	Censored
CR or PR documented centrally	Date of radiological assessment showing response	Event
Two or more NE assessments before CR or PR documented centrally	Date of last radiological assessment before the second NE assessment	Censored
No CR or PR documented centrally	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored

The distribution of TTR times will be estimated using the KM product limit method. The 25th percentile, median and 75th percentile TTR times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median TTR as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with response, the numbers and percentages of observed and censored subjects. The summaries will also include the median TTR as well as the 25th and 75th percentiles, the percentage of subjects who had a response at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16), and the associated 95 % CIs for each of these outcomes. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16).

The SAS Lifetest procedure will be used as follows:

CCI [redacted]

3.2.1.2.4 Duration of response

Duration of response (DOR) is 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 assessed locally and also centrally afterwards in separate analyses.

Subjects without any PR or CR will not be taken into account in the analyses. Additionally, subjects with response occurring after more than one missed visit and subjects taking prohibited medication/therapy prior to PR or CR declaration will not be taken into account in the analyses.

3.2.1.2.4.1 Local assessment

DOR is defined as time from the date of the first radiological assessment when PR or CR can be declared locally to the date of the first radiological assessment when PD can be assessed locally after a PR or CR local declaration.

Definition of censoring date:

Censoring dates are defined only for subjects with PR or CR assessed locally before the end of study, withdrawal, lost to follow-up or death.

- Subjects without PD assessed locally before end of study, withdrawal, lost to follow-up or death will be censored at the last date on which response was 'adequately' assessed i.e. the date of the last radiological assessment.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.
- PD assessed locally occurring after more than one missed visit will be censored in the analysis at the last adequate assessment before the missing assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the investigator.

Definition of DOR time:

The DOR time will be calculated as the time from the date of the first radiological assessment when PR or CR can be declared locally to the date of the first radiological assessment when PD can be assessed locally after a PR or CR declaration.

- DOR time = [(Date of local progression or censoring – date of first local PR or CR radiological assessment) + 1] / 7 (weeks)

Table 8 specifies the event and censoring dates to be used in the analysis of DOR via local review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 8 DOR analysis assessed locally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Not applicable	Not included in the analysis
No PR or CR declared locally	Not applicable	Not included in the analysis
Two or more NE assessments before PR or CR local declaration	Not applicable	Not included in the analysis
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies) before a local assessment of CR or PR for the given subject	Not applicable	Not included in the analysis
PD documented locally	Date of radiological assessment showing PD	Event
Two or more NE assessments before PD local declaration	Date of last radiological assessment before the second NE assessment	Censored
No PD documented locally	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies) after local response declaration	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored
PD documented locally after more than one missed visit	Date of last radiological assessment prior to PD	Censored

The distribution of DOR times will be estimated using the KM product limit method. The 25th percentile, median and 75th percentile DOR times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median DOR as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with response tabulated by the number and percentage of responders with progression and of censored subjects. The summaries will also include the median DOR as well as the 25th and 75th percentiles. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 24, 36 and 52 weeks (i.e. V9, V12 and V16).

The SAS Lifetest procedure will be used:

CCI [redacted]

3.2.1.2.4.2 Central assessment

DOR is defined as time from the date of the first radiological assessment when PR or CR can be declared centrally to the date of the first radiological assessment when PD can be assessed centrally after a PR or CR central declaration and without prior local PD declaration.

Definition of censoring date:

Censoring dates are defined only for subjects with PR or CR assessed centrally before the end of study, withdrawal, lost to follow-up or death.

- Subjects without PD assessed centrally before end of study, withdrawal, lost to follow-up or death will be censored at the last date on which response was 'adequately' assessed i.e. the date of the last radiological assessment.
- Subjects with PD assessed locally before a PD is assessed centrally will be censored at the date of the local PD assessment.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.
- PD assessed locally occurring after more than one missed visit will be censored in the analysis at the last adequate assessment before the missing assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the investigator.

Definition of DOR time:

The DOR time will be calculated as the time from the date of the first radiological assessment when PR or CR can be declared locally to the date of the first radiological assessment when PD can be assessed locally after a PR or CR declaration.

- DOR time = [(Date of local progression or censoring – date of first local PR or CR radiological assessment) + 1] / 7 (weeks)

Table 9 specifies the event and censoring dates to be used in the analysis of DOR via local review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 9 DOR analysis assessed centrally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Not applicable	Not included in the analysis
No PR or CR declared centrally	Not applicable	Not included in the analysis
Two or more NE assessments before PR or CR central declaration	Not applicable	Not included in the analysis
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies) before a central assessment of CR or PR for the given subject	Not applicable	Not included in the analysis
PD documented centrally	Date of radiological assessment showing PD	Event
Two or more NE assessments before PD central declaration	Date of last radiological assessment before the second NE assessment	Censored
No PD documented centrally	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies) after central response declaration	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored
PD documented centrally after more than one missed visit	Date of last radiological assessment prior to PD	Censored

The distribution of DOR times will be estimated using the KM product limit method. The 25th percentile, median and 75th percentile DOR times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median DOR as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with response tabulated by the number and percentage of responders with progression and of censored subjects. The summaries will also include the median DOR as well as the 25th and 75th percentiles. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 24, 36 and 52 weeks (i.e. V9, V12 and V16).

The SAS Lifetest procedure will be used:

CCI [redacted]

3.2.1.2.5 Time to progression

Time to progression (TTP) is defined as the time from first treatment administration to the first objective tumor progression (PD) according to RECIST criteria v 1.1. TTP will be assessed locally and also centrally.

3.2.1.2.5.1 Local assessment

Time to progression according to local review will include investigator assessed PD and the other data will be censored.

Clinical progression (i.e. locally assessed documented progression where the subject is withdrawn from the study due to clinical judgement of progression, however the progression is not confirmed by the independent centralized review) is considered as a progression endpoint in this analysis.

Definition of progression date:

The PD date is assigned to the first time at which PD can be declared.

- For PD based on a new lesion, the PD date is the date of the first radiological assessment when the new lesion was detected.
- For PD based on an increase in the sum of the target lesion measurements, the PD date is the date of the last radiological assessment of target lesions that shows the predefined increase in the sum of the target lesion measurements.

Definition of censoring date:

- Censoring dates are defined in subjects with no PD before end of study or withdrawal. In these subjects, the censoring date is defined as the last date on which progression status was 'adequately' assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by local investigator review.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.
- PDs occurring after more than one missed visit will be censored in the analysis at the last adequate assessment before the missing assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the investigator.

Definition of TTP time:

The TTP time will be calculated as the time from first treatment administration to locally assessed PD.

TTP time = [(Date of event – date of first treatment administration) + 1] / 7 (weeks)

Table 10 specifies the event and censoring dates to be used in the analysis of TTP via local review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 10 TTP analysis assessed locally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Date of first treatment administration	Censored
PD documented locally (either based on new lesion or increase in the sum of the target lesion measurements during the study)	Date of radiological assessment showing PD	Event
Two or more NE assessments before PD	Date of last radiological assessment before the second NE assessment	Censored
No PD	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored
Death (due to any cause) before first PD assessment	Date of last radiological assessment	Censored
Death (due to any cause) between adequate assessment visits	Date of last radiological assessment	Censored
Death or progression after more than one missed visit	Date of last radiological assessment	Censored

The distribution of TTP times will be estimated using the Kaplan-Meier (KM) product limit method. The 25th percentile, median and 75th percentile TTP times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median TTP as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with local progression, the numbers and percentages of observed and censored subjects. The summaries will also include the median TTP as well as the 25th and 75th percentiles, the percentage of subjects who had progressed at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16), and the associated 95 % CIs. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16).

The SAS Lifetest procedure will be used as follows:

CCI [redacted]

3.2.1.2.5.2 Central assessment

Time to progression according to central review will include centrally assessed PD and the other data will be censored including investigator assessed PD occurring before centrally assessed PD.

Clinical progression (i.e. centrally assessed documented progression even though the progression is not assessed by the investigator) is considered as a progression endpoint in this analysis.

In case of centrally assessed PD followed by death, the first event will be considered in the analysis unless an investigator assessed PD occurred before then the data would be censored.

Definition of progression date:

The PD date is assigned to the first time at which PD can be declared.

- For PD based on a new lesion, the PD date is the date of the first radiological assessment when the new lesion was detected.
- For PD based on an increase in the sum of the target lesion measurements, the PD date is the date of the last radiological assessment of target lesions that shows the predefined increase in the sum of the target lesion measurements.

Definition of censoring date:

- Censoring dates are defined in subjects with no PD before end of study or withdrawal. In these subjects, the censoring date is defined as the last date on which progression status was 'adequately' assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by independent review.
- In the case of locally declared PD not confirmed by the independent radiologist, the subject will be censored at the date of local PD.
- In the case of prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.
- PDs occurring after more than one missed visit will be censored in the analysis at the last adequate assessment before the missing assessments, where adequate assessment is considered to be the last radiological assessment that was considered evaluable by the central review.

Definition of TTP time:

The TTP time will be calculated as the time from first treatment administration to centrally assessed PD without prior locally assessed PD.

TTP time = [(Date of event – date of first treatment administration) + 1] / 7 (weeks)

Table 11 specifies the event and censoring dates to be used in the analysis of TTP via central review; these are based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Table 11 TTP analysis assessed centrally

Situation	Date of event or censoring	Outcome
No screening evaluable assessment	Date of first treatment administration	Censored
PD documented centrally (either based on new lesion or increase in the sum of the target lesion measurements during the study)	Date of radiological assessment showing PD	Event
PD documented locally only (either based on new lesion or increase in the sum of the target lesion measurements during the study)	Date of radiological assessment showing PD	Censored
Two or more NE assessments before PD	Date of last radiological assessment before the second NE assessment	Censored
No PD	Date of last radiological assessment	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment	Censored
Initiation of medications or therapies not permitted during the study (including new anti-cancer therapies)	Date of last radiological assessment before initiation of non-permitted medication or therapy	Censored
Death (due to any cause) before first PD assessment	Date of last radiological assessment	Censored
Death (due to any cause) between adequate assessment visits	Date of last radiological assessment	Censored
Death or progression after more than one missed visit	Date of last radiological assessment	Censored

The distribution of TTP times will be estimated using the KM product limit method. The 25th percentile, median and 75th percentile TTP times and their corresponding two-sided 95 % CI will be estimated. Confidence intervals for median TTP as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982), which is the default method within SAS® version 9 and higher.

The results of the analysis will be presented in summary tables and KM plots will be constructed. Summary tables will present the numbers and percentages of subjects with central progression, the numbers and percentages of observed and censored subjects. The summaries will also include the median TTP as well as the 25th and 75th percentiles, the percentage of subjects who had progressed at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16), and the associated 95 % CIs for each of these outcomes. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 12, 24, 36 and 52 weeks (i.e. V6, V9, V12 and V16).

The SAS Lifetest procedure will be used as follows:

CCI [redacted]

3.2.1.2.6 Best overall response

Best overall response (BOR) to study treatment according to RECIST criteria v 1.1 will be derived as the highest objective response achieved by the subject from the time of first treatment until disease progression/recurrence or the end of study and will be classified as: CR > PR > Non-CR/Non-PD (NCR/NPD) > SD> PD > ND > NE. Confirmation with a

similar response is not required and response could be assessed only once to be considered as the BOR, however the delay between an observation of stability of the disease (SD) and screening should be ≥ 4 weeks and the duration of objective response (CR or PR) or stability (SD) should be ≥ 4 weeks before a progression (PD) to be considered as confirmed. The following results will be displayed: "N" the number of subjects in the ITT/Safety population, "n" the number and percentages of evaluable subjects by overall response categories and "Missing" the number of missing observations, with n CR + n PR + n SD + n NCR/NPD + n PD + n NE+ Missing = N.

Two separate descriptive summaries of BOR will be presented, first showing BOR assessed locally and second showing BOR assessed centrally.

3.2.1.2.7 Objective response rate

The objective response rate (ORR), i.e. the proportion of subjects with CR or PR will be described along with the 95 % CI at 9 and 12 months. Two separate descriptive summaries of the ORR will be presented, one using local review and the second using central review displaying the number and percentages of subjects by response, considering subjects with PD prior to 9 and 12 months with respectively PD at 9 and 12 months, and subjects withdrawn before the assessment for reason other than PD or missing as failures.

3.2.1.2.8 Disease control rate at 12 months

DCR at 12 months will be assessed locally and centrally.

As specified in section 3.2.1.1.1, the number of assessed subjects at 12 months according to their response status with the number of subjects in PD prior or at 12 months, and the number of withdrawn subjects before 12 months with reason other than PD or missing will be displayed. The DCR will be based on all subjects in the ITT/Safety population with subjects with PD prior or at 12 months as well as withdrawn subjects from any reason considered as failures.

The DCR will be analysed by an exact binomial proportion test for one-way tables in the ITT/Safety population and will then be compared to the thresholds of 30 % and 10 %.

The proportion of responders will be displayed along with the two-sided 95 % Clopper-Pearson CI using the following SAS Freq procedure for the local assessment compared to 30 % and 10 %:

CCI [redacted]

3.2.1.2.9 Influence of type of carcinoid

The influence of type of carcinoid (derived as typical, atypical or carcinoid neuroendocrine tumor according to foci of necrosis and mitotic count at screening as defined in Appendix 2) on the local and central DCR at 9 months will be analysed using a frequency table in the ITT/Safety population. For definition of DCR at 9 months, see section 3.2.1.1.

The proportion (with its 95 % CI) of subjects with DCR will be tabulated by derived carcinoid type and compared with a Fisher exact test using the following SAS Freq procedure (e.g. for the local assessment):

CCI

3.2.1.2.10 CgA and NSE levels

Raw values and corresponding changes from baseline, as well as parameter expressed in ULN and corresponding changes from baseline will be described for CgA and NSE at baseline and at 1, 3, 6, 9 and 12 months (EOS) or EW using summary statistics and 95 % CI of the mean at each timepoint. Classes of ULN (< 1 ULN, 1-2 ULN, > 2 ULN) will also be derived and presented using summary statistics. Shift tables between baseline and each post-baseline visit will also be presented using classes of ULN (< 1 ULN, 1-2 ULN, > 2 ULN).

In addition, CgA and NSE will be analysed on change from baseline of the parameter expressed in ULN by an analysis of covariance (ANCOVA) for repeated measures, using baseline values and the derived carcinoid type as covariates. Two models will be tested: a full model with the interaction between derived carcinoid type and visit, and an additive model without the interaction.

The following SAS Mixed procedure will be used for the additive model:

CCI

Where R2A1HI is the change from baseline of the value expressed in ULN as defined in ADaM implementation guide and R2BL is the baseline of the value expressed in ULN.

The following SAS Mixed procedure will be used for the full model:

CCI

If the interaction is found significant (p-value of interaction < 0.1), the model will be run by visit.

The type of covariance matrix will be chosen using the AIC criterion. The covariance matrix minimizing the AIC criterion will be chosen for the final analysis. The following covariance matrices will be tested: variance components (VC), compound symmetry (CS), unstructured (UN). Models will be rerun using the different matrices and the corresponding outputs will be provided in the statistical appendices, the model with the smallest AIC will be displayed in the summary table.

If the ANCOVA normality hypothesis (i.e. non-normality of the residuals) does not hold, a Friedman ANOVA will be used.

3.2.1.2.11 Biochemical response

CgA plasma levels will be measured at baseline (V2) and during the treatment period at 1 and 3 months and every 3 months as a surrogate efficacy endpoint (i.e. at V4, V6, V9, V12 and V16). Subjects with baseline CgA level greater than ULN will be assessed for biochemical response and classified as responders if they have a decrease in CgA ≥ 50 % compared to baseline CgA, as having a stable disease if they have a decrease < 50 % or an increase ≤ 25 % compared to baseline CgA and as non-responders if they have an increase > 25 % compared to baseline.

The number and proportion of subjects in each of the biochemical response categories (i.e. biochemical responder, biochemical stable disease and biochemical non-responder) will be summarised at each evaluated visit along with the 95 % CI.

3.2.1.2.12 Prognostic and predictive value of NSE and CgA levels on PFS

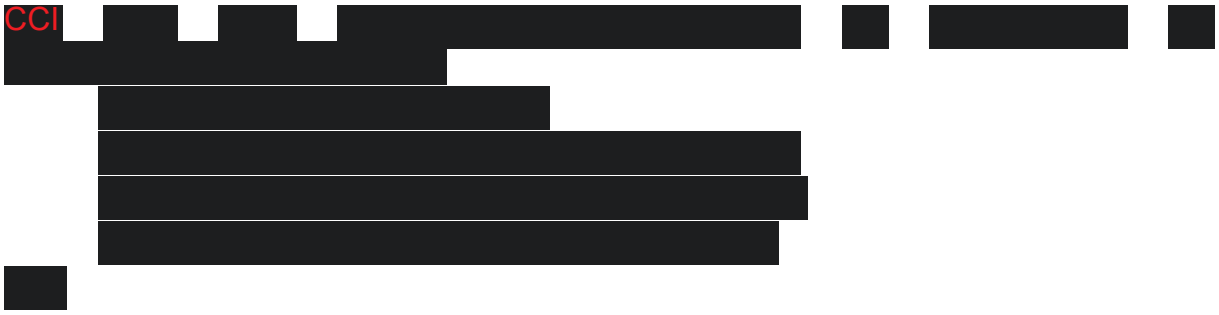
The classes (< 1 ULN, 1-2 ULN, > 2 ULN) of baseline NSE and CgA levels will be investigated as prognostic and predictive value of PFS assessed locally and centrally.

The following steps will be followed to assess the prognostic factors of CgA and NSE on PFS locally assessed.

Step 1:

NSE, CgA and derived carcinoid type will be tested in separate Cox proportional hazards models. Any factors found to be significant at $p \leq 0.20$ (via the Wald chi-square test statistic) will be considered to be potentially important. The association between each covariate and treatment will be further explored by presenting separate KM plots for each level of the covariate.

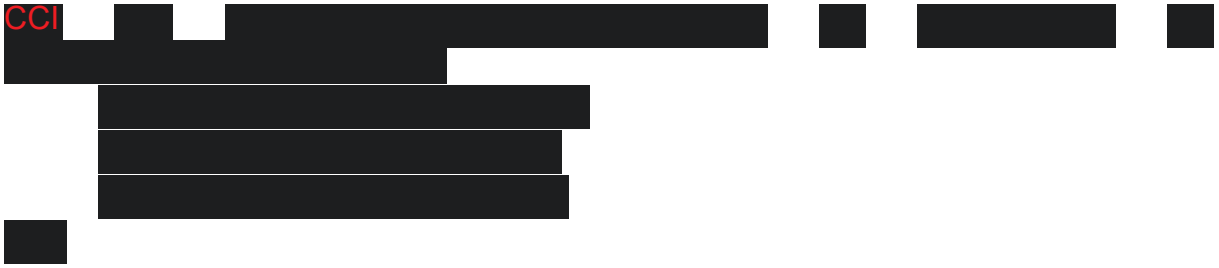
An example of SAS® code implementation follows:



Step 2:

In a second step, each pre-selected parameter will be tested with the other retained parameters at the 0.001 level to confirm that there is no strong link between them (using a chi-square test). If independence is not met for 2 parameters ($p < 0.001$), the choice will be made according to clinical and statistical relevance.

An example of SAS® code implementation follows:



Step 3:

All selected parameters will be entered into a multivariate Cox model. The stepwise variable selection method in the SAS® procedure PHREG will be performed with p <= 0.20 to enter variables in the model, and p >= 0.05 to remove variables from the model, to select the best model. The final model will be adjusted on derived carcinoid type regardless of the parameters significance.

The maximum likelihood estimates of model coefficients (with associated standard error, degrees of freedom, Wald Chi-square statistic and p-value) will be presented for the final model along with the HRs and 95 % CIs.

An example of SAS® code implementation follows:

The assumptions of proportional hazards (PH) will be examined graphically by plotting ln(-ln(S(t))) versus t or ln(t) and looking for parallelism. The corresponding assessments will be displayed in the statistical appendices and a footnote stating that the assumptions hold will be added in the table presenting the final model.

Similar steps will be followed to assess the prognostic factors of CgA and NSE on central PFS replacing PARQUAL='Local Assessment' by PARQUAL='Central Assessment'.

3.2.1.2.13 Prognostic and predictive value of NSE and CgA levels on ORR and DCR

The classes (< 1 ULN, 1-2 ULN, > 2 ULN) of baseline NSE and CgA levels will be investigated as prognostic and predictive value on ORR and DCR assessed locally and centrally at 9 and 12 months.

The following steps will be followed to assess the prognostic factors of CgA and NSE on ORR locally assessed at 9 months.

Step 1:

NSE, CgA and derived carcinoid type will be tested in separate logistic regression models. Any factors found to be significant at $p \leq 0.20$ (via the Wald chi-square test statistic) will be considered to be potentially important.

An example of SAS® code implementation follows:

CCI

Step 2:

In a second step, each pre-selected parameter will be tested with the other retained parameters at the 0.001 level to confirm that there is no strong link between them (using a chi-square test). If independence is not met for 2 parameters ($p < 0.001$), the choice will be made according to clinical and statistical relevance.

An example of SAS® code implementation follows:

CCI

Step 3:

All selected parameters will be entered into a multivariate logistic regression model. The stepwise variable selection method in the SAS® procedure Logistic will be performed with $p \leq 0.20$ to enter variables in the model, and $p \geq 0.05$ to remove variables from the model, to select the best model.

The maximum likelihood estimates of model coefficients (with associated standard error, degrees of freedom, Wald Chi-square statistic and p-value) will be presented for the final model along with the adjusted proportions and 95 % CIs.

An example of SAS® code implementation follows:

CCI

The Hosmer and Lemeshow goodness-of-fit test for the final selected model will be assessed.

Similar steps will be followed to assess the prognostic factors of CgA and NSE on central ORR replacing PARQUAL='Local Assessment' by PARQUAL='Central Assessment' and on DCR replacing PARAMCD='ORR' by PARAMCD='DC'.

3.2.1.2.14 Prognostic value of biomarkers expression on PFS, ORR and DCR

Biomarkers expression, i.e. immunohistochemistry assay SSTR2 (including categories of HER-2 score (0, 1+, 2+, 3+ and positive versus negative), H-score (from 0 to 300 as quantitative variable and positive versus negative according to the Specht publication) and

IRS score (categories of scores according to the Specht publication), Ki67 (as class: < 4, [4-25[, ≥ 25 according to Rindi publication) and MGMT status (including percentage of positive nuclei stained (quantitative variable and positive versus negative according to Schmitt publication), H-score (from 0 to 300 as quantitative variable) and percentage of methylated sites (quantitative variable and positive versus negative according to Schmitt publication) for protein levels in tissue obtained from paraffin embedded primary tumour surgery specimens or biopsies, will be described at baseline using summary statistics. If any of those biomarkers are not collected at screening in all subjects, its evaluation as a prognostic factor might be compromised, so the relevance of its inclusion in the analyses will be reviewed prior to database lock.

As described above, the prognostic value of the biomarkers expression at screening on PFS will be assessed locally and centrally using Cox proportional hazard models.

As described above, the prognostic value of the biomarkers expression at screening on ORR and DCR at 9 and 12 months assessed locally and centrally will be analysed using logistic regression models.

3.2.1.2.15 Agreement of the central assessment of tumor radiological response and the local one on the DCR

Differences between central radiology review and local investigator review will be assessed according to the DCR status at 9 months as defined in section 3.2.1.1. Summary tables will present the number of agreements and disagreements between the evaluators (central versus local) along with the p-values from the kappa test.

A kappa statistic will be employed to evaluate the concordance between the central and the local review. If either result from the central review or the local review is not applicable, the outcome will be denoted as “disagreement”. An example of SAS® code implementation follows:

CCI [redacted]

3.2.1.2.16 WHO performance status (ECOG)

WHO performance status (ECOG) will be described at each visit and a shift table between screening and each visit will be produced.

3.2.2 Safety

All safety data will be included in the data listings and the summary tables will be based on the ITT/Safety population.

3.2.2.1 Adverse events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 20.0.

Listings will be presented and sorted by subject, start date of AEs, primary system organ class, preferred term and verbatim text for all AEs recorded during the study.

Listings of death, of serious adverse events (SAE), of drug-related AEs, of AEs with NCI-CTCAE grade > 2, of AEs leading to drug withdrawal, of AEs leading to drug reduction and of AEs leading to drug interruption will also be presented.

Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the AEs listing and will be summarised.

A TEAE is defined as any AE that occurs during the active phase of the study (i.e. between the start of the first treatment and 4 weeks after the end of the last study treatment) if:

(1) it was not present prior to receiving the first dose of IMP, or

(2) it was present prior to receiving the first dose of IMP but the intensity/grade increased or the AE became serious during the active phase of the study, or

(3) it was present prior to receiving the first dose of IMP, the intensity/grade is the same but the causality changed to "related" during the active phase of the study.

An overall summary table of all TEAEs will be presented. For this table, in the event of multiple episodes of the same event being reported by the same subject, the NCI-CTCAE worst grade and related causality (if any) will be described and in the cross classification of causality and NCI-CTCAE worst grade, any subject experiencing multiple AEs with different intensities for each causality category will be counted for each grade.

TEAEs will be summarised with the number and percentage of subjects with TEAEs classified by primary system organ class and preferred term (ordered alphabetically) and by associated NCI-CTCAE worst grade. The number of occurrences of a TEAE will also be presented.

In addition, summary tables will also be presented for serious TEAEs, serious TEAEs by associated NCI-CTCAE worst grade, non-serious TEAEs by associated NCI-CTCAE worst grade, TEAEs per decreasing frequency, related TEAEs by associated NCI-CTCAE worst grade, non-related by associated NCI-CTCAE worst grade TEAEs, TEAEs by associated NCI-CTCAE worst grade and worst causality, TEAEs by associated NCI-CTCAE worst grade and worst causality including subject identification, TEAEs leading to drug withdrawal by associated NCI-CTCAE worst grade, TEAEs leading to dose reduction of Temozolomide by associated NCI-CTCAE worst grade and TEAEs leading to dose interruption by associated NCI-CTCAE worst grade.

In the event of multiple occurrences of the same AEs (same PT term) being reported by the same subject, the NCI-CTCAE worst grade (grade 5 > grade 4 > grade 3 > grade 2 > grade 1 > missing > not applicable) and the worst causality (related > missing > not related) will be chosen.

Deaths will also be summarised with the number and percentage of dead subjects and the cause of death (disease progression, adverse event or other) overall and by period (i.e. during the treatment period, defined from the first drug intake to the last drug intake plus 4 weeks, or the follow-up period for deaths occurring after the last intake plus 4 weeks).

3.2.2.2 Laboratory data

A listing of NCI-CTCAE grades with corresponding laboratory ranges will be provided.

Laboratory data (haematology, biochemistry and urinalysis) will be listed in SI units and abnormal values will be flagged (High [H] for values above the upper limit of normal range (ULN), Low [L] for values below the lower limit of normal range (LLN), clinically significant [CS], not clinically significant [NCS]) where applicable with also the NCI–CTCAE grade (for haematology, biochemistry). Any unscheduled laboratory assessments will be flagged [U] in the listings.

A listing will present all values for a subject with at least one clinically significant abnormal value for haematology, biochemistry and urinalysis.

In some local laboratories, the parameters have been collected as percentages instead of the standard units expected, so these data will only be listed and considered as missing in the tables.

3.2.2.2.1 Haematology and biochemistry

For haematology and biochemistry parameters, the baseline will be defined as the last measurement collected prior to the first dose of study drug.

For haematology and biochemistry parameters, summary statistics will be presented at each scheduled assessment for actual values and changes from baseline. Shift tables for all parameters will be presented of the number and percentage of subjects with low, normal or high values.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI–CTCAE criteria, version 4.03, dated: 14 June 2010. A listing of NCI–CTCAE grade 3 and 4 toxicities will be produced. And the number and percentage of subjects with NCI–CTCAE grades 3 and 4 toxicities will be summarised by parameter and worst NCI-CTCAE grade during the treatment period (defined from the first intake to the last intake plus 4 weeks i.e. from V2 to V16).

Additionally, a listing of out of range values with all parameters including those not graded with NCI- CTCAE will be provided with the H and L flags.

3.2.2.2.2 Urinalysis

For categorical urinalysis data (absent/trace/positive and normal/abnormal/not evaluable), frequency tables will be presented at each scheduled assessment. In addition, shift tables between screening and each scheduled assessment will also be presented.

For continuous urinalysis data, summary statistics will be presented at each scheduled assessment for actual values and changes from screening.

Additionally, a listing of abnormal clinical significant values will be provided.

3.2.2.3 Vital signs

Vital signs (supine, sitting and standing systolic and diastolic blood pressures, heart rate and weight) will be listed at each assessment by subject. Any unscheduled vital signs will be flagged [U] in the listing.

Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study drug.

Summary statistics will be presented at each scheduled assessment for actual values and changes from baseline.

3.2.2.4 ECG

ECG results will be listed at each timepoint by subject. Any unscheduled assessment will be flagged [U] in the listings.

Continuous ECG parameters will be presented using summary statistics at each scheduled assessment for actual values and changes from screening.

ECG interpretation of clinical significance (within normal limits / abnormal, not clinically significant / abnormal, clinically significant / not evaluable) will be presented using a

frequency table at each post-dose assessment and a shift table between baseline and post-baseline assessments of the number and percentage of subjects.

Additionally, the worst ECG interpretation between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable > within normal limits) will be described.

3.2.2.5 Echocardiography

Echocardiography results will be listed at each timepoint by subject. Any unscheduled assessment will be flagged [U] in the listings.

Continuous parameters will be presented using summary statistics at each scheduled assessment for actual values and changes from screening.

Qualitative parameters will be presented using a frequency table at each scheduled assessment.

For echocardiography interpretation of clinical significance (normal / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable > normal).

3.2.2.6 Gallbladder echography

Gallbladder echography examinations will be listed at each assessment by subject. Any unscheduled assessment will be flagged [U] in the listings.

Presence and absence of lithiasis and sludge and whether the lithiasis/sludge is symptomatic will be summarised at each assessment in frequency tables. Shift tables will also be presented between screening and each scheduled assessment.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

No missing value will be replaced.

In the description of qualitative parameters, subjects with a value counted as “missing” at a visit will be presented.

If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, prior to the database lock.

Any repeat or additional assessments performed will be included in the individual subject data listings.

- Efficacy endpoints

When tumour assessment visits are completely missing, rules from FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 will be implemented as described in section 3.2.1 Efficacy.

- Safety endpoints

If a value requires a retest (for laboratory values, vital signs, ECG, cardiac echography examination, and gallbladder echography), the last reliable non-missing value will be taken into account if measured before the administration; and the first non-missing reliable value for post-treatment assessments. An assessment is considered reliable if it is performed without

any technical problem and if the result is within the range of plausible values. For adverse events with missing information for the intensity and causality, the value will not be replaced and will be summarized as a separate category.

For all other variables, no imputation will be made for missing data.

3.2.3.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e. an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly a medication with partial start and stop dates could be considered as prior and concomitant treatment).

Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥ 2", similarly the duration of ongoing AEs or medication will be "≥ xx" according to the start and last visit dates).

3.2.3.3 Outliers

A search of outliers should be performed before the database lock and actions with the sponsor should be defined.

3.2.4 Subject disposition

The number and percentage of subjects enrolled and included in each population will be presented by centre for the screened population.

A listing of the inclusion and exclusion criteria will be provided by subject, and subject eligibility will also be listed.

A summary table and a flow chart will be provided for the ITT/Safety population presenting the number of subjects at each visit (scheduled and attended according to time windows) and in the flow chart identifying the number of subjects who continued, withdrew or completed over time.

The reasons for subject exclusions from each population will also be tabulated on the screened population.

All the major protocol deviations identified prior to unblinding will also be listed by subject. Additionally major protocol deviations with impact on the populations will be summarised on the ITT/Safety population.

A summary table will present the extent of subject exposure in the study. The length of exposure is calculated from the date of consent to the last study visit.

Listings of dates of assessments (relative day) and of study duration will be presented by subject. The number and percentage of subjects at each planned visit during the study will be presented on the ITT/Safety population.

3.2.5 Withdrawals

The number of subjects who were treated, and who discontinued and completed the study (local progression or completed all visits see Appendix 2) will be tabulated and listed.

Primary reasons for discontinuation of study will be tabulated. Primary reasons for study discontinuation will also be presented by visit.

3.2.6 Demographic and baseline characteristics

The baseline is the last available assessment prior to the first dose of study drug (Day 1).

All demographic and baseline characteristics will be listed by subject.

Summary statistics will be provided for demographic and baseline characteristics (i.e. sex, race, age, age class (< 65, ≥ 65), height, weight, Body Mass Index (BMI) and BMI class (< 18.5, $[18.5; 25[$, ≥ 25)), for the ITT/Safety population overall and by derived type of carcinoid.

The following tumour characteristics (history and tissue analysis) will also be described:

- Time since diagnosis (in months),
- Location of the primary tumor (Thymus/Lung),
- Foci of necrosis (local assessment at screening) and type if present,
- Mitotic count (local assessment at screening),
- Type of carcinoid (derived from absence/presence of foci of necrosis and mitotic count see Appendix 2),
- TNM Staging according to UICC/AJCC 7th Edition TNM System assessed by the investigator,
- TNM Staging according to UICC/AJCC 8th Edition TNM System, assessed centrally,
- Octreoscan or GA-DOTA/TATE/TOC-PET result within 12 months,
- SSTR2 status (central assessment including categories of HER-2 score (0, 1+, 2+ 3+ and positive versus negative), H-score (from 0 to 300 as quantitative variable and positive versus negative according to the Specht publication) and IRS score (qualitative variable according to the Specht publication),
- Ki67 status (central assessment as score and in class: < 4, $[4\text{-}25[$, ≥ 25),
- MGMT status (central assessment including percentage of positive nuclei stained (quantitative variable and positive versus negative according to Schmitt publication), H-score (from 0 to 300 as quantitative variable) and percentage of methylated sites (quantitative variable and positive versus negative according to Schmitt publication)).

NYHA functional classification, serum pregnancy test examinations and serology results will also be listed and summarised.

3.2.7 Medical and surgical history

Significant medical and surgical history will be coded using MedDRA Version 18.1 or later.

The listings will present the preferred term and verbatim text and be sorted by subject, primary system organ class, preferred term and verbatim text.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary system organ class and preferred term.

3.2.8 Subject compliance

Duration of study drug exposure and compliance will be summarized separately for TMZ and Lanreotide ATG including number of cycles (i.e. for TMZ with one cycle means at least one capsule taken) and number of injections planned and performed (according to the treatment period duration) respectively and cumulative dose received, and study drug exposure will also be described overall. In addition, the percentage of subjects by level of compliance for each drug defined as follows will be provided: < 70 %, [70 %; 100 %[, 100%,]100 %; 130 %[and ≥ 130 %. Additionally, the number of subjects with TMZ titration (down from 250 mg to 180 mg, since up titration is not permitted) will be described by visit and overall.

Listings will present the drug administrations (dose, quantity, date) by subject and visit for TMZ and Lanreotide ATG. In addition, the listings will present the difficulties recorded during drug administrations. Besides, a table will be produced to describe the reasons for discontinuation of study medications by visit.

3.2.9 Prior and concomitant medications, therapies and surgical procedures

All prior and concomitant medications as well as prior therapies and surgical procedures for the study disease will be recorded on the eCRF.

Any medications or therapies given to a subject for another indication within 28 days before study drug administration or during study drug administration will be indicated on the eCRF as well as concomitant surgical procedures. Dose and generic name or tradename will be indicated. All recorded data will be included in data listings.

Prior and concomitant medications/therapies/procedures will be coded using World Health Organization – Drug dictionary (WHO-DD) Version of March 2016 or later. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, which corresponds to the first 3 digits.

The date of first administration of study drug (study day 1) will be used as the cut-off date for the definition of prior and concomitant. A drug that started before study day 1 and is continuing at time of Day 1 will be considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant will be flagged P, C and PC respectively, in all listings.

The listings will be presented for the medications, therapies and surgical procedures for T-NETs (separating prior chemotherapies, prior targeted therapies, prior other medications, prior radiotherapies, prior locoregional therapies and/or peptide receptor radionuclide therapies, prior surgical procedures and concomitant medications for T-NETs) and other than for T-NETs independently (separating prior and concomitant non-drug therapies and other medications) and will be sorted by subject, chronological start date, therapeutic class, preferred name and verbatim name.

Frequency tables of the number and percentage of subjects with prior medications/therapies/procedures will be provided by category (i.e. for T-NETs: prior surgical procedures, prior radiotherapies, prior locoregional therapies and/or peptide receptor radionuclide therapies, prior chemotherapies, prior targeted therapies, prior other medications; and other than for T-NETs: prior non-drug therapies and prior other medications).

Frequency tables of the number and percentage of subjects with concomitant medications/therapies/procedures will be provided by category (i.e. concomitant medications for T-NETs and concomitant medication other than for T-NETs as well as concomitant non-drug therapies and concomitant surgical procedures) will be provided by therapeutic class and preferred name.

Prohibited therapies will be identified, to do so the therapeutic class and preferred name will be specified in Appendix 1 to enable the database to be searched and to flag the concerned therapies in the listings.

3.2.10 Derived data

The derived data are data which are calculated from the raw data in the eCRF and not included in the database. The list of derived data is displayed in Appendix 2.

3.2.11 Visit windows

All data will be organised and analysed according to the derived attended visits. Since actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit using the assessment, evaluation and sample dates rather than the visit date which could be delayed. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected then the following rule should be applied: for pre-study assessments the last non-missing result prior to study drug administration should be used; for post-treatment assessments the closest non-missing result to the scheduled visit should be used.

Table 12 Visit windows

Study phase	Visit	Time interval (days)
Pre treatment	Screening	-28 to –1
Treatment period	Baseline	1 (prior to first dose)
	Week 2	2 to 17
	Week 3	18 to 24
	Week 4	25 to 42
	Week 8	43 to 70
	Week 12	71 to 98
	Week 16	99 to 126
	Week 20	127 to 154
	Week 24	155 to 182
	Week 28	183 to 210
	Week 32	211 to 238
	Week 36	239 to 266
	Week 40	267 to 294
	Week 44	295 to 322
	Week 48	323 to 350
End of study	Week 52	351 to 378

A listing with visits as reported by the investigators and reallocated visits with time windows will be produced in order to identify visits according to the time they occurred including reallocated early withdrawal and appendix visits.

3.2.12 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics, the following will be presented: number of available observations (n), number of missing observations (missing), arithmetic mean and 95 % CI of the mean, standard deviation, median and the range (minimum, maximum). For categorical or discrete variables, the absolute and relative (percentage) numbers based on the available number of observations for each category will be presented, including 95 % CI (if required).

Mean, 95 % CI, median, standard deviation and standard error of the mean values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be based on the number of subjects in the specified analysis population with non-missing observations and will be reported to one decimal place and 0 % will not be presented (i.e. missing values will not be taken into account in the denominator). For description by visit, percentages will be based on the number of subjects in the specified analysis population attended the visit with non-missing observations. The denominator will be specified in a footnote to the tables for clarification if necessary.

Lower and upper CI values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '< 0.0001'.

All values below or above a limit of detection (e.g. < 0.1 or > 100) will be listed as such. For each parameter for which it is possible to have values below or above a limit of quantification, the rule to be used in the statistical tables is to replace values below or above a limit of quantification by the limit of quantification.

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, < 4.5, …) must be decimal justified. Dates and time will be presented in the format YYYY-MM-DDTHH:MM or YYYY-MM-DD if time is missing or not recorded.

3.2.13 Pooling of centres

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.2.14 Interim analysis

No interim analysis will be performed.

3.2.15 Role of independent data monitoring committee (DMC)/interim data review committee [if applicable]

No independent data monitoring committee/interim data review committee will be used in this study.

3.2.16 Covariates and analysis of subgroups

If the frequency of subjects in each category allows it, subgroup analyses of typical versus atypical carcinoid type will be produced for the primary analysis.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using a PC on a Windows 7 operating system.

4.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS v 9.4 or higher. All outputs will be in Microsoft Word format.

4.3 Validation programs

Biotrial Biometrics will provide a Quality Control (QC) and Validation Plan to Ipsen identifying the methods of validation like the double programming of the main safety and efficacy endpoint.

The study statistician is responsible for reviewing each project program and output associated with the deliverable product. Program logs are reviewed for logical, syntax and fatal errors. The review in SAS includes, but is not limited to, all ERRORS, WARNINGS, BY-VALUE merge messages, NOTES, and UNINITIALIZED variables. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.

The study statistician is responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g., SAS code review, hand calculation, etc.) to reassure of the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the statistical and analysis plan. Outputs are cross-checked against each other for accuracy and consistency. For statistical tables, listings, appendix listings, and figures, this procedure includes comparison of subject group numbers, counts of subjects at each observation point, and consistency of results for variables between outputs.

Findings of the QC reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

During the whole process of production and validation of the deliverables, the statistical programmer, the assistant and the study statistician complete the QC and statistical analysis results follow-up validation checklist. Once the validation of the deliverables is complete, i.e. when all analysis datasets and/or outputs are produced, integrated (where applicable) and reviewed, and no further change is required, the study statistician ticks the approved deliverables to indicate to the assistant that the outputs are ready to be compiled by section and then delivered to the sponsor. The summary QC forms produced will be printed and signed by the participants during the validation process at each outputs delivery and provided to the sponsor to support the validation at the end of the study.

4.4 Restitution of the programs

All programs (including macros and analysis datasets) producing the tables, listings and statistical outputs along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analyses will be finalised.

Moreover, ADaM datasets will be provided to the sponsor with the first draft at 50 % of subjects, soft lock, first draft of the TFLs post lock and final TFLs.

5 CHANGES FROM PROTOCOL

In the protocol section 3 "STUDY DESIGN" paragraph 3.1 "GENERAL DESIGN AND STUDY SCHEMA", it is stated that “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.”. However, the steering committee advised as more appropriate for the primary objective to consider the subjects attending the 9 months assessment and to consider the subjects withdrawn before 9 months with PD as PD, while the other subjects withdrawn for reason other than PD or missing reason would also be considered as failure for disease control.

The content of the echocardiography assessments was discussed during the eCRF design and were not described in the protocol.

It was planned in the protocol to have a deviation when the compliance to Temozolomide is < 80 %, but to be consistent with other similar studies the threshold was updated to 70 %.

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