STATISTICAL AND ANALYSIS PLAN

A Phase 3, Prospective, Randomized, Double-Blind, Multi-Center, Study of the Efficacy and Safety of Lanreotide Autogel/Depot 120 mg Plus BSC vs. Placebo Plus BSC for Tumour Control in Subjects with Well Differentiated, Metastatic and/or Unresectable Typical or Atypical, Lung Neuroendocrine Tumours

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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:

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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	

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-HIAA	5-Hydroxyindoleacetic Acid
ADaM	Analysis Data Model
AC	Atypical Carcinoid
ADA	Antidrug Antibodies
ADL	Activities of Daily Living
AE	Adverse Event/Experience
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BSC	Best Supportive Care
CBR	Clinical Benefit Rate
CgA	Chromogranin A
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organisation
CT	Computerized Tomography
CV%	Percent Coefficient of Variation
DB	Double-blind
DBP	Diastolic Blood Pressure
CCI	[redacted]
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
eGFR	Estimated Glomerular Filtration Rate
ENETS	European Neuroendocrine Tumor Society
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
HbA1c	Glycated Hemoglobin/ Hemoglobin A1c
HR	Hazard Ratio
HR	Heart Rate
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
ITT	Intention to Treat
IWRS	Interactive Web Response System
Ki67	Proliferation Index
KM	Kaplan-Meier
LAN	Lanreotide Autogel/Depot 120 mg
LLN	Lower Limit of Normal

Abbreviation	Definition
LOQ	Limit of Quantification
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTT	Molecular Targeted Therapy
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NET	Neuroendocrine Tumor
Non-CR	Non-complete response
Non-PD	Non-progressive disease
NYHA	New York Heart Association
OL	Open Label
OLITT	Open Label Intention to Treat
ORR	Objective Response Rate
PD	Progressive Disease
PDM	Pharmacokinetics & Drug Metabolism
PET	Positron Emission Tomography
PFS	Progression Free Survival
PH	Proportional Hazards
CCI	[redacted]
PP	Per Protocol
PR	Partial Response
PR	Prothrombin ratio
PT	Prothrombin Time
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
QRS	QRS Interval Duration
QT	Time Interval for Ventricular Depolarisation and Repolarisation
QTc	Corrected QT Interval
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	[redacted]
SAE	Serious Adverse Event/Experience
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SD	Stable Disease
SDC	Statistics and Data Corporation, Inc.
SDTM	Study Data Tabulation Model
SE	Standard Error of the Mean
SI	System International

Abbreviation	Definition
SOP	Standard Operating Procedure
SPECT	Single Photon Emission Computed Tomography
SRI	Somatostatin Receptor Imaging
SSA	Somatostatin Analogs
SSTR	Somatostatin Receptors
StD	Standard Deviation
TC	Typical Carcinoid
TEAE	Treatment-Emergent Adverse Event/Experience
TFLs	Tables, Figures and Listings
CCI [redacted]	[redacted]
TNM	Tumor-node-metastasis
TPN	Total Parenteral Nutrition
TPR	Time Point Response
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal
US(A)	United States (of America)
WBC	White Blood Cell
WHODRUG	World Health Organization Drug Dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study Objectives

The purpose of this study is to describe the role of Lanreotide Autogel/Depot 120 mg (LAN) monotherapy plus best supportive care (BSC) in the management of metastatic and/or unresectable, well differentiated, typical carcinoid (TC) or atypical carcinoid (AC) lung neuroendocrine tumors (NET). There have been very limited data in this subject setting, except for sub-analyses of larger randomized studies, but there is a clear molecular rationale that establishes the potential role of somatostatin analogues (SSA) like LAN plus BSC in advanced lung NETs.

Recent updates of National Comprehensive Cancer Network (NCCN) and European Neuroendocrine Tumor Society (ENETS) guidelines recommend SSA in first line for the treatment of locoregional unresectable or metastatic lung NETs as an option beyond "observation," which was considered to be in part responsible for the limitation of the recruitment of the population. Consequently, it was decided to prematurely stop recruitment and to transition subjects still treated in the Double-Blind (DB) Phase to the Open Label (OL) Treatment Phase, regardless of treatment assignment. The transition to the OL Treatment Period was to be done per subject at the planned scheduled visit (i.e., approximately 28 days from the previous injection) following the country approval of Protocol Amendment #5.

1.1.1 Primary Objective

- To describe the antitumor efficacy of LAN monotherapy plus BSC every 28 days, in terms of progression free survival (PFS), measured by central review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung NETs in either the DB Phase, or in the OL period.

1.1.2 Secondary Efficacy Objectives

- To describe the antitumor efficacy during the DB Phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of PFS, measured by central review using RECIST v1.1, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung NETs. To describe the antitumor efficacy during the DB Phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of PFS, measured by local review using RECIST v1.1, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung NETs.
- To describe the objective response rate (ORR) of LAN monotherapy plus BSC every 28 days and placebo plus BSC, as assessed by RECIST v1.1 (proportion of subjects with an objective response of partial response [PR] or complete response [CR]) in the DB Phase.
- To describe time to treatment failure (Kaplan-Meier [KM] estimates) of LAN monotherapy plus BSC every 28 days and placebo plus BSC in the DB Phase.
- To describe the changes from Baseline in the biomarker chromogranin A (CgA) during the DB and the OL Treatment Phases.
- To describe the proportion of subjects with a decrease of CgA ≥30% at week 8 in the population of subjects with an elevated CgA (≥2 x upper limit of normal [ULN]) at Baseline during the DB and the OL Treatment Phases.

- To describe the change in Quality of Life (QoL) from Baseline, as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) questionnaire during the DB, the OL Treatment and the Follow-up Phases.
- To describe the time to deterioration of QoL (using EORTC QLQ-C30) during the DB, the OL Treatment and the Follow-up Phases.
- To describe the changes in urinary 5 hydroxyindoleacetic acid (5-HIAA) in subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline during the DB and the OL Treatment Phases.

1.1.3 Secondary Safety Objectives

- To evaluate the clinical and biological safety profile.

CCI [redacted]

1.2 Study Design

This is a Phase 3, prospective, multi-center, randomized, double-blind, study describing the efficacy and safety of LAN plus BSC and placebo plus BSC for the treatment of well differentiated, metastatic and/or unresectable, typical or atypical lung NETs.

This study contains two phases: the DB Phase, and the OL Extension Phase. The DB Phase includes: Screening, Baseline and Treatment Period. The OL Extension Phase consists of two periods: Treatment Period and Follow-up Period.

As planned initially, a total of 216 eligible subjects with well-differentiated typical or atypical, metastatic and/or unresectable lung NETs, and a positive somatostatin receptor imaging (SRI) (Octreoscan® ≥ grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background) will be randomized 2:1 to either LAN (120 mg/28 days) plus BSC or placebo plus BSC following the stratification of (1) typical versus atypical and (2) prior chemotherapy versus no prior chemotherapy (cytotoxic chemotherapy or molecular targeted therapy [MTT] or interferon).

The DB Phase includes a Screening Visit to establish protocol eligibility and disease characteristics. The Baseline Visit confirms eligibility prior to randomization and treatment. The DB Phase of the study will end with Protocol Amendment #5 and will be followed by the OL Extension Treatment Period or Follow-up.

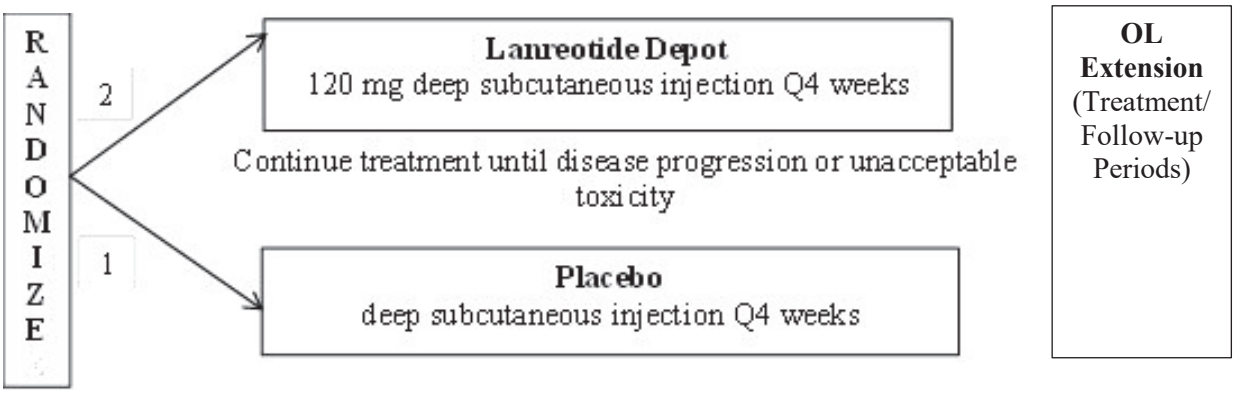
At the end of the OL Extension Treatment Phase, if subjects are still benefiting from treatment (i.e., not progressed nor died and no safety issues with the drug), the subjects will have the option to continue to receive LAN every 28 days up to disease progression or unacceptable toxicity. In such a situation, as permitted by local regulations, LAN will be provided free of charge by the Sponsor to the sites under its commercial packaging. During this period, the physician will report immediately to Ipsen Pharmacovigilance Contact any safety concerns arising from the use of the product.

Due to a premature stop in recruitment (as per Protocol Amendment #5), only 77 subjects have been included in this study. All subjects still treated in the DB Phase will enter the OL Extension Period (either for OL treatment or OL follow-up) regardless of DB treatment. The transition to the OL Extension Period will be done by country and per subject at the next planned scheduled visit (i.e., approximately 28 days from the last injection).

Subjects enrolled into the study will stay on LAN therapy (i.e., OL Treatment Phase) until evidence of disease progression (assessed locally and confirmed centrally), development of unacceptable toxicity, or premature withdrawal for any reason or up to 18 months after the last subject randomized. After disease progression subjects will be followed for survival, QoL and all subsequent anticancer treatments for lung NET up to the end of the study.

Study Schema

Injection every 28 days (4 weeks)



1.2.1 Double-Blind Phase

Subjects will be randomized 2:1 to receive either LAN plus BSC or placebo plus BSC following the stratification of:

1. atypical (mitotic index ≤10 mitoses/2 mm^2 and/or foci of necrosis) versus typical (mitotic index <2 mitoses/2 mm^2); and
2. prior chemotherapy (cytotoxic chemotherapy or MTT or interferon) versus no prior chemotherapy therapy.

Subjects will undergo a safety and efficacy assessment as defined in Table 1.

As described above, the DB Phase will end with Protocol Amendment #5 and will be followed by the OL Treatment Phase.

Prior to approval of Protocol Amendment #5:

- If a subject progressed during the DB Phase, the subject was proposed to enter the OL Extension Phase:
  - If the subject was on placebo and progressed during the DB Phase, the subject was offered the opportunity to enter the treatment period of the OL Extension Phase and to receive LAN every 28 days.
  - If the subject was on LAN and progressed during the DB Phase, the subject entered the Follow-up Period of the OL Extension Phase and was followed for QoL/survival and all subsequent anticancer treatments for lung NET were recorded.

Following approval of Protocol Amendment #5:

- All ongoing subjects in the DB Phase, who have not yet progressed and who agree to continue in the study, will enter the OL Treatment Period. The subjects in the OL Treatment Period will be followed up to disease progression (assessed locally and confirmed centrally), development of unacceptable toxicity, or withdrawal from the study treatment for any other reason or up to 18 months after the last subject randomized.
- The OL Treatment Period will stop once all subjects have progressed (assessed locally and confirmed centrally) or 18 months has occurred since the last subject randomized (i.e., end of study).
- If disease progression occurs for those receiving LAN during the DB phase, the subject can enter the OL follow-up period.
- If disease progression occurs during the OL Treatment Period, the subject can enter the OL follow-up period.
- The follow-up period will stop at the same time as the OL Treatment Phase (i.e., end of study – up to 18 months after the last subject randomized).

1.2.2 Open Label Extension Phase

The OL Extension Phase consists of:

- the Treatment Period, where all subjects receive OL LAN plus BSC,
- and the Follow-up Period.

1.2.2.1 Treatment Period (Optional Open Label Lanreotide Autogel/Depot) of the Open Label Extension Phase

Prior to approval of Protocol Amendment #5, subjects qualified for optional OL LAN plus BSC if inclusion criteria 9-11 and exclusion criteria 6, 9-15, 17-22 listed in Protocol Section 4.1 and Section 4.2 continued to be satisfied. In addition, subjects must also meet the following additional inclusion criteria:

(14) Subjects have central review confirmed/documented disease progression according to RECIST v1.1

(15) There is a request from the subject to receive OL LAN plus BSC

(16) Subjects were randomized in the Placebo plus BSC arm

Following approval of Protocol Amendment #5, all ongoing subjects in the DB Phase who have not yet progressed (assessed locally and confirmed centrally), do not have a safety issue with the drug, and who agreed to continue the study will enter the OL Treatment Period. The subjects in the Treatment Period of the OL Phase will be followed up to disease progression (assessed locally and confirmed centrally), development of unacceptable toxicity, or withdrawal from the study treatment for any other reason or up to 18 months after the last subject randomized.

Please refer to Protocol Section 5.2.3 for more details.

Subjects who qualify to receive OL LAN plus BSC will receive LAN plus BSC via deep subcutaneous (s.c.) injection every 4 weeks (28 days) within the Treatment Period of the Extension Phase until:

1. Documentation of disease progression (local review confirmed by the central review via RECIST v1.1) or death;
2. Development of intolerable toxicity;
3. Appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of any SSA (short acting and/or long acting release SSA);
4. Subject noncompliance with required safety and efficacy assessments;
5. Subject voluntary discontinuation; or
6. Study termination by Sponsor except those subjects who will continue in the Study, or up to 18 months after the last subject randomized.

Subjects who discontinue OL LAN plus BSC during the Treatment Period of the Extension Phase will complete the Post Treatment/Early Withdrawal Visit assessments as detailed in Table 2 and enter the Follow-up Period (except in case of consent withdrawal) for assessment of QoL and survival, and all subsequent anticancer treatments for lung NET will be recorded up to the end of the study.

1.2.2.2 Follow-up Period of the Open Label Extension Phase

Subjects who experience disease progression during the DB Phase and who do not enter or qualify for the optional OL Extension Treatment Period Phase may enter the Follow-up Period of the Extension Phase after completing the Post Treatment/Early Withdrawal Visit assessments listed in Table 1.

Subjects who enter the optional OL LAN plus BSC Treatment Period of the Extension Phase and who have experienced disease progression or subsequently discontinued OL LAN plus BSC administration may enter the Follow-up Period after completing the Post Treatment/Early Withdrawal Visit assessments listed in Table 2.

During the Follow-up Period of the OL Extension Phase, subjects will undergo follow-up visits every 12 weeks for QoL and survival. All anticancer treatments for lung NETs will be recorded until the time of death or up to 18 months after the last subject randomized.

The Follow-up Period of the OL Extension Phase will continue as long as the study subject is alive, or until discontinuation of survival follow-up by the Sponsor or up to the end of the study.

1.2.3 Study Population

The study population consists of 77 randomized subjects (i.e., number of subjects enrolled at time of enrolment termination) who meet the selection criteria detailed in Protocol Section 4.1 and Protocol Section 4.2.

1.2.4 Study Exposure

- Trial recruitment: approximately 25 months
- DB Phase: approximately 36 months
- OL Extension Phases end 18 months after the last subject randomized

1.3 Methods and Procedures

1.3.1 Subject Identification and Allocation to Study Treatment

At Screening, subjects are allocated a subject number. Following confirmation of eligibility for the study, subjects will be randomly allocated to one of the following treatment groups in a 2:1 ratio:

- Lanreotide Autogel/Depot 120 mg plus BSC, deep s.c., every 28 days; or
- Placebo plus BSC, deep s.c., every 28 days.

1.3.2 Subject Assessments

1.3.2.1 Efficacy Assessments

For the timing of assessments in this study, refer to the schedule in Table 1 and Table 2, for the DB Phase and the OL Extension Treatment Period, respectively. Methods for describing efficacy data are described below.

Time to Disease Progression or Death

PFS (central) is defined as time from randomization to the first documentation of disease progression measured by central review according to RECIST v1.1 or death from any cause, whichever occurs first.

PFS (local) is defined as time from randomization to the first documentation of progression measured by local review according to RECIST v1.1 or death from any cause, whichever occurs first.

Tumor Response

All tumor assessments will be performed using the RECIST v1.1 every 12 weeks throughout the study (Table 1 and Table 2). The same imaging technique will be used for each subject throughout the study in order to ensure comparability between tumor assessments. Subjects will receive either computerized tomography (CT) scan of the thorax and abdomen, or a Magnetic Resonance Imaging (MRI) scan of the abdomen with CT scan of the thorax. Routine use of MRI with early arterial phase is strongly recommended, especially to assess liver and bone metastasis. At the Post Treatment/Early Withdrawal Visit, scans will only be conducted if not performed within the previous 4 weeks. For a given subject, it is recommended to use the same scanner(s) and imaging parameters across all time points throughout the study to ensure comparability between tumor assessments. Further, it is preferred that all scans undergo a local review by the same reader designated for the study at each site, according to the study schedule.

An independent central review of all scans will be performed in an ongoing manner and used for the analysis of the primary endpoint. Details of the procedure to handle the central reading of the CT scans/MRI are provided in the central reading site manual. A Best Overall Response of SD can only be made after the subject is on study for a minimum of 7 weeks (49 days). If the subject is on study less than 7 weeks (49 days), any tumor assessment indicating SD before this time period will have a Best Response of “non evaluable” (NE) unless progressive disease (PD) is identified. In addition, at Baseline, the Central Reading Contract Research Organization (CRO) will measure the hepatic and intrathoracic tumor load. From the imaging data, PFS, CBR, ORR, and time to treatment failure will be estimated.

Biomarkers (Chromogranin A and 5-Hydroxyindoleacetic Acid)

Chromogranin A

Plasma CgA is assessed according to the schedules in Table 1 and Table 2. At each time point a 5 mL blood sample for analysis of CgA is taken, prepared and shipped as specified in the Central Laboratory Services Manual.

In the DB Phase, blood samples for CgA are collected at Baseline and repeated at Week 8, Week 12, every 12 weeks thereafter, and at the Post Treatment/Early Withdrawal Visit.

Blood samples for CgA are also collected at the OL Treatment Extension Baseline and repeated every 12 weeks thereafter and at the Post Treatment/Early Withdrawal Visit of the OL Treatment Extension.

5-Hydroxyindoleacetic Acid

Urinary 5-HIAA is assessed according to the schedules in Table 1 and Table 2.

At Baseline (Visit 2), urinary 5-HIAA levels will be assessed for all subjects. Urinary 5-HIAA levels are assessed at Week 8, Week 12, and every 12 weeks thereafter and at the Post Treatment/Early Withdrawal Visit, only for subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline of the DB Phase, or if clinically indicated.

The assessment of urinary 5-HIAA requires subjects to collect their urine for the 24-hour period prior to the study visit. Subjects are provided with a receptacle for this purpose and are asked to come with it to the next treatment period visit.

The collection period will begin once the subject has emptied his/her bladder (not into the collection receptacle) after waking up on the morning of the day prior to the study visit. This time is recorded on the receptacle.

In addition, urinary creatinine will be analyzed in order to assess compliance with the 24-hour collection period.

Quality of Life

Quality of life is assessed using the EORTC QLQ-C30 v3.0 questionnaire. The questionnaire will be completed at Baseline (Visit 2), every 12 weeks (throughout the DB Phase and both OL Phases), and at the Post treatment/Early Withdrawal Visit at the end of the DB Phase and both OL Phases. If necessary, the investigator or delegated personnel can explain the questions, which are provided in paper format, to the subject. The subject will complete the questionnaires in the same conditions throughout the study (i.e., prior to study medication administration) and the investigator or delegated personnel will check that all questions are answered.

1.3.2.2 Safety Assessments

Adverse Events

Adverse events (AE) will be monitored starting at the time the subject gives informed consent and throughout the study and up to 30 days after the last study drug administration. Adverse events will be elicited by direct, non-leading questioning or by spontaneous reporting. Details for AE reporting can be found in Protocol Section 8.1.2.

Recording and Follow-up of Adverse Events

At each visit (during the DB and OL Treatment Phases), the subject will be asked a non-leading question such as: "How have you felt since the last visit?"

"Injection only" visits will not be considered as study visits; however, any AEs reported at these visits will be recorded on the electronic case report form (eCRF), reported to the Sponsor (within 24 hours if a serious AE [SAE]), and followed up as appropriate by the responsible investigational site staff.

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbations of pre-existing illnesses are recorded according to the National Cancer Institute (NCI) terminology if applicable.

Any AEs already recorded and designated as "continuing" will be reviewed at each subsequent assessment.

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

Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs is distinguished from discontinuation/ withdrawal due to insufficient response to the study drug (see Protocol Section 4.3).

If the study drug is discontinued due to an SAE, it is reported immediately to the Sponsor's designated representative (see Protocol Section 8.1.4).

In all cases, the investigator ensures the subject receives appropriate medical follow-up (see Protocol Section 8.1.3).

The investigator assesses the ongoing benefit risk for each subject during their participation in the study, in consideration of any AEs and the potential benefit of continued treatment with the study drug or any alternative therapies.

The study drug is to be temporarily discontinued in case of:

- Severe unremitting gastrointestinal intolerance: NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03) Grade ≥3 diarrhoea (Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living [ADL]) or vomiting (≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, total parenteral nutrition (TPN) or hospitalization indicated) despite optimal antidiarrheal or antiemetic treatment.
- Poorly controlled diabetes mellitus: NCI-CTCAE Grade ≥4 hyperglycaemia (blood glucose >500 mg/dL, >27.8 mmol/L) that does not resolve to NCI-CTCAE Grade ≤2 (fasting glucose ≤250 mg/dL, ≤13.9 mmol/L) within 14 consecutive days after starting optimal antidiabetic treatment.
- Pancreatitis: NCI-CTCAE Grade ≥3 amylase (>2 x ULN) or lipase (>2 x ULN) with symptoms, or for >7 consecutive days without symptoms.
- Acute renal injury: NCI-CTCAE Grade ≥3; Creatinine >3x baseline or >4.0 mg/dL or hospitalization indicated.
- Hepatic impairment: NCI-CTCAE Grade ≥3 alanine aminotransferase (ALT; >5 x ULN) or aspertate aminotransferase (AST; >5 x ULN) or Bilirubin (>2 x ULN).
- Any other AE or lesser severity of the AEs listed above that, in the opinion of the investigator, could jeopardise the subject's safety.

The investigator is to assess whether permanent discontinuation or reintroduction of study drug is appropriate in the event of recovery from any such AE, considering the assessment of the relationship to the study drug, underlying disease, intercurrent illness or concomitant medications, and the overall benefit risk for the subject continuing in the study.

Clinical Laboratory Tests

During the DB Phase and OL Extension Treatment Phase, blood samples are collected at Screening, Baseline, Week 12 and then every 12 weeks until the Post Treatment/Early Withdrawal Visit (see Table 1 and Table 2).

The investigator reviews the safety laboratory test results, documents the review, and records any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Protocol Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs). Laboratory test results reported as AEs are graded according to NCI-CTCAE criteria (see Protocol Section 8.1.2.1).

All clinically relevant abnormal laboratory tests occurring during the study are repeated at appropriate intervals until the values return to Baseline 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.

Hematology

Blood samples are collected in a potassium ethylenediaminetetraacetic acid (EDTA) tube to assess the following parameters: red blood cell (RBC) count, hemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin

(MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others) and platelet count.

Blood Biochemistry

Blood samples are collected in an activator gel tube to assess the following parameters: urea, creatinine, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, phosphate, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase, lipase, amylase, albumin, total protein, total cholesterol, triglycerides, fasting glucose, and glycated hemoglobin (HbA1c).

Coagulation

Blood samples are collected at Screening in a citrated tube to assess the following coagulation parameters: activated partial thromboplastin time (aPTT), prothrombin time (PT) and its derived measures of prothrombin ratio (PR) and international normalized ratio (INR).

CCI [redacted]

Physical Examination

Physical examinations are assessed at Screening, Baseline, Week 8, and every 12 weeks thereafter until the last study visit. Please see Table 1, Table 2 and Table 3 for details.

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

Vital Signs

Vital signs are assessed at Screening, Baseline, and every 12 weeks thereafter until the last study visit. Please see Table 1, Table 2 and Table 3 for details.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) are assessed with an automated device so that measurements will be independent of the observer. Blood pressure and HR are recorded in the supine position after five minutes of rest and in the standing position after 1 minute of standing.

Weight is recorded at Screening, Baseline, Week 8, and every 12 weeks thereafter until the last study visit. Height is measured at Screening (Visit 1) only.

Electrocardiogram

Electrocardiogram (ECG) variables (sinus rhythm, HR, RR duration, PR duration, QRS duration, QT duration, corrected QT interval (QTc) Bazett, QTc Fridericia, QTc manual, and overall interpretation of clinical significance), will be assessed at Screening, Week 24, Week 48, and every 24 weeks thereafter, and at the Post Treatment/Early Withdrawal Visit during the DB and OL Treatment Extension Phases. Please see Table 1 and Table 2 for details.

Abnormal ECG findings as judged by the investigator as clinically significant that result in a change in study drug dosage or administration schedule, or in discontinuation of the study drug, or require intervention or diagnostic evaluation to assess the risk to the subject, will be recorded as AEs.

New York Heart Association scales

New York Heart Association (NYHA) scales for functional capacity and objective assessment will be assessed at Screening, Week 24, Week 48, and every 24 weeks thereafter, and at the Post Treatment/Early Withdrawal Visit during the DB and OL Treatment Extension Phases (as per investigator judgement). Please see Table 1 and Table 2 for details.

Eastern Cooperative Oncology Group

The Eastern Cooperative Oncology Group (ECOG) Performance status will be assessed at Screening, Baseline, and every 12 weeks thereafter, and at the Post Treatment/Early Withdrawal Visit during the DB and OL Treatment Extension Phases. Please see Table 1 and Table 2 for details.

Gallbladder Echography

Gallbladder echography is performed if biological abnormalities and/or clinical inflammatory symptoms appear during the course of the study. The gallbladder echography parameters that are collected are the presence/absence of lithiasis and sludge.

1.3.2.3 Other Assessments

- Demography (age, sex, race, ethnicity; note that race is collected in the US and only certain European countries and that ethnicity is only collected in the US).
- Baseline characteristics (date of NET diagnosis, location of primary tumor [lung, lung hilum, lung left, lung right, unknown, other], type of tumor (TC or AC), mitotic count, grading according to mitotic index, foci of necrosis, hepatic and intrathoracic tumor load assessments, proliferation index (Ki67) if available, presence of hormone related syndrome, tumor-node-metastasis (TNM) staging, metastasis (number and location), ECOG performance status, and subject status in terms of somatostatin receptors (SSTR).
- Significant medical or surgical history (any past or current significant medical or surgical conditions excluding the lung NETs under investigation), prior chemotherapy for lung NET, prior radiotherapy for lung NET, prior surgery for lung NET and prior medication for lung NET.
- Concomitant treatment for lung NET.
- Somatostatin receptor imaging by Octreoscan or Ga-PET-scan performed within the last 6 months is collected if available in the subject file. If not available in the subject file, a new SRI is required before inclusion. SRI positivity could be confirmed according to the rules described below:
  - (1) Octreoscan®
    - (a) Synonym: Indium In 111-Pentetreotide, Indium In-111 Pentetreotide, Indium-111 Octreotide Dtpa, Indium-111-Dtpa-D-Phe-1-Octreotide, Indium-In 111 Pentetreotide, Indium-In-111-Pentetreotide)
    - (b) Method: Planar or SPECT
    - (c) Evaluation: Krenning Scale
      0 = no uptake by tumor
      1 = uptake by tumor but < background liver
      2 = uptake by tumor equal to background liver
      3 = uptake by tumor greater than background liver
      4 = very intense uptake by tumor
    - (d) Result: SRI by Octreoscan® is positive if Krenning scale is equal or greater than grade 2 (Krenning scale ≥2)
  - (2) Ga-PET-Scan
    - (a) Synonym: Ga-68 DOTATATE PET/CT, Gallium-68 DOTA-DPhe1, (68)Ga-DOTA-TATE, 68Ga-DOTATATE, Ga-68 DOTA0-Tyr3-octreotide, Ga-68 DOTATOC
    - (b) Method: CT + PET
    - (c) Evaluation: Krenning scale does not “fully” apply to Ga-PET-scan
    - (d) Result: SRI by Ga-PET-scan is positive if “Uptake is greater than background liver”

- Details of all new cancer therapies during the OL Extension Follow-up Phase will be collected.
- Pregnancy test are collected for female subjects of childbearing potential.
- Blood samples are collected from a subset of subjects (n=20 from selected sites in US only) during the DB Phase for assay of LAN serum levels.

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 according to the investigator's clinical judgement.

Subjects are also withdrawn from the study treatment if any of the following occurred (see Protocol Section 4.3):

- Disease progression as per local review, but not confirmed by central review RECIST v1.1: the local investigator always has the option of taking a subject off study.
- Occurrence of any AE or SAE that may jeopardise the subject's health.
- A need to administer any of the drugs prohibited by the study protocol to a subject, as described in Protocol Section 6.2.2.
- Appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of SSAs (rescue octreotide and/or long acting release SSA).
- Appearance of biological and/or clinical symptoms for gallbladder inflammation confirmed by an echography
- Pregnancy (see Protocol Section 8.1.5)
- Deviations from protocol
- Investigator's discretion

Subjects are also withdrawn from the study if any of the following occurred:

- Withdrawal of consent
- Investigator's discretion
- Subject is lost to follow-up
- Study is completed or terminated

If a subject decides to withdraw from the study after administration of study drug, or if the investigator decides 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 will be conducted and an explanation given of why the subject withdrew or is being withdrawn from the study.

1.3.3 Schedule of Assessments

Table 1 Schedule of Visits and Procedures in the Double-Blind Phase

STUDY PHASE		DB RANDOMIZATION AND TREATMENT PHASE														
Study Period	Screening [a]	Baseline [a]	Wk 4	Wk 8	Wk 12 [b]	Wk 16	Wk 20	Wk 24 [b]	Wk 28	Wk 32	Wk 36 [b]	Wk 40	Wk 44	Wk 48 [b]	Every 4/12 weeks [*,b]	Post treatment/Early Withdrawal Visit [n]
	V1	V2		V3	V4			V5			V6			V7	V8 to Vx	Vx+1
Day	Day -28 To Day -1	Day 1	Day 28 (±3)	Day 56 (±3)	Day 84 (±3)	Day 112 (±3)	Day 140 (±3)	Day 168 (±3)	Day 196 (±3)	Day 224 (±3)	Day 252 (±3)	Day 280 (±3)	Day 308 (±3)	Day 336 (±3)	Day 364-Day 504 (±3) Per Visit Day	Within 30 days from last injection/When applicable
Written informed consent	X															
Inclusion / exclusion	X	X														
Randomization		X														
Demographics	X															
Prior surgery, radiotherapy, chemotherapy and medications related to lung NETs	X															
Medical /surgical History	X															
Disease history/disease diagnosis [h]	X															
Clinical Evaluation [d]	X	X [a]		X	X			X			X			X	X	X
ECOG status [d]	X	X [a]			X			X			X			X	X	X
ECG, NYHA classification [c]	X							X						X	X [c]	X
Hematology & Biochemistry [e]	X	X [a]			X			X			X			X	X	X
Pregnancy test [f]	X	X														X
Biochemical markers (CgA & Urinary 5-HIAA) [g]		X		X	X			X			X			X	X	X
CT/MRI [i]	X [i]	X			X			X			X			X	X	X
SRI [j]	X															
Gallbladder echography [k]	TO BE DONE IN CASE OF BIOLOGICAL AND/OR CLINICAL SYMPTOMS															
QoL (EORTC QLQ-C30) [l]		X			X			X			X			X	X	X
LAN or placebo injection every 28 days		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CCI CCI CCI	CCI															
AEs/SAEs [q]	THROUGHOUT THE STUDY															
Prior and concomitant medications	THROUGHOUT THE STUDY															
Prior and concomitant non drug therapies	THROUGHOUT THE STUDY															

STUDY PHASE		DB RANDOMIZATION AND TREATMENT PHASE														
Study Period	Screening [a]	Baseline [a]	Wk 4	Wk 8	Wk 12 [b]	Wk 16	Wk 20	Wk 24 [b]	Wk 28	Wk 32	Wk 36 [b]	Wk 40	Wk 44	Wk 48 [b]	Every 4/12 weeks [*,b]	Post treatment/Early Withdrawal Visit [n]
	V1	V2		V3	V4			V5			V6			V7	V8 to Vx	Vx+1
Day	Day -28 To Day -1	Day 1	Day 28 (±3)	Day 56 (±3)	Day 84 (±3)	Day 112 (±3)	Day 140 (±3)	Day 168 (±3)	Day 196 (±3)	Day 224 (±3)	Day 252 (±3)	Day 280 (±3)	Day 308 (±3)	Day 336 (±3)	Day 364-Day 504 (±3) Per Visit Day	Within 30 days from last injection/When applicable
Concomitant surgical procedures	THROUGHOUT THE STUDY															
Concomitant medication/ chemotherapy/targeted therapy related to lung NET	THROUGHOUT THE STUDY															

5-HIAA=5-hydroxyindoleacetic acid; AE=adverse event; CgA=chromogranin A; CT=computed tomography; CCI [redacted] ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EW=early withdrawal; LAN=lanreotide; MRI=magnetic resonance imaging; NET=neuroendocrine tumor; NYHA=New York Heart Association; OL=Open label; PET=positron emission tomography; CCI [redacted] QoL=Quality of Life; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; CCI [redacted] SPECT=single photon emission computed tomography; SRI= somatostatin receptor imaging; TNM=tumor-node-metastasis; V=Visit; Wk=week

* Subjects will continue to receive LAN Injection or Placebo every 28 days up to centrally confirmed disease progression, development of unacceptable toxicity, withdrawal for any reason or up to 18 months after the last subject randomised.

(a) The Baseline assessment should be performed on Day 1, prior to treatment. The Screening assessments can serve as Baseline if performed within 3 days (72 hours) before Day 1 (randomization).
(b) Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures.
(c) ECGs will be performed at Screening, Week 24, Week 48, every 24 weeks thereafter and at the Post Treatment/Early Withdrawal Visit. The NYHA classifications will be performed as per investigator judgement.
(d) Physical examination and vital signs (supine and standing blood pressure and heart rate), height (Screening only) and weight will be performed at Screening, Baseline, Week 8 and every 12 weeks thereafter until the Post Treatment /Early Withdrawal Visits
(e) Blood samples for hematology and biochemistry (fasting for biochemistry); Refer to Protocol Section 8.2.1 and 8.2.2 for details
(f) Urine or serum test; must be completed within 72 hours of randomization; if positive with urine, confirm with serum
(g) CgA will be measured for all the subjects at Baseline, Week 8, Week 12 and every 12 weeks thereafter and at the Post Treatment/Early Withdrawal Visit, urinary 5-HIAA will be measured at Baseline, and if elevated at Baseline or clinically indicated, again at Week 8, Week 12 and every 12 weeks thereafter and at the Post Treatment/Early Withdrawal Visits.
(h) Disease history/diagnosis includes: mitotic count and foci of necrosis, Ki67 value if available, TNM staging, location of primary tumor, number of metastatic organs, presence/absence of hormone related syndrome
(i) CT/MRI of the thorax and abdomen should be performed within 28 days prior to Day 1. During the DB Phase, tumor assessments (by RECIST v1.1) will be performed every 12 weeks. At the Post treatment /Early Withdrawal Visit, scans will only be conducted if not performed within the previous 4 weeks. For subjects being followed with abdominal MRI, the requirement for gallbladder echography is eliminated. Should CT scans/MRIs, performed within 12 months of baseline, be available they should be sent for analysis by central review as part of an ancillary study.
(j) SRI if not available within the previous 6 months (Octreoscan® ≥ grade 2 Krenning Scale; Ga-PET scan: uptake greater than liver background);
(k) A gallbladder echography has to be performed if the subject presents biological and/or clinical symptoms of gallbladder inflammation. This assessment is not required for subjects undergoing abdominal MRI. Gallbladder inflammatory changes are included in the study discontinuation criteria.
(l) Subjects will complete the QoL (EORTC QLQ-C30) at Screening, Baseline, then every 12 weeks thereafter until the Post Treatment /Early Withdrawal Visit. As it is preferable to reduce all sources of potential bias it is recommended that the questionnaire is completed prior to seeing the physician.
C [redacted]
CI [redacted]
(n) For subjects continuing into the OL Extension Treatment Period, the Post Treatment/Early withdrawal Visit can serve as the Baseline visit for the OL Extension Phase.
C [redacted]
(p) Predose sample and 2 hours post-dose sample.
(q) If a subject presents thyroid function disturbances (identified through thyroid function abnormalities (TSH, FT4) considered clinically significant by the investigator) these should be reported as AEs in the eCRF.

Table 2 Schedule of Visits and Procedures in Open Label Extension Treatment Period

Period	OL Extension Baseline [a, b] Day 1	Every 4 Weeks	Every 12 Weeks	Post-Treatment/ Early Withdrawal Visit[n]
Inclusion/Exclusion	X			
Clinical Evaluation[e]	X		X	X
ECOG status[c]	X		X	X
NYHA classification, ECG[d]	X		X[d]	X
Hematology & Biochemistry[f]	X		X	X
Pregnancy Test[g]	X			X
CgA and urinary 5-HIAA[h]	X		X	X
CT/MRI[i]	X		X	X
Gallbladder Echography[j]	IF BIOLOGICAL AND/OR CLINICAL SYMPTOMS			
QoL (EORTC QLQ-C30)	X		X	X
LAN Injection Every 28 days	X	X	X	
CCI [redacted]	CCI [redacted]			
[redacted] CCI [redacted]	CCI [redacted]			
AEs/SAEs[m]	THROUGHOUT THE STUDY			
Concomitant medications	THROUGHOUT THE STUDY			
Concomitant non drug therapies	THROUGHOUT THE STUDY			
Concomitant surgical procedures	THROUGHOUT THE STUDY			
Concomitant medication/ chemotherapy/ molecular targeted therapy related to lung NET	THROUGHOUT THE STUDY			

5-HIAA=5-hydroxyindoleacetic acid; AE=adverse event; CgA=chromogranin A; CT=computed tomography; CCI [redacted] ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EW=early withdrawal; LAN=lanreotide; MRI=magnetic resonance imaging; NET=neuroendocrine tumor; NYHA=New York Heart Association; OL=Open label; PET=positron emission tomography; CCI [redacted] QoL=Quality of Life; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; CCI [redacted]

(a) OL Extension Baseline assessments should be performed on Day 1 of the Extension Treatment Period, prior to treatment. Assessments from the Post Treatment Visit in the DB Phase can serve as Baseline values for the OL Extension.

(b) Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures.

(c) ECOG status will be assessed at OL Extension Baseline, and every 12 weeks thereafter and at the Post Treatment / Early Withdrawal Visit.

(d) ECGs will be performed at Baseline, Week 24, Week 48, every 24 weeks thereafter and at the Post Treatment / Early Withdrawal Visit. The NYHA classification will be performed as per investigator judgement.

(e) A physical examination and vital signs (supine and standing blood pressure and heart rate), and weight will be performed at OL Extension Baseline and every 12 weeks thereafter and at the Post-Treatment Extension / Early Withdrawal Visit.

(f) Blood samples for hematology and biochemistry (fasting for biochemistry); Refer to Protocol Sections 8.2.1 and 8.2.2 for details

(g) Urine or serum test: if positive with urine, confirm with serum

(h) CgA will be assessed at Baseline and will be repeated subsequently every 12 weeks. Urinary 5-HIAA will be repeated subsequently every 12 weeks only if elevated (≥2 x ULN) at Baseline of the DB Phase or if clinically indicated.

(i) CT/MRI of the thorax and abdomen will be performed at Baseline (if not performed within the previous 4 weeks; CT/MRI used for disease progression documentation may be used if performed within the previous 4 weeks), and every 12 weeks. At the Post Treatment/Early Withdrawal Visit, scans will only be conducted if not performed within the previous 4 weeks.

(j) A gallbladder echography has to be performed if the subject presents biological and/or clinical symptoms of gallbladder inflammation. Gallbladder inflammatory changes are included in the study discontinuation criteria as part of AEs leading to study discontinuation.

C [redacted]
CI [redacted]
C [redacted]
C [redacted]

(m) If a subject presents thyroid function disturbances (identified through thyroid function abnormalities (TSH, FT4) considered clinically significant by the investigator) these should be reported as AEs in the e-CRF.

(n) End of Post Treatment Visit assessments of the OL Extension Period have to be performed prior to any administration of commercial product (if applicable).

Table 3 Schedule of Visits and Procedures in the Open Label Extension Follow-up Phase

Period	OL Extension Follow-up Baseline [a] Day 1	Every 12 Weeks	Post-Extension Follow-up Visit /Early Withdrawal Within 30 days from last injection/When applicable
Clinical Evaluation[b]	X	X	X
Survival status form	THROUGHOUT THE STUDY		
Concomitant medication/ chemotherapy/ molecular targeted therapy related to lung NET	THROUGHOUT THE STUDY		
QoL (EORTC QLQ-C30)[c]	X	X	X

EORTC QLQ C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; OL=Open label; QoL=Quality of Life.

(a) OL Extension Follow-up Baseline assessments should be performed on Day 1 of the Extension Follow-up Phase, prior to any other treatment. The values from the Post Treatment/Early Withdrawal Visit assessments in the DB Phase or OL Extension Treatment Period can serve as the Baseline for OL Extension Follow-up Period.

(b) A physical examination and vital signs will be performed at OL Extension Follow-up Baseline and every 12 weeks thereafter and at the Post-Extension Follow-up Period/ Early Withdrawal Visit.

(c) Subjects will complete the EORTC QLQ-C30 at Baseline and every 12 weeks thereafter and at the Post-Extension Follow-up / Early Withdrawal Visit. As it is preferable to reduce all sources of potential bias it is recommended that the questionnaire is completed prior to seeing the physician.

1.3.4 Planned Sample Size

Eligible subjects are stratified by:

- Typical versus atypical tumor characteristics; and
- Prior chemotherapy (cytotoxic chemotherapy or MTT or interferon) versus no prior chemotherapy

and randomly assigned 2:1 (two subjects in the LAN plus BSC group for each subject in the placebo plus BSC group). The limited published data on PFS in subjects with typical and atypical, well differentiated metastatic lung NETs provide a range of median PFS from 5.6 months, up to 24 months according to the typical or atypical characteristics of the disease. It is considered that an overall difference of 4 months in median PFS between the two groups (LAN versus Placebo) is clinically meaningful. Due to the premature stop of the recruitment, the sample size as originally calculated will not be achieved.

Prior to approval of Protocol Amendment #5:
The following assumptions were used to derive the original sample size for the study:

- Exponential distribution of survival on both treatment groups with constant event rate;
- Expected median PFS times of 6 and 10 months in the control and experimental arms, respectively (expected hazard ratio (HR) of 0.6);
- Type 1 error $\alpha = 0.05$ using a 2-sided log-rank test for the primary endpoint of PFS in the ITT population;
- Type 2 error $\beta = 0.10$ (90% power);
- A uniform accrual time of 18 months;
- An additional follow-up period of 18 months after the last subject is randomized; and

- A 2:1 random assignment ratio.

Under these assumptions, using SAS® procedure POWER, a total of 201 randomized subjects will be necessary to observe an estimated 175 disease progression events as assessed centrally or death events in both treatment groups and to detect a statistically significant treatment effect. Assuming a 5% drop-out rate of subjects to be lost-to-follow-up and the stratification factors, 216 subjects will have to be randomized in the study (144 subjects in the LAN plus BSC group and 72 subjects in the placebo plus BSC group).

A blinded sample size reassessment was originally planned to be performed prior to the end of the recruitment period. Sample size could be increased should the rate of censored subjects be higher than anticipated.

Following approval of Protocol Amendment #5:

- The planned blinded sample size reassessment will not be conducted.
- Due to the premature stop of recruitment, the sample size as originally calculated will not be achieved.
- Study results will be underpowered and hence, statistical analyses will only be descriptive. Results should therefore be interpreted with caution.

At the time of the premature stop, 77 subjects are included in the study. Assuming a 2:1 randomization, 52 subjects should be included in experimental arm and 25 in placebo arm. This should ensure an estimation accuracy of 13% for an expected median PFS of 10 months.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

The following populations will be used during statistical analyses:
The Screened population, the Intention to Treat (ITT) population, Open Label Intention to Treat (OLITT) population, Per Protocol (PP) population, Safety population, Follow-up population CCI [redacted] as described below.

2.1 Screened Population

The Screened population includes all subjects who sign an informed consent.

2.2 Intention to Treat Population

The ITT population includes all randomized subjects. Subjects will be analyzed as randomized, regardless of the treatment received.

2.3 Open Label Intention to Treat Population

The OLITT population includes all ITT subjects entering the OL Extension Treatment Phase who receive at least one injection of LAN in the OL Extension

Treatment Phase. Subjects will be grouped into the following three treatment arms for efficacy and safety analysis purposes:

(a) Subjects randomized to LAN plus BSC who had not progressed at the time of entering the OL Treatment Phase;
(b) Subjects randomized to placebo plus BSC who had not progressed at the time of entering the OL Treatment Phase; and
(c) Subjects randomized to placebo plus BSC who progressed during the DB Phase, and subsequently entered the OL Treatment Phase.

2.4 Per Protocol Population

The PP population includes all subjects in the ITT population with no major protocol violations/deviations impacting analyses, as defined in the Protocol Deviation Document and Protocol Deviation Specification Document. Any major protocol deviation will be described in the Protocol-Deviation Specification Document. Listings of subjects regarding inclusion in each population and satisfying the population definition and associated data will be reviewed during the blinded data review meeting held prior to database lock. The list will be updated to include any additional major protocol deviations impacting inclusion in the PP population.
Subjects will be analyzed as randomized, regardless of the treatment received.

2.5 Safety Population

The Safety population includes all subjects who receive at least one injection of study treatment. Subjects will be analyzed as treated.

2.6 Follow-up Population

All ITT subjects who enter the Follow-up Extension Phase (with at least one post-OL Extension Follow-up Baseline assessment) will comprise the Follow-up population. All subjects will be combined into one group for analysis.

CCI [redacted]

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with the International Conference on Harmonization (ICH) E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated. Statistics and Data Corporation, Inc. (SDC) will perform the statistical analyses of the efficacy and safety data. SDC will be managed by the Sponsor's Medical Affairs Biometry Department.

For all RECIST v1.1 based efficacy endpoints, the analyses will be performed using data from local and central review.

3.1.1 Analysis populations

The primary analysis of efficacy will be performed on the ITT population. The PP population will be used in secondary analyses of the primary endpoint as well as all PFS-based efficacy endpoints. All other secondary endpoints will be analyzed using only the ITT population (for the DB Phase). All analyses based on the PP population will be considered supportive in nature. All safety data related to the DB Phase will be analyzed on the Safety population according to the treatment received.

All safety and efficacy data related to the OL Extension Treatment Phase will be analyzed on the OLITT population according to the status at the end of the DB Phase (see Section 2.3).

All safety and QoL data related to the OL Extension Follow-up Phase will be analyzed on the Follow-up population, with all subjects combined.

3.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS for subjects randomized in LAN plus BSC group, assessed by central review using RECIST v1.1 every 12 weeks.

PFS is defined as the time from randomization to the first documentation of progression by the central review according to RECIST v1.1 in assessments every 12 weeks or death from any cause, whichever occurs first in either the DB Phase or in the OL Treatment Phase.

3.1.3 Secondary Efficacy Endpoints

The secondary endpoints will be assessed for subjects in the LAN plus BSC and placebo plus BSC groups.

The secondary efficacy endpoints are:

a) Progression-free survival (PFS), assessed by central review using RECIST v1.1 every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the DB Phase.

b) Progression-free survival (PFS), assessed by local review using RECIST v1.1 every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the DB Phase.

c) ORR: objective response rate of CR or PR measured by RECIST v1.1 every 12 weeks until the Post Treatment/Early Withdrawal Visit during the DB Phase.

d) Time to treatment failure during the DB Phase, defined as the time from randomization to disease progression (defined as the minimum [time to event according to central review, time to event according to local review]) using RECIST v1.1, death, consent withdrawn, an AE, protocol deviations, lost to follow-up, the appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of SSAs (rescue octreotide and/or long acting release SSA), or initiation of anticancer treatment.

e) Mean changes from Baseline in biomarker CgA at Week 8, Week 12, and every 12 weeks thereafter until the Post DB and in the OL Extension Treatment Phase.

f) Proportion of subjects with decrease in CgA ≥30% at Week 8, in the population of subjects with an elevated CgA (≥2 x ULN) at Baseline during the DB and the OL Treatment Phases.

g) Change in QoL, as assessed by EORTC QLQ-C30 questionnaire from Baseline to Week 12, every 12 weeks, and at the Post Treatment/Early Withdrawal Visit and in OL Extension Treatment and Follow-up Phases.

h) Time to QoL deterioration, defined by a decrease from Baseline in EORTC QLQ-C30 score of at least 10 points during the DB, the OL Treatment and the Follow-up Phases.

i) Mean changes from Baseline in urinary 5-HIAA levels at Week 8, every 12 weeks thereafter, and at the Post Treatment/Early Withdrawal Visit and in OL Extension Treatment in subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline.

CCI [redacted]

3.1.5 Safety Endpoints

Safety and tolerability assessments throughout the study include:

a) AEs grouped by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term and graded by the NCI-CTCAE v4.03;

b) Clinical evaluations (medical and surgical history and physical evaluations, including biochemistry, hematology, vital signs, ECG, CCI [redacted] ECOG, NYHA classification); and

c) Gallbladder echography if biological abnormalities and/or clinical inflammatory symptoms appear during the course of the study.

3.1.6 Multiplicity

Not applicable. All statistical analyses will be descriptive.

3.1.7 Significance testing and estimation

Not applicable. All statistical analyses will be descriptive.

3.2 Analysis Methods

3.2.1 Efficacy

The efficacy analyses using the centralized review performed by Bioclinica will only be performed using the accepted evaluation (defined as either the main reader evaluation if there is no adjudication, or the read chosen by the adjudicator if there was an adjudication).

3.2.1.1 Primary Efficacy Analysis

Progression Free Survival – Central Review (LAN Group)

The primary efficacy endpoint of PFS for subjects randomized in the LAN plus BSC group will include only documented PD according to the centralized review and deaths that occur in either the DB or OL Phase. Only subjects randomized to LAN plus BSC in the DB Phase will be included in this analysis. Other data will be censored as described in Table 4 below.

Clinical progression (i.e., unconfirmed or undocumented 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 not considered as a progression endpoint.

In case of 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 first (of the scans provided at the given visit) 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 confirmed 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 new anticancer treatment or prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.

Definition of PFS Time:
The PFS time will be calculated as the time from randomization to either confirmed PD or death.

PFS Time (months) = [(Date of Event – Date of Randomization) + 1] / 30.4375

Table 4 specifies the event and censoring dates to be used in the primary analysis of PFS; these are based on the Food and Drug Administration (FDA) Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Secondary analyses of the primary efficacy endpoint will be conducted using the PP population to assess robustness of the outcome from the ITT population.

Table 4 Censoring Rules for PFS via Central Review

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
Progression documented (centrally)	Date of radiological assessment of centrally measured lesions showing progression	Event
Progression documented (locally) and withdrawal	Date of last radiological assessment of centrally measured lesions	Censored
No progression	Date of last radiological assessment of centrally measured lesions	Censored
Treatment discontinuation for undocumented progression (not confirmed centrally)	Date of last radiological assessment of centrally measured lesions	Censored
Treatment discontinuation for toxicity or other reasons	Date of last radiological assessment of centrally measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of centrally measured lesions prior to initiation of an anticancer treatment	Censored
Death before first PD assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after more than one missed visit	Date of last radiological assessment of centrally measured lesions prior to death or progression	Censored
Prohibited medication/therapy	Date of last radiological assessment of centrally measured lesions prior to initiation of prohibited medication/therapy	Censored
Unblinded event	Date of last radiological assessment of centrally measured lesions prior to unblinding event	Censored

PD = progressive disease.

In the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007, it is stated that "Death or progression after more than one missed visit will be censored in the analysis at the date of last radiological assessment of measured lesions." This rule will be implemented as follows: Deaths or PDs occurring after more than one missed visit after the last adequate radiological assessment) 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 independent central review. Table 5 displays the event status for various scenarios with missing data.

Table 5 Event Status for Various Scenarios with Missing Data

Scan Time	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Event Status
Scenario 1	Mis	PD				Event at Week 24

Scan Time	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Event Status
Scenario 2	Mis	Mis	PD			Censored at baseline
Scenario 3	Mis	SD	PD			Event at Week 36
Scenario 4	Mis	Mis	SD	PD		Event at Week 48
Scenario 5	SD	SD	Mis	PD		Event at Week 48
Scenario 6	SD	SD	Mis	SD	PD	Event at Week 60

The distribution of PFS times in the LAN plus BSC group will be estimated using the Kaplan-Meier (KM) product limit method. The median, 25th percentile and 75th percentile PFS times with two-sided 95% confidence intervals (CI) will be estimated in the LAN plus BSC group, together with the estimates of PFS rates at 6-, 12-, 18-, and 24-month intervals after randomization. The results of the analyses will be presented both in summary tables and graphically in KM plots.

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.

For ITT and PP analyses, subjects will be stratified by the tumor subtype (typical/atypical) used in IWRS for randomization. Prior to Protocol Amendment #5, it was planned to also include stratification by prior chemotherapy (received/naïve, corresponding to prior chemotherapy versus no prior chemotherapy), however the number of randomized subjects who received prior chemotherapy was very small and the analyses will not account for this stratification factor. A summary table of the KM estimates in each of the tumor subtype stratum levels will also be provided, and KM curves of PFS in each of the tumor subtype strata levels will be constructed.

The reasons for which subjects were censored will be summarized for both the ITT and PP populations.

3.2.1.2 Secondary Efficacy Analysis

The secondary efficacy endpoints are detailed below. All secondary efficacy endpoints in the DB Phase will be analyzed using the ITT population, with the exception of all PFS-based endpoints, which will be analyzed on both the ITT and the PP populations. The analyses will compare LAN plus BSC and placebo plus BSC.

All secondary efficacy endpoints in the OL Phase will be analyzed using the OLITT population. All secondary efficacy data will be displayed in subject listings.

a) <u>Progression Free Survival – Central Review</u>

- Progression-free survival, assessed by central review using RECIST v1.1 every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the DB Phase.

This secondary efficacy endpoint of PFS will include only documented PD according to the centralized review and deaths that occur in the DB Phase. Other data will be censored.

The definitions for date of progression, censoring date, and PFS time are as described for the primary endpoint (Section 3.2.1.1).

The distribution of PFS times for each treatment arm will be estimated using the KM product limit method. The median, 25th percentile and 75th percentile PFS times and the corresponding two-sided 95% CIs will be estimated for each treatment group, together with the estimates of PFS rates at 6-, 12-, 18-, and 24-month intervals after randomization. Confidence intervals for median time to progression or death due to any cause, as well as the 25th and 75th percentile, will be calculated using the method of Brookmeyer and Crowley (1982). The results of the analysis will be presented in summary tables and KM plots will be constructed.

A summary table of the KM estimates in each of the tumor subtype strata levels will also be provided and KM curves of PFS in each of the tumor subtype strata levels will be constructed.

The reported hazard ratio (HR) estimate (LAN plus BSC to placebo plus BSC) and its two-sided 95% CI will use a Cox proportional hazards model stratified for tumor subtype (typical/atypical) with the exact likelihood method accounting for ties. Stratification levels are based on the Interactive Web Response System (IWRS) used for randomization. The maximum likelihood estimates of model coefficients (with associated standard error, degrees of freedom, Wald Chi-square statistic and p-value) will be presented in the Statistical Appendix; the Cox model assumptions will be checked, and the output will be included in the Statistical Appendix.

Summary tables for the time to progression or death due to any cause will present the numbers and percentages of subjects with progression or death due to any cause, the numbers and percentages of observed and censored subjects and the p-value from the stratified log-rank test where stratification will be tumor subtype (typical/atypical). The summaries will also include the median, 25th percentile, and 75th percentile time to progression or death due to any cause, and the percentage of subjects who had progressed or had died at 6, 12, 18, and 24 months. Kaplan-Meier curves will be constructed and will display the number of subjects at risk at 6, 12, 18, and 24 months (AVAL).

[redacted]

The assumptions of proportional hazards (PH) will be examined both graphically and statistically.

The graphical methods that will be used to check the PH assumptions are:

- Plot ln (-ln(S(t))) versus t or ln(t) and evaluate for parallelism;
- Plot Observed and Predicted S(t) and examine for close fit; and
- Use the PH graph by using the ASSESS option of the PHREG procedure of SAS®. ASSESS statement in SAS® includes plot of randomly generated residual processes to allow for graphical assessment of the observed residuals in terms of what is "too large," i.e., the path from the actual data is compared to the randomly generated paths under PH.

[redacted]

The statistical method to check the PH assumptions will be using the time-dependent covariates, i.e., time*treatment interactions will be added to the model. An example of SAS® code implementation follows:

[redacted]

If the added interaction is not statistically significant at the level of 0.10, this indicates that the PH assumption is satisfied.

On the contrary, if the interaction is statistically significant, it means that the effect of treatment is not constant over time, so PH assumption is violated. To solve this problem (i.e., to model the non-PH), the interaction will be left in the model.

In an additional Cox model, the effect of the interaction of the stratification factor with treatment will be checked. If there is significant interaction from either a clinical or statistical ($p \leq 0.10$) perspective, then the conclusions based on the model with no interaction terms will be interpreted cautiously.

[redacted]

CCI [redacted]

Results of the assessment of interaction will be included in the Statistical Appendix.

The following secondary analyses will be conducted based on central review and using the ITT population only. The analyses that will be performed for this sensitivity analysis of PFS are the same as those described for the secondary endpoint analysis of PFS.

1. PFS if more than 5% of subjects are mis-stratified in tumor type

If more than 5% of the subjects are mis-stratified, i.e., the IWRS stratification criteria used for randomization does not agree with the eCRF data regarding the mitotic count and foci of necrosis status impacting the typical/atypical classification, the secondary endpoint analysis of PFS will be repeated according to the actual stratum captured in the eCRF.

2. PFS without regard to stratification

The secondary endpoint analysis of PFS will be repeated using a non-stratified log rank test and the HR resulting from a non-stratified Cox model. The event and censoring rules will be the same as those described for the secondary endpoint analysis of PFS (central review).

The reported HR estimate (LAN plus BSC to placebo plus BSC) and its two-sided 95% CI will use an unstratified Cox proportional hazards model with the exact likelihood method accounting for ties. The maximum likelihood estimates of model coefficients (with associated standard error, degrees of freedom, Wald Chi-square statistic and p-value) will be presented in the Statistical Appendix.

3. Assessment intervals of PFS

In order to assess similarity of assessment intervals in both treatment groups, product limit estimates of time from randomization to each radiologic assessment during the DB Phase will be summarized by treatment group. A subject will be considered as having an event if they have a radiological assessment conducted at the given scheduled visit; a subject with no radiological assessment for a given scheduled visit will be censored at the last known radiological assessment provided.

Summary tables for the time to each radiological assessment will present the numbers and percentages of subjects with an assessment at each visit, the numbers and percentages of observed and censored subjects and the p-values from the unstratified log-rank tests at each visit. The summaries will also include the median time to each radiological assessment as well as the 25th and 75th percentiles. An example of SAS® code implementation follows:

CCI [redacted]

CCI [redacted]

4. Differences in PFS assessments between central radiology review and local investigator review

Differences between central radiology review and local investigator review with regards to PFS (progression versus no progression) will be assessed according to the date of 1st progression during the DB Phase. Summary tables will present the number of agreements and disagreements between the evaluators (central versus local) for each treatment group along with the p-values from the kappa tests.

A kappa statistic will be employed to evaluate the concordance in PFS between central and local review for each treatment group. If either result from the central review or the local review is not applicable (N/A), the outcome will be denoted as "disagreement." CCI [redacted]

CCI [redacted]

b) **Progression Free Survival – Local Review**

- Progression-free survival, assessed by local review using RECIST v1.1 every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the DB Phase.

This secondary efficacy endpoint of PFS will include only documented PD according to the local review and deaths that occur in the DB Phase. 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 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 through local review.

- 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 first (of the scans provided at the given visit) 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 confirmed PD or non-confirmed (i.e. local review) 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 assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by local review.

In the case of new anticancer treatment or prohibited medication/therapy, this is taken to be the last date of radiological assessment prior to the initiation of such medications/therapies.

Definition of PFS Time:
The PFS time will be calculated as the time from randomization to investigator-assessed PD or death, where date of event is defined as the minimum of date of event according to the local review and death.

PFS Time (months) = [(Date of Event – Date of Randomization) + 1] / 30.4375

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

Table 6 Censoring Rules for PFS via Local Review

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
Progression documented (locally)	Date of radiological assessment of locally measured lesions showing progression	Event
No progression	Date of last radiological assessment of locally measured lesions	Censored
Treatment discontinuation for undocumented progression (not confirmed locally)	Date of last radiological assessment of locally measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of locally measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of locally measured lesions prior to initiation of an anticancer treatment	Censored
Death before first PD assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after more than one missed visit	Date of last radiological assessment of locally measured lesions prior to death or progression	Censored
Prohibited medication/therapy	Date of last radiological assessment of locally measured lesions prior to initiation of prohibited medication/therapy	Censored
Unblinded event	Date of last radiological assessment of locally measured lesions prior to unblinding event	Censored

PD = progressive disease.

The analyses that will be performed for this analysis of PFS on local review data are the same as those described for the secondary endpoint analysis of PFS on central

review data (Section 3.2.1.2. a)), i.e Kaplan-Meier analyses and Hazard-Ratio analyses will be performed. No sensitivity analysis will be performed on local review data.

c) Objective Response Rate

- ORR: objective response rate of CR or PR measured by RECIST v1.1 every 12 weeks until the Post Treatment/Early Withdrawal Visit during the DB Phase.

The best overall response to study treatment is the highest objective response achieved by the subject during the DB Phase, ordering response categories from best to worst: CR, PR, SD, PD, and NE, per RECIST v1.1. The ORR during the DB Phase is defined as the proportion of subjects who achieve a best overall response of CR or PR during the DB Phase. A best overall response of SD can only be made after the subject is on study for a minimum of 7 weeks (49 days).

Two separate analyses of ORR will be conducted, one using central review and the second using local review.

The ORR in each treatment arm for the DB Phase, with the corresponding 95% Clopper-Pearson CIs, estimated using the exact method for binomial distributions, will be computed. In addition, the difference in response rates, along with an exact unconditional 95% CI, will be calculated.

d) Time to Treatment Failure

- Time to treatment failure (TTF) during the DB Phase, defined as the time from randomization to disease progression (defined as the minimum [time to event according to central review, time to event according to local review]) using RECIST v1.1, death, consent withdrawn, an AE, protocol deviations, lost to follow-up, the appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of SSAs (rescue octreotide and/or long acting release SSA), or initiation of anticancer treatment.

Table 7 specifies the event and censoring dates to be used in the secondary endpoint analysis of TTF via local or 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 Censoring Rules for TTF

Situation	Date of Treatment Failure or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
Progression documented (centrally or locally, whichever occurs first)	Date of radiological assessment of measured lesions showing progression	Event
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression (not centrally confirmed, nor locally documented)	Date of treatment discontinuation due to undocumented progression	Event
Treatment discontinuation for toxicity or other reason not otherwise specified	Date of treatment discontinuation due to toxicity or other reason not otherwise specified	Event
New anticancer treatment started	Date of treatment discontinuation due to initiation of a new anticancer treatment	Event
Consent withdrawn	Date of treatment discontinuation due to withdrawal of consent	Event
AE	Date of treatment discontinuation due to AE	Event
Protocol deviations	Date of treatment discontinuation due to major protocol deviation	Event
Lost to follow-up	Date of last contact	Event
Appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of SSAs (rescue octreotide and/or LAR SSA)	Date of treatment discontinuation due to appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of SSAs	Event
Death before first PD assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions prior to death or progression	Censored
Prohibited medication/therapy	Date of initiation of prohibited medication/therapy	Event

PD = progressive disease.

The distribution of TTF for each treatment arm will be estimated using the KM product limit method. The median, 25th percentile and 75th percentile TTF times and the corresponding two-sided 95% CIs will be estimated for each treatment group, together with the estimates of TTF rates at 6-, 12-, 18-, and 24-month intervals after randomization. Confidence intervals for median TTF, as well as the 25th and 75th percentile, will be calculated using the method of Brookmeyer and Crowley (1982). The results of the analysis will be presented in summary tables and KM plots will be constructed.

Summary tables for the TTF will present the numbers and percentages of subjects with treatment failure, and the numbers and percentages of observed and censored subjects. The summaries will also include the median, 25th percentile and 75th percentile TTF, and the percentage of subjects who failed treatment at 6, 12, 18, and 24 months. Kaplan-Meier curves will be constructed and will display the number of

subjects at risk at 6, 12, 18, and 24 months. [redacted] CCI [redacted]

e) **Biomarker CgA**

- Mean changes from Baseline in biomarker CgA at Week 8, Week 12, and every 12 weeks thereafter until the Post Treatment/Early Withdrawal Visit and in the OL Extension Treatment Phase.

Raw CgA values, CgA as a x of ULN and the changes from DB Baseline will be summarized by time point in the DB Phase. The x of ULN will be calculated as Raw Value/ ULN.

Raw CgA values, CgA as a x of ULN and change from OL Treatment Baseline (for Placebo/LAN subjects) or DB Baseline (for LAN/LAN subjects) will be summarized by time point in the OL Treatment Phase.

f) **Biomarker CgA – 30% Decrease**

- Proportion of subjects with decrease in CgA ≥30% at Week 8 in the population of subjects with an elevated CgA (≥2 x ULN) at Baseline during the DB Phase and the OL Treatment Phase.

The proportion of subjects with a 30% or more decrease in CgA from DB Baseline to Week 8 of the DB Treatment Phase will be estimated (in the population of subjects with an elevated CgA [≥2 x ULN] at DB Baseline), with the corresponding 95% Clopper-Pearson CIs in each treatment arm.

The proportion of subjects with a 30% or more decrease in CgA from OL Treatment Baseline (for Placebo/LAN subjects) or DB Baseline (for LAN/LAN subjects) to Week 12 of the OL Treatment Phase will be estimated (in the population of subjects with an elevated CgA [≥2 x ULN] at DB Baseline), with the corresponding 95% Clopper-Pearson CIs.

h) EORTC QLQ-C30

- Change in QOL, as assessed by the EORTC QLQ-C30 questionnaire from Baseline to Weeks 12, every 12 weeks thereafter, at the Post Treatment/Early Withdrawal Visit, and in the OL Extension Treatment and Follow-up Phases.

The EORTC QLQ-C30 consists of 30 individual questions. Following the EORTC recommendations, fifteen scales can be derived from the initial 30 questions:

- A global health status/QoL scale
- Five functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning)
- Nine symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea, Financial Difficulties)

Each of the scales includes a different set of items and no item occurs in more than one scale.

Each scale in the questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-C30 Scoring Manual.

A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score.
2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

The scoring method is summarized below. In this summary, Q_i refers to the i^{th} question on the EORTC QLQ-C30.

Table 8: EORTC QLC-30 Scoring and Scale Dimension

	Number of Items (Range*)	Item Number
Global health status / QoL		
Global health status/QoL	2 (6)	29, 30
Functional scales		
Physical functioning	5 (3)	1 to 5
Role functioning	2 (3)	6, 7
Emotional functioning	4 (3)	21 to 24
Cognitive functioning	2 (3)	20, 25
Social functioning	2 (3)	26, 27
Symptom scales / items		
Fatigue	3 (3)	10, 12, 18
Nausea and vomiting	2 (3)	14, 15
Pain	2 (3)	9, 19
Dyspnoea	1 (3)	8
Insomnia	1 (3)	11
Appetite loss	1 (3)	13
Constipation	1 (3)	16
Diarrhoea	1 (3)	17
Financial difficulties	1 (3)	28

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

For all scales, the RawScore, RS, is the mean of the component items:

$$RawScore\ (RS) = (I_1 + I_2 + \ldots + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales/ items** and **Global health status/ QoL**:

$$Score = \left\{\frac{(RS-1)}{\text{range}}\right\} \times 100$$

Missing value (item) consideration for scoring:
The scale scores will only be calculated if at least half of the items from the scale have been answered. Otherwise, no score will be calculated, and the scale score will be set to missing.

For single-item measures, the score will be missing if the question is not answered.

The EORTC QLQ-C30 questionnaire deals with missing data via its scoring algorithm; therefore, imputation methods will not be applied to missing data for the EORTC QLQ-C30 responses.

Individual question responses will be summarized at each visit using frequency counts and percentages, for each study phase.

Continuous descriptive statistics will be used to summarize the derived scales.

Each of the derived scales and their changes from DB Baseline will be summarized by time point in the DB Treatment Phase.

Each of the derived scales and their changes from OL Treatment Baseline (for Placebo/LAN subjects) or DB Baseline (for LAN/LAN subjects) will be summarized by time point in the OL Treatment Phase.

Each of the derived scales and their changes from OL Follow-up Phase Baseline will be presented by time point in the OL Follow-up Phase.

All raw and derived scores will be displayed in a subject listing.

i) EORTC QLQ-C30 – Time to Deterioration

- Time to QoL deterioration, defined by a decrease from Baseline in EORTC QLQ-30 score of a least 10 points during the DB, the OL Treatment and the Follow-up Phases.

The proportion of subjects with a 10-point or more decrease from DB Baseline in the global health status/QoL score will be estimated, with the corresponding 95% Clopper-Pearson CIs in each treatment arm, for each visit during the DB Phase.

The proportion of subjects with a 10-point or more decrease in global health status/QoL score from OL Baseline (for Placebo/LAN subjects) or DB Baseline (for LAN/LAN subjects) will be estimated, with the corresponding 95% Clopper-Pearson CIs in each treatment arm, for each visit during the OL Treatment Phase.

The proportion of subjects with a 10-point or more decrease from OL Follow-up Baseline in the global health status/QoL score will be estimated, with the

corresponding 95% Clopper-Pearson CIs in each treatment arm, for each visit during the OL Follow-up Phase.

j) Urinary 5-HIAA

- Mean changes from Baseline in urinary 5-HIAA levels at Week 8, every 12 weeks thereafter, and at the Post Treatment/Early Withdrawal Visit, and in OL Extension Treatment Phase in subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline.

Raw urine 5-HIAA values, 5-HIAA as a x of ULN, and changes in urine 5-HIAA values from the DB Baseline will be summarized overall and by treatment group for each visit during the DB Phase (in the population of subjects with an elevated urinary 5-HIAA [≥2 x ULN] at the DB Baseline). Note that these analyses will also be performed excluding subjects who had eaten contraindicated foods within 72 hours prior to testing.

Raw urine 5-HIAA values and changes in urine 5-HIAA values from the OL Treatment Baseline (for Placebo/LAN subjects) or DB Baseline (for LAN/LAN subjects) will be summarized overall and by treatment group for each visit during the OL Treatment Phase (in the population of subjects with an elevated urinary 5-HIAA [≥2 x ULN] at the DB Baseline). Note that these analyses will also be performed excluding subjects who had eaten contraindicated foods within 72 hours prior to testing.

A listing will be presented for the subset of subjects with an elevated urinary 5-HIAA (≥2 x ULN) at DB Baseline, by study phase, visit and treatment group and will include the indicator variable for whether or not the subject had eaten contraindicated foods within 72 hours prior to testing.

CCI [redacted]

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CCI [redacted]

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[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

e) PFS for Subjects Randomized to Placebo

- Progression-free survival – central review.

Progression-free survival, assessed by central review using RECIST v1.1 every 12 weeks, is defined as the time from date of first LAN administration in the OL Extension Treatment Phase to disease progression or death from any causes during the OL Extension Treatment Phase.

This endpoint will be analyzed similarly to the primary endpoint (Section 3.2.1.1).

- Progression-free survival – local review.

Progression-free survival, assessed by local review using RECIST v1.1 every 12 weeks, is defined as the time from date of first LAN administration in the OL Extension Treatment Phase to disease progression or death from any causes during the OL Extension Treatment Phase.

This endpoint will be analyzed similarly to the secondary objective (Section 3.2.1.2 □b).

3.2.1.4 Adjustment for Country/Center Effect

No adjustment for country/center effect is planned.

3.2.2 Safety

All safety data will be included in the data listings. Summary tables will be provided by study phases.

Safety analyses of the DB Phase will be performed on the safety population by treatment group (according to the treatment received) and overall.

Safety analyses of the OL Treatment Phase will be performed on the OLITT population, by treatment group (according to groups defined in section 2.3) and overall.

Safety analyses of the OL Extension Follow-up Phase will be performed on the OL Follow-up population, with all subjects combined.

3.2.2.1 Adverse Events

Adverse events will be graded by the investigators using the NCI-CTCAE classification (version 4.03, dated 14 June 2010) and coded using the MedDRA Version 23.0 and will be classified by MedDRA primary system organ class and preferred term.

A treatment-emergent AE (TEAE) is defined as any AE that occurs from receiving the first dose of study drug (of the concerned study phase) to end of study/withdrawal if it meets one of the following criteria:

- It was not present prior to receiving the first dose of study drug.
- It was present prior to receiving the first dose of study drug but the intensity increased or became serious after receiving the first dose of study drug.
- It occurred within 30 days of last dose of study drug (i.e., AEs starting >30 days after last dose of study drug will not be considered as TEAEs).

TEAEs will be defined for both the DB and OL Treatment Phases as follows:

	Start Date of Analysis Period	**End Date of Analysis Period**
DB Treatment Phase		
Subject subsequently entered OL Treatment Phase	Date of first dose of study drug	Date of first dose in OL Treatment Phase – 1 day
Subject did not enter OL Treatment Phase (i.e., subject discontinued or entered Follow-up Phase)	Date of first dose of study drug	Date of last dose of study drug + 30 days
OL Treatment Phase		
Subject entered OL Treatment Phase	Date of first dose in OL Treatment Phase	Date of last dose of study drug + 30 days

TEAEs will be defined for overall LAN exposure as follows:

	Start Date of Analysis Period	**End Date of Analysis Period**
Lanreotide Exposure Period		
Subjects exposed to Lanreotide, regardless of exposure began (i.e., LAN started at Day 1 of DB Phase or Day 1 of OL Treatment Phase)	Date of first dose Lanreotide	Date of last dose Lanreotide + 30 days

Listings will be presented and sorted by treatment group (or groups defined in Section 2.3 as appropriate), stratification factors (tumor subtype and prior chemotherapy), subject, primary system organ class and preferred term for all AEs recorded during the study. Where applicable, LAN exposure phase will also be reported in listings.

Listings of the following categories will be presented:

- SAEs
- Drug-related AEs
- AEs with NCI-CTCAE Grade >2
- AEs leading to drug interrupted
- AEs leading to drug (study treatment) withdrawal
- AEs leading to death

Treatment-emergent adverse events will be flagged in the AE listing and will be summarized. Non-TEAEs will be included in the listings and provided in the overall summary table of all AEs.

An overall summary table of all TEAEs will be presented by treatment group and overall. These tables will also be produced by sex (male versus female), age group (≤65 years of age versus >65 years of age), and region (North America versus Europe).

TEAEs will be summarized by treatment group and overall, with the number and percentage of subjects with TEAEs, classified by primary system organ class and preferred term (ordered alphabetically). The number of occurrences of a TEAE will also be presented. These tables will also be produced by sex, age group, region, and NCI-CTCAE worst grade.

In addition to summarizing by study phase (DB and OL Treatment Phases), the TEAEs by system organ class and preferred term will be summarized for the overall LAN Exposure. The LAN exposure summary will include data from subjects exposed to at least one dose of LAN, including any TEAEs that occurred on or after first dose of LAN.

Additionally, incidence of all reported TEAEs will be tabulated by treatment group and overall, by system organ class and preferred term, for the following categories:

- SAEs (SAE tables will also be produced by sex, age group and region)
- SAEs related to study drug
- SAEs by associated NCI-CTCAE worst grade
- Non-SAEs (non-SAE tables will also be produced by sex, age group and region)
- Non-SAEs by associated NCI-CTCAE worst grade
- TEAEs by associated NCI-CTCAE worst grade and by causality
- TEAEs related to study drug
- TEAEs associated with drug interruptions
- TEAEs associated with premature drug (study treatment) withdrawal

In the event of multiple occurrences of the same AE (same preferred term) being reported by the same subject, the maximum intensity (grade 5> grade 4> grade 3> grade 2> grade 1> missing) and the most serious causality (related> missing> not

related) will be chosen. For the intensity*causality combined description, the most serious causality prevails. In case of missing data for relationship and/or intensity, the AE will be presented as related and/or grade 4 when crossing intensity and relationship.

3.2.2.2 Laboratory Data

Hematological and biochemistry toxicities will be recorded and graded according to the NCI-CTCAE criteria (Version 4.03, dated 14 June 2010).

A central laboratory will be used for analysis of all laboratory data. All laboratory data will be analyzed separately by study phase (DB Phase and OL Treatment Phase). Note that all summaries for the OL Treatment Phase will be presented according to the groups defined in section 2.3.

A separate listing of normal ranges for system international (SI) units will be provided by sex and age where relevant. Laboratory data (hematology, biochemistry) will be listed by treatment group, stratification factors (tumor subtype and prior chemotherapy), subject, and visit in SI units. Abnormal values will be flagged (High, Low, Abnormal Not Clinically Significant, Abnormal Clinically Significant), and NCI-CTCAE grade will be presented where applicable. Results from urine pregnancy tests will also be listed by subject.

The laboratory parameters collected are listed in Section 1.3.2.2.

For hematology and biochemistry parameters, the DB Baseline will be defined as the last measurement collected prior to the first dose of study drug. The OL Treatment Baseline will be defined as the last measurement collected at the OL Treatment Baseline Visit for Placebo/LAN subjects or the DB Baseline Visit for LAN/LAN subjects.

For hematology and biochemistry parameters, summary statistics, by study phase (DB Phase and OL Treatment Phase) and treatment group, will be presented at each scheduled assessment for raw values and changes from Baseline.

During the DB Phase, the changes from Baseline will be relative to the DB Baseline. During the OL Treatment Phase, the changes from Baseline will be relative to the DB Baseline (for the subjects who were randomized to LAN) or the OL Treatment Baseline (for subjects who were randomized to placebo, with or without disease progression).

Shift tables for all hematology and biochemistry parameters will be presented for the number and percentage of subjects with low, normal or high values. Note that glucose will be analyzed separately for subjects who fasted prior to testing and subjects who did not fast prior to testing.

Coagulation parameters are collected only at the Screening Visit. Summary statistics will be presented for the raw values by treatment group.

The NCI-CTCAE grade (0 to 4) of hematology and biochemistry by visit and by subject will be listed. Summaries of the laboratory parameters will be displayed and will include summaries for the worst NCI-CTCAE Grade 3 and 4 for hematological toxicities and biochemical toxicities for both the DB Phase and OL Treatment Phase.

The NCI-CTCAE grade 3 and 4 hematology and biochemistry parameters will be listed by treatment, subject and visit.

A listing will also be produced for out-of-range biochemistry parameters that could not be graded using NCI-CTCAE grade (below lower limit of normal [LLN], normal, above ULN).

At DB Baseline (Visit 2), urinary creatinine will be analyzed for all subjects. If urinary 5-HIAA is elevated (>=2 x ULN) at DB Baseline or clinically indicated, urinary creatinine will be assessed again at Week 8 and every 12 weeks thereafter and at the Post Treatment/Early Withdrawal Visit. The estimated glomerular filtration rate (eGFR) will be calculated using the formula developed by Cockgroft and Gault and is given by:

$$eGFR = \frac{(140 - age)\ x\ weight\ (kg)}{Creatinine\ \left(\frac{mg}{dl}\right) x\ 72}\ (x\ 0.85\ for\ females)$$

Summary statistics for eGFR, by study phase (DB Phase and OL Treatment Phase) and treatment group, will be presented at each scheduled assessment for raw values and changes from Baseline.

3.2.2.3 Vital Signs

All vital signs data will be analyzed separately by study phase (DB Phase and OL Treatment Phase). Note that all summaries for the OL Treatment Phase will be presented according to the groups defined in Section 2.3.

Vital signs will be listed by treatment group, subject, and visit.

The vital signs collected are listed in Section 1.3.2.2.

The DB Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study drug. The OL Treatment Baseline values will be defined as the vital sign measurement collected at the OL Treatment Baseline Visit for Placebo/LAN subjects or the DB Baseline Visit for LAN/LAN subjects. Summary statistics by treatment group will be presented at each scheduled visit for raw values and changes from Baseline by study phase.

During the DB Phase, the changes from Baseline will be relative to the DB Baseline. During the OL Treatment Phase, the changes from Baseline will be relative to the DB Baseline (for the subjects who were randomized to LAN) or the OL Treatment Baseline (for subjects who were randomized to placebo, with or without disease progression).

3.2.2.4 ECG

All ECG data will be analyzed separately by study phase (DB Phase and OL Treatment Phase). Note that all summaries for the OL Treatment Phase will be presented according to the groups defined in Section 2.3.

ECG results will be listed treatment group, subject, and visit.

The ECG measurements collected are listed in Section 1.3.2.2.

The DB Baseline will be defined as the last ECG measurement collected prior to the first dose of study drug. The OL Treatment Baseline will be defined as the ECG measurement collected at the OL Treatment Baseline Visit for Placebo/LAN subjects or the DB Baseline Visit for LAN/LAN subjects. For continuous ECG parameters, summary statistics, by treatment group, will be presented at each scheduled visit for raw values and changes from Baseline separately for each study phase (DB Phase and OL Treatment Phase).

During the DB Phase, the changes from Baseline will be relative to the DB Baseline. During the OL Treatment Phase, the changes from Baseline will be relative to the DB Baseline (for the subjects who were randomized to LAN) or the OL Treatment Baseline (for subjects who were randomized to placebo, with or without disease progression).

For sinus rhythm, a frequency table by treatment group will be presented at each scheduled visit separately for each study phase (DB Phase and OL Treatment Phase).

For interpretation of clinical significance (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Missing), a frequency table will be presented separately for each study phase (DB Phase and OL Treatment Phase) by treatment group at each visit.

3.2.2.5 Gallbladder Echography

The gallbladder echography parameters collected are listed in Section 1.3.2.2.

Note that gallbladder assessments will only be performed in the case that a subject has biological and/or clinical symptoms. Therefore, gallbladder echography will only be presented in listings by treatment group, subject, and visit.

3.2.2.6 Physical Examinations

Physical examination results will be listed separately by treatment group, subject, and visit.

The DB Baseline will be defined as the last physical examination conducted prior to the first dose of study drug. The OL Treatment Baseline will be defined as the physical examination conducted at the OL Treatment Baseline Visit for Placebo/LAN subjects or the DB Baseline Visit for LAN/LAN subjects.

3.2.2.7 New York Heart Association Scale

All NYHA data will be analyzed separately by study phase (DB Phase and OL Treatment Phase). Note that all summaries for the OL Treatment Phase will be presented according to the groups defined in Section 2.3.

The NYHA scale results will be listed separately by treatment group, subject, and visit.

The DB Baseline will be defined as the last NYHA scale administered prior to the first dose of study drug. The OL Treatment Baseline will be defined as the NYHA scale administered at the OL Treatment Baseline Visit for Placebo/LAN subjects or the DB Baseline Visit for LAN/LAN subjects. For each study phase (DB Phase and OL Treatment Phase), frequency counts and percentages, by treatment group, will be presented at each scheduled visit.

3.2.2.8 Eastern Cooperative Oncology Group Performance Status Scale

All ECOG data will be analyzed separately by study phase (DB Phase and OL Treatment Phase). Note that all summaries for the OL Treatment Phase will be presented according to the groups defined in Section 2.3.

The ECOG performance status scale results will be listed by treatment group, subject, and visit.

The DB Baseline will be defined as the last ECOG scale administered prior to the first dose of study drug. The OL Treatment Baseline will be defined as the ECOG scale administered at the OL Treatment Baseline Visit for Placebo/LAN subjects or the DB Baseline Visit for LAN/LAN subjects. For each study phase (DB Phase and OL Treatment Phase), frequency counts and percentages, by treatment group, will be presented at each scheduled visit.

3.2.3 Missing Data and Outliers

3.2.3.1 Missing Data

In the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007, it is stated that "Death or progression after more than one missed visit will be censored in the analysis at the date of last radiological assessment of measured lesions." This rule will be implemented as follows: 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 independent central review. Table 5 displays the event status for various scenarios with missing data.

The EORTC QLQ-C30 deals with missing data via the scoring algorithm; therefore, imputation methods will not be applied to missing data for the EORTC QLQ-C30 responses.

If a value requires a retest (for laboratory values, vital signs, ECG, gallbladder echography), the closest non-missing reliable value to the scheduled visit will be used

in the summary tables. 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 all other variables, no imputations will be performed for missing data.

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

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

3.2.3.2 Missing or Incomplete Dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, in determining treatment period and/or days since a certain time point, the following conservative approach will be used to impute missing date values:

Medical History/Disease Diagnosis

- missing/incomplete dates will be assumed to have occurred prior to any study treatment, unless there is evidence to prove otherwise
- partial dates should be reviewed to ensure they did not occur following any study treatment; i.e., if study treatment begins on 02Mar2019 and the disease diagnosis is Oct2019, this should not be classified as a 'prior disease diagnosis'

Tumor Assessments with partial dates for efficacy endpoints

- Day only missing
  a. The 1st day of the month should be imputed for the missing day value. Note, if this imputed date produces a date before the first injection of study treatment, then the date of start of study treatment will be imputed as the missing date value.

AE/Concomitant Medication

- Day only missing
  a. If year/month of AE/Conmed equals year/month of first injection of study treatment, then impute start day of first injection of study treatment
  b. If year of AE/Conmed is equal to the year of the first injection of study treatment and month of AE/Conmed is less than the month of the first injection of study treatment, then impute the last day of the month
  c. If year of AE/Conmed is equal to the year of the first injection of study treatment and month of AE/Conmed is greater than the month of the first injection of study treatment, then impute the first day of the month
  d. If year of AE/Conmed is greater than the year of first injection of study treatment, then impute the first day of the month

e. If year of AE/Conmed is less than the year of first injection of study treatment, then impute the last day of the month

- Month/Day missing

  a. If year of AE/Conmed equals year of first injection of study treatment, then impute the start day and month of the first injection of study treatment

  b. If year of AE/Conmed is less than the first injection of study treatment, then impute 31Dec

  c. If the year of AE/Conmed is greater than the first injection of study treatment, then impute 01Jan

- Start date is completely missing

  a. If the first injection of study treatment date is greater than the AE/Conmed end date, then the AE/Conmed start date equals the AE/Conmed end date

  b. If the first injection of study treatment date is less than or equal to the AE/Conmed end date, then the AE/Conmed start date equals the start date for the first injection of study treatment

  c. If the AE/Conmed end date is missing, then the AE/Conmed start date equals the start date for the first injection of study treatment

- Imputed start date, where end date is not missing

  a. Check, if the imputed AE/Conmed start date is greater than the AE/Conmed end date, then the imputed start date should be updated to match the AE/Conmed end date

3.2.3.3 Outliers

A search of outliers by SDC should be performed before the unblinding and actions with the Sponsor should be defined.

3.2.4 Subject Disposition

A listing of dates of assessments (relative day) and their study treatment and days on study will be presented by subject for each treatment group and study phase.

The number and percentage of subjects included in each of the populations will be tabulated by treatment group, region (North America versus Europe) and center.

The reasons for subject exclusion from each population will also be tabulated.

In addition, the number of subjects who were randomized, treated, discontinued and completed at each of the study phases will be summarized by treatment group and overall for the DB Phase (as randomized), according to treatment and progression status at the time of entering the OL Treatment Phase and overall for the OL Treatment Phase, and overall for the OL Extension Follow-up Phase.

Primary reasons for discontinuation of study treatment will be tabulated for each study phase.

A summary table will be presented for the ITT population presenting the number of subjects in each treatment group at each visit and study phase and identifying the number of subjects who withdrew over time.

A summary table will present the number of subjects who attended each visit of each phase as well as the last attended visit of each phase.

A summary table will present the extent of study exposure for each treatment group and study phase, as well as overall. The definition of the duration of treatment exposure during the DB Phase is:
For subjects that continued to the OL Treatment Phase, duration of treatment exposure is:
First Injection Date in the OL Treatment Phase – First Injection Date of Study Drug

For subjects that did not continue to the OL Treatment Phase, duration of treatment exposure is:
(Last Injection Date – First Injection Date of Study Drug + 1 Day) + 30 Days

The definition of the duration of treatment exposure during the OL Treatment Phase is:
(Last Injection Date in the OL Treatment Phase – First Injection Date in the OL Treatment Phase + 1 Day) + 30 Days

The definition of the duration of treatment exposure for subjects who received at least one injection of Lanreotide is:
(Last Injection Date of Lanreotide – First Injection Date of Lanreotide + 1 Day) + 30 Days

3.2.5 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented by treatment group for each phase of the study (DB and OL Treatment)

3.2.6 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be listed by treatment group and subject. Summary statistics will be provided for demographic (age, sex, race, and ethnicity [only for United States (US) subjects]) and baseline characteristics (height, weight, and body mass index [BMI] at Screening), childbearing potential, pregnancy test results (both urine and serum), and prior chemotherapy according to IWRS and according to eCRF (received, naïve), by treatment group, for the ITT and Safety populations.

Baseline tumor characteristics summary statistics will be provided for time since diagnosis, location of primary tumor (lung, lung hilum, lung left, lung right, unknown, other), tumor subtype according to IWRS and according to eCRF (typical carcinoid,

atypical carcinoid), mitotic index (according to IWRS and according to eCRF using the categories: <2; ≥2 to ≤10 and >10), mitoses (10HPF), foci of necrosis according to IWRS and according to eCRF (absent, present), Ki67 if available (using <10 and ≥10 as well as >0 to <3, ≥3 to <10, ≥10 to <20 and ≥20), number of metastatic organs and location of metastases, TNM, hepatic tumor load (≤25%, >25%), intrathoracic tumor load (≤25%, >25%), and subject status in terms of somatostatin receptors (Krenning scale and Ga-PET scan), by treatment group, for the ITT and Safety populations. Data will also be presented for the PP population should there be a difference of more than 10% between the number of subjects in the ITT and the PP population.

An analysis of mis-stratification will be performed. Frequency tables of the number and percentage of subjects will be provided by treatment group for tumor status (typical/atypical) and prior chemotherapy (received/naïve, corresponding to prior chemotherapy versus no prior chemotherapy) according to the IWRS and according to the eCRF. Differences between IWRS and eCRF with regard to both tumor status and prior chemotherapy will be assessed. The frequency table will present the number of agreements and disagreements between IWRS and eCRF for each treatment group for tumor status and prior chemotherapy and kappa tests will be performed.

3.2.7 Medical and Surgical History

Medical and surgical history not related to lung NET and prior surgical procedures related to lung NET will be coded using MedDRA Version 23.0.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history not related to lung NET by primary system organ class and preferred term for each treatment group.

Additionally, a frequency table of the number and percentage of subjects will be provided for all prior surgical procedures related to lung NET by primary system organ class and preferred term for each treatment group.

A listing of medical and surgical history not related to lung NET will be presented by system organ class, preferred term and verbatim term. The subject listing for medical and surgical history not related to lung NET will be sorted by treatment group, subject, primary system organ class, preferred term and verbatim term.

A listing of prior surgical procedures related to lung NET will be presented by system organ class, preferred term and verbatim term. The subject listing for prior surgical procedures related to lung NET will be sorted by treatment group, subject, primary system organ class, preferred term and verbatim term.

3.2.8 Subject Compliance

A listing will be presented for drug administration by subject for each treatment group and study phase (DB Phase and OL Treatment Phase). Note that all summaries and listings for the OL Treatment Phase will be presented according to treatment and progression status at the time of data cut-off. Deviations from observed and scheduled times will be presented.

The compliance (%) will be calculated as the ratio of the actual number of injections received over the planned number of injections, then multiplied by 100. The planned number of injections will be determined based on the planned study day of the last visit within each study phase divided by 28 days (e.g., Visit 6 Week 36 Day 252 would indicate a planned number of injections of 9). If a subject's last visit within the study phase is Baseline, the planned number of injections is 1 for that study phase. A summary table of compliance for each study phase, by treatment group and overall, will be presented. Additionally, the number and percentage of subjects with a compliance ≤ 80% or > 80% will be provided for each study phase, by treatment group and overall. A listing of subjects who had difficulties during study drug administration will also be provided.

Additionally, a summary table of compliance for subjects who received LAN will be presented. The number and percentage of subjects with a compliance ≤ 80% or > 80% will be provided. The treatment groups that will be presented are LAN (for subjects who progressed during the DB Phase), LAN/LAN (for subjects who had not progressed at the time of entering the OL Treatment Phase) and PB/LAN (for subjects who were randomized to placebo during the DB Phase and received at least one injection of LAN during the OL Treatment Phase, regardless of disease progression status in the DB Phase).

The numbers and percentages of subjects with at least one delayed injection (defined as an injection that was given >3 days late), and the number of delayed injections per subject will be summarized for each study phase, by treatment group and overall. Additionally, the numbers and percentages of subjects with at least one injection given in anticipation (defined as an injection that was given >3 days early), and the number of injections given in anticipation per subject will be summarized for each study phase, by treatment group and overall. Difficulties during injection, delayed injections and injections given in anticipation will be listed by subject for each treatment group and study phase (DB Phase and OL Treatment Phase).

A listing will be presented for prohibited concomitant medication for any subject who has received this prohibited medication. Subjects excluded from the PP population due to receiving prohibited concomitant medication will be flagged (+).

A summary table of protocol deviations will be produced for each treatment group and study phase (DB Phase and OL Treatment Phase). All protocol deviations identified prior to unblinding will also be listed by subject for each treatment group. The impact of major protocol deviations on the primary efficacy analysis will be investigated by comparing the results of the ITT and PP population analyses.

3.2.9 Prior and Concomitant Therapies

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODRUG) Global B3, March 2020. The therapeutic class will correspond to the second level of Anatomical Therapeutic Chemical (ATC) code, which corresponds to the first 3 characters.

Prior and concomitant therapies not related to lung NET, prior radiotherapy related to lung NET, and concomitant surgical procedures will be coded using MedDRA Version 23.0.

Summary statistics for all therapies will be provided by treatment group for the Safety populations.

3.2.9.1 Prior Lung NET Related Treatment

Prior lung NET related treatment will be summarized and will include the number of subjects with a prior surgery for lung NET, descriptive statistics for prior surgery for lung NET (continuous and categorical formats), descriptive statistics on the intent of surgery for lung NET, the number of subjects with prior radiotherapy for lung NET, descriptive statistics for prior radiotherapy for lung NET (continuous and categorical), the number of subjects with prior chemotherapy for lung NET, continuous descriptive statistics for overall duration of cycles for prior chemotherapy for lung NET, descriptive statistics on the intent of chemotherapy for lung NET, number of subjects with prior medication related to lung NET, descriptive statistics for prior medication related to lung NET (continuous and categorical), and descriptive statistics of overall duration of previous medication related to lung NET (continuous and categorical format).

3.2.9.2 Prior Radiotherapy Related to Lung NET

A frequency table of the numbers and percentages of subjects will be provided for prior radiotherapy related to lung NET for each treatment group.

A listing of prior radiotherapy related to lung NET will be presented by system organ class, preferred term and verbatim term.

The subject listing for prior radiotherapy related to lung NET will be sorted by treatment group, subject, primary system organ class, preferred term and verbatim term.

3.2.9.3 Prior Medications Related to Lung NET

A frequency table of the numbers and percentages of subjects will be provided for prior medications related to lung NET for each treatment group.

A listing of prior medications related to lung NET will be presented by ATC class, preferred term, and verbatim term.

The subject listing for prior medications related to lung NET will be sorted by treatment group, subject, ATC class, preferred term, and verbatim term.

3.2.9.4 Prior Chemotherapy Related to Lung NET

A frequency table of the numbers and percentages of subjects will be provided for prior chemotherapy related to lung NET for each treatment group.

A listing of prior chemotherapy related to lung NET will be presented by ATC class, preferred term, and verbatim term.

The subject listing for prior chemotherapy related to lung NET will be sorted by treatment group, subject, ATC class, preferred term, and verbatim term.

3.2.9.5 Prior and Concomitant Therapies Not Related to Lung NET

A prior therapy is defined as a therapy with start and end dates prior to first dose of study treatment. A prior/concomitant therapy is defined as a therapy with a start date prior to first dose of study treatment and an end date after the first dose of study treatment. A concomitant therapy is defined as a therapy with a start date on or after the date of the first dose of study treatment. Summary tables on prior therapies not related to lung NET will include only prior therapies; whereas, summary tables on concomitant therapies not related to lung NET will include both prior/concomitant and concomitant types of therapies.

A frequency table of the numbers and percentages of subjects will be provided for prior therapies not related to lung NET for each treatment group.

A frequency table of the number and percentage of subjects will be provided for concomitant therapies not related to lung NET by system organ class, and preferred term for each study phase and treatment group (DB Phase and OL Treatment Phase). The frequency table for the OL Follow-up Phase will be provided by system organ class, and preferred term.

A listing of prior and concomitant therapies not related to lung NET will be presented by system organ class, preferred term and verbatim term. The subject listing will be sorted by treatment group, subject, chronological start date, primary system organ class, preferred term and verbatim term.

Note that the table for the OL Treatment Phase will be presented according to treatment received during the DB Phase and progression status at the time of entering the OL Treatment Phase (see Section 2.3).

3.2.9.6 Concomitant Medications, Chemotherapy, and Targeted Therapy for Lung NET

A frequency table of the number and percentage of subjects will be provided for concomitant medications, chemotherapy and targeted therapy for lung NET by ATC and preferred term for each study phase (DB Phase and OL Treatment Phase) and treatment group. The frequency tables for the OL Follow-up Phase will be provided by ATC and preferred term.

A listing of concomitant medications, chemotherapy and targeted therapy for lung NET will be presented by ATC, preferred term and verbatim term. The subject listing will be sorted by treatment group, subject, chronological start date, ATC, preferred term and verbatim term.

Note that the table for the OL Treatment Phase will be presented according to treatment received during the DB Phase and progression status at the time of entering the OL Treatment Phase (see Section 2.3).

3.2.9.7 Prior and Concomitant Medications Not Related to Lung NET

A prior medication is defined as a medication with start and end dates prior to first dose of study treatment. A prior/concomitant medication is defined as a medication with a start date prior to first dose of study treatment and an end date after the first dose of study treatment. A concomitant medication is defined as a medication with a start date on or after the date of the first dose of study treatment. Summary tables on

prior medications not related to lung NET will include only prior medications; whereas, summary tables on concomitant medications not related to lung NET will include both prior/concomitant and concomitant types of medications.

A frequency table of the numbers and percentages of subjects will be provided for prior medications not related to lung NET for each treatment group.

A frequency table of the number and percentage of subjects will be provided for concomitant medications not related to lung NET by ATC and preferred term for each study phase (DB Phase and OL Treatment Phase) and treatment group. The frequency table for the OL Follow-up Phase will be provided by ATC and preferred term.

A listing of prior and concomitant medications not related to lung NET will be presented by ATC, preferred term and verbatim term. The subject listing will be sorted by treatment group, subject, chronological start date, ATC, preferred term and verbatim term.

Note that the table for the OL Treatment Phase will be presented according to treatment received during the DB Phase and progression status at the time of entering the OL Treatment Phase (see Section 2.3).

3.2.9.8 Concomitant Surgical Procedures

A frequency table of the number and percentage of subjects will be provided for concomitant surgical procedures by system organ class, and preferred term for each study phase (DB Phase and OL Treatment Phase) and treatment group. The frequency table for the OL Follow-up Phase will be provided by system organ class, and preferred term.

A listing of concomitant surgical procedures will be presented by system organ class, preferred term and verbatim term. The subject listing will be sorted by treatment group, subject, chronological start date, system organ class, preferred term and verbatim term.

Note that the table for the OL Treatment Phase will be presented according to treatment received during the DB Phase and progression status at the time of entering the OL Treatment Phase.

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

3.2.12 Derived Data

The derived data are variables which are calculated from the raw data recorded in the eCRF or any other support and not included in the database. The derived data will be calculated to be included in tables and listings.

Some specifications of the data derivations necessary for this study are provided in Appendix 1 Derived Data.

3.2.13 Visit Windows

All data will be organized and analyzed according to the scheduled visits outlined in the protocol and as assigned during the data collection process, unless otherwise stated.

3.2.14 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 descriptive analyses, summary statistics will be presented at each scheduled visit. Summary statistics will include sample size, number of available observations (n), number of missing observations (missing), mean, 95% CI of the mean, StD, and median for continuous variables and scores.

For categorical or discrete variables, the absolute and relative (percentage) numbers based on the non-missing number of observations for each category will be presented.

Mean and its corresponding CI and the median values will be reported to one decimal place greater than the raw/derived data that they summarize. The StD and standard errors of the mean (SE) values will be reported to two decimal places greater than the raw/derived data that they summarize. Minimum and maximum values will be reported with the same precision as the raw data. The CV% will be reported to one decimal place.

CCI [redacted]

Note that rounding will only be applied to decimal digits not to whole numbers.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects with available data in a specified population. The denominator will be specified in a footnote to the tables for clarification if necessary.

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," and p-values which are greater than 0.9999 will be presented as ">0.9999."

All values below or above a limit of detection will be listed as such.

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 will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

3.2.15 Pooling of Centers

No adjustment for country/center effect is planned.

3.2.16 Interim Analysis

No interim analysis will be performed.

3.2.17 Covariates

The analyses of PFS or death due to any cause will include the IWRS stratification factor tumor type (typical/atypical) as covariate to adjust the treatment effect for this prognostic factor. Due to the premature stop of the recruitment, the sample size is smaller than anticipated and the number of subjects in the "Prior Chemotherapy Received" stratification level was very small, and this stratification factor will not be included in the statistical modelling.

3.2.18 Subgroup Analyses

No subgroup analyses will be performed.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using Windows Server 2012 R2.

4.2 Software

All tables, listings and figures will be produced, and statistical analysis performed using SAS version 9.4 or higher. All output will be in Microsoft Word Format.

4.3 Validation programs

Validation of all programming output, including Study Data Tabulation Model (SDTM) datasets, Analysis Data Model (ADaM) datasets, tables, listings and figures, will be performed by following SDC CCI . Independent programming by a primary and validation programmer will be used to program and validate all of the above items and a comparison of SAS output created by the two independent programmers will be performed using SAS PROC COMPARE or other relevant procedures to assess consistency between the independently programmed outputs.

A Validation Plan will be created identifying the methods of validation for each output and will be completed prior to the database lock.

The Primary and Validation Programmers are 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 Reviewing/QC 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 assure the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check for consistency with the statistical analysis plan (SAP). Outputs

will be 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 quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

After final review, and when no further changes are required to produce the deliverable, the Primary and Validation Programmers and Reviewing/QC Statisticians will complete and sign SDC's Form 153: Statistical Programming Validation Tracker to indicate that all responsibilities have been successfully performed.

Copies of the internal QC reports produced for the validation process and SDC's sign-off forms will be provided to the sponsor to support the validation.

4.4 Restitution of the programs

All programs (including macros and analysis datasets) producing the tables, figures, listings, and statistical output along with associated logs as well as SDTM and ADaM definition documentation will be given to the sponsor at the time of delivery of the final tables, figures, and listings.

5 CHANGES FROM PROTOCOL

The following differences from the statistical section of the protocol are noted:

1. Section 3.2.6 of the SAP currently states demographics will be summarized for both Safety and ITT populations; whereas, the protocol only references the ITT population (section 10.4.1). The addition of a demographic report on the safety population has been added to summarize demographics for those subjects by actual treatment received.
2. Section 2 (Subject Populations) of the SAP has been updated from the protocol (section 10.1) to provide more detail around the definitions of the OLITT, Per Protocol, and Follow-up populations.
3. Section 2.6 of the SAP has been updated from the protocol (section 10.1) for the Follow-up population to include all ITT subjects, instead of only OLITT subjects. This definition is being updated as subjects are able to complete the DB phase and then move directly to follow-up without entering the OLT phase; thus, excluding them from the OLITT population.
4. Section 3.2.1.3 e), has been added to the SAP to include additional exploratory analyses focusing on the OL Treatment Phase when subjects are taking LAN. These analyses are not in the protocol but were added to provide an overall picture of LAN survival in the OL treatment phase.
5. Table 4 and Table 6 of the SAP differ from Tables 7 and 8 of the protocol. The situations/date of progression/censoring described in the SAP are more representative of how the data has been collected and describe in more detail how each situation is assessed for this study.

C
CI [redacted]

7. Section 3.2.1.2 d) Table 7 updated to add more details pertaining to some of the situations not previously discussed in the protocol.
8. PP population definition is modified in the SAP by adding the text “impacting analyses, as defined in the Protocol Deviation Document and Protocol Deviation Specification Document” for precision and to be consistent with the definition of the PP population defined in the PDD and PDS Documents.
9. Sensitivity analysis of primary efficacy analysis based on PFS of local review data planned in the protocol (section 10.4.5.1) is removed in the SAP as it cannot be analyzed with the data collected. Indeed a new baseline of tumor assessments were considered by the investigators in the OLT phase and thus a PFS of local review data on the period DB or OL phase cannot be calculated.

6 REFERENCES

1. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

2. Ferté C, Fernandez M, Hollebecque A, et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. Clinical Cancer Research. 2014 Jan;20(1): 246-252.

3. Ferté C, Koscielmy S, Albiges L, Rocher L, Soria JC, Iacovelli R, Loriot Y, Fizazi K, Escudier B. Tumor growth rate provided useful information to evaluate sorafenib and everolimus treatment in metastatic renal cell carcinoma patients:

an integrated analysis of the TARGET and RECORD phase 3 trial data. European Urology. 2014 Jan;65(1): 713-720.

4. Dromain et al, Tumor growth rate as a metric of progression, response, and prognosis in pancreatic and intestinal neuroendocrine tumors; BMC Cancer 2019; doi: 10.1186/s12885-018-5257-x.

7 APPENDICES TO THE SAP TEMPLATE

Appendix 1: Derived Data

The following derived data will be calculated and included in the listings:

BMI

BMI (kg/m^2) will be derived as Weight (kg)/[Height(cm)/100]^2 and rounded to the nearest decimal.

Changes from baseline

Changes from Baseline will be calculated as a difference from Baseline (e.g., Assessment at the Visit – Assessment at Baseline).

Percent change from baseline

Percent change from Baseline will be calculated as a percentage of change from Baseline (e.g., 100*((Assessment at the Visit – Assessment at Baseline) / (Assessment at Baseline))).

Time since last dose for adverse event

If the start date of the AE is identical to the date of last administration, then"1" day will be presented. If the start date is partial, the time since last dose will be presented as a superior inequality (i.e., for an AE started in FEB2004 after the only administration performed on 31JAN2004, the time since last dose will be "≥2" days). If the start date is missing the time since last dose will not be presented although the AE will be assigned to each dose received before its end date.

Days since previous dose for study drug administration or discontinued subject

The days since previous dose for study drug administration will be calculated as: (Drug Administration Date - Previous Administration Date) + 1.

The days since last dose for discontinued subjects will be calculated as: (Discontinued Date - Last Administration Date) + 1.

Concomitant therapy duration

The duration of concomitant treatments/physiotherapy, etc., will be calculated as: (End Date - Start Date) + 1. If the recorded end date is CONT. (for continuing) then the end date will be listed as "ongoing" and the duration will be approximated as "≥ (Last Attended Visit Date – Start Date) + 1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥ xx" day(s) [i.e. ≥ 2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004]; but if both are partial or one is missing, the duration will not be presented.

Study day

Study day will be defined as '-1' for the day prior to treatment and as '1' for the day of treatment (i.e. day 0 does not exist).

Cumulative dose / Mean Dose per 28 Days

The cumulative dose is the sum of all doses from injection 1 up to last injection; whereas, mean dose per 28 days will be calculated as: Cumulative Dose / 28 Days.

Compliance

Compliance (%) = (Actual Number of Injections Received/Planned Number of Injections) * 100 and will be calculated for each treatment group and study phase (DB Phase and OL Treatment Phase).

Duration of Study Treatment Exposure

Duration of Treatment Exposure for OL Treatment Phase and DB Phase Combined (months) = (Last Injection Date of LAN - First Injection Date of LAN + 31 days) / 30.4375 and will be calculated for each treatment group. Duration of Treatment Exposure by Study Phase (DB Phase and OL Treatment Phase) will be calculated as follows: If subject continued into the OL Treatment Phase, then Duration of Treatment Exposure during the DB Phase = (Date of First Dose in OL Treatment Phase - Date of First Dose in DB Phase)/ 30.4375. If subject did not continue into the OL Treatment Phase, then Duration of Treatment Exposure in the DB Phase = (Last Injection Date - First Injection Date + 31 days)/ 30.4375. Duration of Treatment Exposure in the OL Treatment Phase = (Last Injection Date in the OL Treatment Phase - First Injection Date in the OL Treatment Phase + 31 days)/ 30.4375.

Duration of Study Exposure

The definition of the length of study exposure during the DB Phase is: Date of Last DB Phase Visit – Date of Screening Visit + 1 day. The definition of the length of study exposure during the OL Treatment Phase is: Date of Last OL Treatment Phase Visit – Date of OL Treatment Baseline Visit + 1 day. The definition of the length of study exposure during the OL Follow-up Phase is: Date of Last Visit – Date of OL Extension Follow-up Baseline Visit + 1 day. The overall study exposure is defined as: Date of Last Visit – Date of Screening Visit + 1 day.

AE duration

AE duration will be calculated by using: AE Stop Date – AE Start Date + 1, recorded in days. If the end date is missing because the AE was ongoing, then the duration will be listed as "ongoing".

Limit of Quantification

In some cases, lab data may not be reported as they may be difficult to detect. If lab data are reported to < X or > X, they will be reported as such in the listings. However, for the tables the lab value will be imputed as the value of the threshold, i.e., <X would be imputed as X and >X would be imputed as X.

Tumor type

The tumor type will be captured in the IWRS, but will also be derived from collected data as follows:

If [(mitotic index <2 mitoses/2 mm^2) AND foci of necrosis are "absent"], then tumor type = "Typical";

If [(2 mitoses/2 mm^2≤ mitotic index <10 mitoses/2 mm^2) AND/OR foci of necrosis is "present"], then tumor type = "Atypical."

RECIST v1.1 – Derivation of Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known for a given phase (DB or OL). The derivation of time point response using RECIST v1.1 is displayed in Table 9.

Table 9 RECIST v1.1 Time Point Response Criteria

Target Lesions	Non-Target Lesions	New Lesions[1]	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR[2]
PR	NE	No	PR[2]
PR	CR	No	PR
PR	Non-CR/Non-PD	No	PR
SD	NE	No	SD
SD	CR	No	SD
SD	Non-CR/Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
CR	NA[4]	No	CR
PR	NA[4]	No	PR
SD	NA[4]	No	SD
NA[3]	Non-CR/Non-PD	No	Non-CR/Non-PD
NA[3]	CR	No	CR
NA[3]	NE	No	NE
NA[3]	NA[4]	No	NE

CR=Complete Response; NE=Not Evaluable; PD=Progressive Disease; PR=Partial Response; SD=Stable Disease; NA=Not applicable.

1. Identification of new lesions at a post-Baseline time point will result in a time-point response (TPR) of PD. If an identified new lesion subsequently becomes NE, the TPR will be recorded as PD unless the new lesion has proven to have resolved. Note: TPRs assessed after a progression event will not contribute to the determination of the Best Response.
2. If a non-target lesion is classified as NE, a designation of PR may be assigned based on information from the target lesions.
3. No target lesions identified at Baseline.
4. No non-target lesions identified at Baseline.

Best overall response based on local investigator assessments

Using local investigator time point response assessments, the best overall response to study treatment is the highest objective response achieved by the during the DB Phase, and during the OL Treatment Phase, ordering response categories from best to worst: CR, PR, SD, PD, and NE, per RECIST v1.1.

Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). A Best Overall Response of SD can only be made after the subject is on study for a minimum of seven (7) weeks (49 days). If the subject is on study less than seven (7) weeks (49 days), any tumor assessment indicating stable disease before this time period will have a Best Response of "non evaluable" unless PD is identified. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable. Please refer to the RECIST v1.1 guidelines for additional details.

Tumor assessments

In the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007, it is stated that "Death or progression after more than one missed visit will be censored in the analysis at the date of last radiological assessment of measured lesions." This rule will be implemented as follows: 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 independent central (or local) review. Table 10 displays the event status for various scenarios with missing data.

Table 10 Event Status for Various Scenarios with Missing Data

Scan Time	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Event Status
Scenario 1	Mis	PD				Event at Wk 24
Scenario 2	Mis	Mis	PD			Censored at baseline
Scenario 3	Mis	SD	PD			Event at Wk 36
Scenario 4	Mis	Mis	SD	PD		Event at Wk 48
Scenario 5	SD	SD	Mis	PD		Event at Wk 48
Scenario 6	SD	SD	Mis	SD	PD	Event at Wk 60

Appendix 2: List of TFLs

The Table of Contents for Tables, Figures and Listings and the corresponding Shells are included in a separate document.