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

STUDY PROTOCOL
STUDY number: A-US-52030-328

Lanreotide Autogel/Depot
EudraCT number 2015-004992-62

Final Version (including Amendment #5): 28 January 2019

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol A-US-52030-328 entitled 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, with Amendment #5. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:
TITLE: [PRINCIPAL] INVESTIGATOR SIGNATURE:

DATE:
OFFICE:

Sponsor's Representative Signature:

NAME: PPD
TITLE: PPD SIGNATURE:

DATE:
OFFICE:

COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol A-US-52030-328 entitled 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, with Amendment #5. I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: PPD

TITLE: COORDINATING INVESTIGATOR SIGNATURE:

DATE:

OFFICE:

COORDINATING INVESTIGATOR'S AGREEMENT

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NAME: PPD
TITLE: COORDINATING INVESTIGATOR SIGNATURE:

DATE:
OFFICE:

SUMMARY OF CHANGES

The current version of the protocol was released on 28 January 2019 and includes Amendment #5. The amendment forms were prepared and are provided in CCI to CCI (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	14 December 2015	CCI
2	20 April 2016	CCI
3	13 June 2016	CCI
4	05 October 2016	CCI
5	28 January 2019	CCI

SYNOPSIS

Study Title	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.
Sponsor Name, Location	IPSEN 106 Allen Road, Basking Ridge, NJ 07920 Ipsen Contact: PPD
Rationale	Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms originating from neural crest cells, endocrine glands, endocrine islets or the diffuse endocrine system. The majority of NETs are sporadic and little is known about their risk factors. In some cases NETs form part of heritable tumour syndromes such as multiple endocrine neoplasia type 1 or tuberous sclerosis. Although considered rare malignancies, recent data suggest an increase in NETs incidence over the past 30 years, with 5.2 cases per 100,000 population per year. NETs of pancreatic, intestinal and bronchopulmonary origin are the most common, with the incidence of bronchopulmonary or bronchial NETs at 1.35 per 100,000; this is seemingly a drastic increase from the annual incidence of 0.3 per 100,000 of 1973 [Yao 2008]. Bronchial NETs account for approximately 1 to 2 percent of all lung malignancies in adults and roughly 20 to 30 percent of all NETs. NETs of thorax include lung and thymus NETs. There are 4 types of lung neuroendocrine cancers - typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma (NECs), and small-cell lung cancer (SCLC). Like neuroendocrine tumours at other body sites, bronchial NETs are thought to derive from peptide- and amine-producing neuroendocrine cells that have migrated from the embryologic neural crest. While surgery remains the treatment of choice for patients with resectable tumours, there are limited options for those with advanced or metastatic disease with unresectable tumours. The primary goal in the treatment of unresectable, advanced NETs is to prevent tumour progression and reduce the symptoms related to carcinoid syndrome when present. Typical and atypical carcinoid metastatic lung NETs are associated with poor prognosis; with median survival averaging 17 months and the 5-year survival rate approximately at 27%. However, recent studies dedicated to stage IV lung NETs suggest better median

	OS of 5 to 10 years for atypical and typical carcinoids. There is a clear unmet need in patients with advanced lung NETs. Limited data are available regarding treatment for advanced lung NETs due to the rarity of the disease. In most cases, treatment guidelines are extrapolated from the clinical experience with the more common gastrointestinal (GI) NETs or mixed retrospective studies. Recently recommendations issued from the European Neuroendocrine Tumour Society for best practice for typical and atypical pulmonary carcinoid have been published. To date, available data on the application of Somatostatin analogs (SSAs) or other systemic intervention in lung NETs come from two prospective studies conducted in lung NETs progressive patients: - In RADIANT 2 study, the median PFS (measured by local and central review in the lung NET subgroup), was 2.8 and 5.6 months, respectively, in the octreotide group (n=11) versus 8.8 and 13.6 months, respectively, in the everolimus plus octreotide group (n=33). - In RADIANT 4 study, conducted in patients with well-differentiated (G1/G2), advanced, progressive, non-functional NET of lung or GI origin, a reduction of 52% in the relative risk of progression or death with everolimus versus placebo (Hazard ratio = 0.48 (95% CI, 0.35-0.67); p<0.00001) was demonstrated in the overall population. There are also some data reported from retrospective single centre study involving 61 patients with lung NET treated with SSAs, the estimated median PFS was 17.4 months (12.8 months in the AC subgroup and 24.8 months in the TC subgroup). In another study where nine patients were treated with octreotide and 13 patients were treated with lanreotide, a median PFS of 18.1 months was reported for 22 patients (32% of whom had AC). In a further study, a median PFS of 16.5 months was reported in 22 patients treated with SSAs. Recently, the CLARINET study demonstrated that first-line treatment with Lanreotide Autogel/Depot 120 mg, a somatostatin analogue (SSA), significantly prolonged progression free survival among subjects with metastatic grade 1 or 2 enteropancreatic NETs of (Ki 67 <10%) [Caplin 2014]. This is the first and only registration study of an SSA (Lanreotide Autogel/Depot 120 mg) demonstrating a cancer treatment benefit in this gastrointestinal and pancreatic NET population. While, subjects with bronchial neuroendocrine tumours (B-NETs) were not included in CLARINET, there is a well-established basis for the use of SSAs like Lanreotide Autogel/Depot 120 mg in the management of lung NETs the high expression of the somatostatin receptors SSTR2A and SSTR3 Besides their role in imaging for NETs (somatostatin receptor scintigraphy (SRS) or octreotide scan), SSAs are also therapeutically used mainly to control hormone related symptoms, which occur in up

	to 40% of cases of hypersecretion in patients with advanced lung NET tumours. Recent updates of NCCN & ENETS guidelines recommend SSA in first line for the treatment of locoregional unresectable or metastatic lung NETs as an option beyond 'observation'. Consequently, it was decided to prematurely stop the recruitment in the SPINET study and to transition subjects still treated in the double-blind phase to the OL treatment phase. The transition to the OL treatment period, will be done per subject, at the planned scheduled visit (ie, approximately 28 days from the last injection) following the country approval of Amendment #5. The new aim of this Phase 3, multicenter, prospective, randomized placebo controlled clinical study is to describe the antitumour efficacy and safety of Lanreotide Autogel/Depot 120 mg (LAN) plus Best Supportive Care (BSC) in subjects with well differentiated, metastatic and/or unresectable, typical or atypical, lung NETs.
Study Objectives	**Objectives** **Primary Objective** • To describe the antitumour 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 Tumours (RECIST) v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung neuroendocrine tumours in either the double-blind phase or the OL period. **Secondary Efficacy Objectives** • To describe the antitumour efficacy during the double-blind phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of progression free survival (PFS), measured by central review using RECIST v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung NETs • To describe the antitumour efficacy during the double-blind phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of progression free survival (PFS), measured by local review using RECIST v1.1 criteria, 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 v 1.1 criteria (proportion of subjects with an objective response of partial response (PR) or complete response (CR)) in the double-blind phase,
- To describe time to treatment failure (Kaplan Meier estimates) of LAN monotherapy plus BSC every 28 days and placebo plus BSC in the double-blind phase,
- To describe the changes from Baseline in the biomarker chromogranin A (CgA) during the double-blind 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 ULN) at Baseline during the double-blind and the OL treatment phases,
- To describe the change in Quality of Life (QoL) from baseline, as assessed by the EORTC QLQ-C30 questionnaire during the double-blind, the OL treatment and during the OL follow-up phases,
- To describe the time to deterioration of QoL (using EORTC QLQ-C30) during the double-blind, the OL treatment and during the OL 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 double-blind and the OL treatment phases.

Secondary Safety Objective

- To evaluate the clinical and biological safety profile.

CCI

[redacted]

Study Timelines	**Study duration** • Trial recruitment: 25 months • Double Blind (DB) Phase: approximately 36 months • OL Extension Phases will end 18 months after the last subject randomised
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 typical or atypical, metastatic and/or unresectable lung NETs. The study will be conducted at approximately 80 centers in the United States, Canada and Europe. At time of protocol Amendment #5, a total of 38 centers have actively recruited at least one subject (active recruitment is defined by at least one informed consent signed). 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), had to be randomized 2:1 to either LAN plus BSC (120mg/28 days) or placebo plus BSC following the stratification of 1) typical versus atypical and 2) prior chemotherapy versus no prior chemotherapy*. Due to the premature stop of the recruitment (as per Protocol Amendment #5), 77 subjects are enrolled. All subjects still treated in the DB Phase will enter into the OL Extension Period (either for follow-up or for OL treatment). The transition to the OL treatment 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 Period) 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 randomised. After disease progression subjects will be followed for survival, QoL and all subsequent anticancer treatments up to the end of the study. ** cytotoxic chemotherapy or molecular targeted therapy or interferon*. The study contains two phases: the DB Phase, and the OL Extension Phase. The DB Phase included: Screening, Baseline and Treatment periods and the OL Extension Phase consists of two periods: Treatment Period and Follow-Up Period. • The DB Phase included a Screening Period to establish protocol eligibility and disease characteristics. The Baseline Visit confirmed 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 Treatment

	Period. Before approval of Protocol Amendment #5: If a subject progresses during the DB phase, the subject will be proposed to enter the OL Extension phase: • If the subject was on placebo and progressed during the DB phase, the subject will be 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 will enter the follow-up period of the OL extension phase and be followed for QoL/survival and all subsequent anticancer treatments received will be recorded. The OL Treatment Period will stop once all subjects will have centrally progressed or 18 months after the last subject randomised (i.e. end of study). After approval of Protocol Amendment #5: • All ongoing subjects in the DB Phase, who have no yet progressed, 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 randomised. • if a subject progresses during the DB phase, the subject will enter the OL follow-up period • If a subject progresses during the OL Treatment Period, the subject will enter the OL follow-up period. • The follow-up period of the OL extension phase will stop at the same time as the OL Treatment Phase (ie, end of study up to 18 months after the last subject randomised). At the end of the OL Extension Treatment period, if subjects are still benefiting from treatment (i.e. not progressing) and there is sufficient evidence of the safety and efficacy of it, the subjects will have the option, to continue to receive lanreotide 120 mg every 28 days up to disease progression or unacceptable toxicity. In such a situation, as permitted by local regulations, lanreotide 120 mg 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.
Study Population	Study population consists of 77 randomized subjects (i.e. number of subjects enrolled at time of enrolment termination) who met the

	selection criteria specified below: **Inclusion criteria** (1) Provision of written informed consent prior to any study related procedures, (2) Subjects aged ≥ 18 years, (3) Have metastatic and/or unresectable pathologically confirmed well-differentiated, typical or atypical neuroendocrine tumour of the lung, (4) Histologic evidence of well differentiated NETs of the lung (typical and atypical according to the WHO criteria evaluated locally), (5) Has a mitotic index <2 mitoses/2 mm^2 for typical carcinoid (TC) and ≤10 mitoses/2 mm^2 and/or foci of necrosis for atypical carcinoid (AC), (6) At least one measurable lesion of the disease on imaging (CT or MRI; RECIST v1.1), (7) Positive somatostatin receptor imaging (SRI) (Octreoscan® ≥ grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background), (8) ECOG performance status 0-1, (9) Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required, (10) Female subjects who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry, (11) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use an effective method of contraception (see above). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration, (12) Signed HIPAA authorization where required, (13) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the study site for the follow-up evaluation as specified in the protocol.

	Exclusion criteria (1) Poorly differentiated or high grade carcinoma, or subjects with neuroendocrine tumours not of lung origin are excluded, (2) Subjects with Multiple endocrine neoplasia type 1 (MEN 1), (3) Has been treated with an SSA at any time prior to randomization, except if that treatment was for less than 15 days (e.g. peri-operatively) of short acting SSA or one dose of long acting SSA and the treatment was received more than 6 weeks prior to randomization, (4) Has been treated with Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization, (5) Has been treated for Lung NET with chemotherapy* within 4 weeks of randomization (whatever the number of cycles), (6) Has been treated with more than two lines of chemotherapy* for Lung NET, ** cytotoxic chemotherapy or molecular targeted therapy or interferon.* (7) Treated with surgery within 6 weeks prior to randomization, (8) Previous local therapy (e.g. chemo-embolization, bland, or radio-embolization) is allowed if completed > 6 weeks prior to randomization. For subjects who received local therapy prior to randomization, there must be documented growth of measurable disease within the embolization field prior to study, (9) Symptomatic subjects requiring SSA for symptom management (please also note the exclusion criteria 3), (10) Subjects with known ectopic production of adrenocorticotropic hormone (ACTH) or other hormonal secreting subjects allowed ONLY if symptoms adequately controlled without SSAs, (11) Subjects on concomitant Growth Hormone (GH) antagonist, cyclosporine or bromocriptine (12) Inadequate bone marrow function as per investigator's judgement (13) Severe renal insufficiency as defined by a calculated creatinine clearance <30 mL/min, (14) Total bilirubin >2x ULN, AST, ALT or Alk Ph >5xULN, lipase, amylase >2xULN, (15) Serum albumin <3.0 g/dL unless prothrombin time is within the normal range, (16) Known hypersensitivity to the study drug, (17) Present cholecystitis, (18) Uncontrolled congestive heart failure (19) Glycosylated hemoglobin (HbA1c) > 8.5%,

	(20) Abnormal findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, would compromise the subject's safety or the outcome of the study, (21) Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years, (22) Pregnant or lactating women or those of childbearing potential age and not practicing a medically acceptable method for birth control, (23) Subjects who have participated in any therapeutic clinical study/received any investigational agent within 30 days of randomization. (24) Clinically significant cardiac arrhythmia, bradycardia, tachycardia that would compromise patient safety or the outcome of the study (25) Uncontrolled hypothyroidism
Study Treatment	Lanreotide Autogel/Depot 120mg (LAN) plus BSC every 28 days administered via deep subcutaneous (s.c.) injection until disease progression confirmed centrally, development of unacceptable toxicity or premature withdrawal for any reason. OR Placebo plus BSC every 28 days administered via deep s.c. injection until disease progression confirmed centrally, development of unacceptable toxicity or premature withdrawal for any reason. A subject may decide to discontinue participation in the study at any time for any reason (e.g. withdrawal of consent, AE).
Off-Treatment	The investigator and/or sponsor can withdraw a subject from the study at any time for any reason. Subjects will also be withdrawn from the study treatment should any of the following occur: • 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 serious adverse event (SAE) that may jeopardise the subject's health. • A need to administer any of the drugs prohibited by the study protocol to a subject

	• Appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of any SSA (short acting and/or long acting release SSA). • Appearance of biological and/or clinical symptoms for Gallbladder inflammation confirmed by an echography • Pregnancy • Deviations from protocol • Investigator's discretion Subjects will also be withdrawn from the study should any of the following occur: • Withdrawal of consent • Investigator's discretion • Subject is lost to follow-up • Study is completed or terminated Any change in the administration of study drug or its discontinuation will be documented in the electronic case report form (eCRF).
Endpoints	**Primary Endpoint** Progression-free survival (PFS) for subjects randomized in LAN group, assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes in either the double blind phase, or in the open label period. **Secondary Efficacy Endpoints** • Progression-free survival (PFS), assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase, • Progression-free survival (PFS), assessed by local review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase, • ORR: objective response rate of CR or PR measured by RECIST v1.1 criteria every 12 weeks until the Post Treatment/Early Withdrawal Visit during the double-blind phase, • Time to treatment failure during the double-blind 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 LAR SSA), or initiation of anticancer treatment, • 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 treatment phases, • 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 double-blind and the OL treatment phases, • Change in QoL, as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (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, • Time to QoL deterioration, defined by a decrease from baseline in EORTC QLQ-C30 score of at least10 points during the double-blind, the OL treatment and during the follow-up phases, • Mean changes from Baseline in urinary 5-HIAA levels at Week 8, and 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. **Secondary Safety Endpoints** Safety and tolerability assessments throughout the study: • Adverse Events (AEs) grouped by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term, and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03, • Clinical evaluations (medical and surgical history and physical evaluations, including biochemistry/hematology, ECG, CCI [redacted]), • Gallbladder echography, if biological and/or clinical inflammatory symptoms appear during the course of the study.

	[redacted]
Assessments with Brief Summary of Methods and Procedures	A signed and dated informed consent form will be obtained at Visit 1 before screening procedures. [redacted] Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Screening will take place at Visit 1 and the following assessments will be performed: • Eligibility check (inclusion/exclusion criteria) • Demographic data (year of birth, age, sex and, ethnicity and race (as per local regulations)) • Medical and surgical history, including ongoing

	medical history • Prior surgery, radiotherapy chemotherapy and medications related to lung NETs in an adjuvant setting • Pregnancy test • Clinical evaluation • ECOG status • NYHA classification and ECG • Disease history/disease diagnosis (mitotic count and foci of necrosis, Ki67 value if available, tumour-node-metastasis (TNM) staging, location of primary tumour, number of metastatic organs, presence/absence of hormone related syndrome) • CT scans/MRIs performed within 12 months of baseline collected if available (sent for analysis by central review as part of an ancillary study) • SRI, if not available within the previous 6 months (Octreoscan® ≥ grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background) • Gallbladder echography if biological and/or clinical inflammatory symptoms are present • Clinical laboratory tests (blood sampling for haematology and biochemistry panels) • Start collection of AEs/SAEs • Prior and concomitant medications/therapies unrelated to lung NETs • Prior and concomitant non drug therapies unrelated to lung NETs • Concomitant surgical procedures unrelated to lung NETs Under no circumstances will subjects be screened more than once. **Baseline visit** • QoL rated by the EORTC QLQ-C30 • Clinical evaluation • Baseline subject and tumour characteristics • ECOG status • Heamatology/biochemistry • Pregnancy test • CT scan or MRI: CT scan of thorax and abdomen, or MRI of the abdomen with CT scan of the thorax • CCI

- CgA and urinary 5-HIAA
- CCI [redacted]
- CCI [redacted]
- AEs/SAEs
- Concomitant medications
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

During treatment in the Double Blind Phase

- QoL rated by the EORTC QLQ C30
- Clinical evaluation
- ECOG status
- Hematology and biochemistry
- ECG and NYHA classification
- CT or MRI (thorax & abdomen) using the same mode as per baseline, utilising the RECIST 1.1
- Urinary 5-HIAA (only for subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline Visit) and plasma CgA.
- Gallbladder echography, if biological and/or clinical inflammatory symptoms appear during the course of the study.
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- AEs/SAEs
- Concomitant medications
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

	During OL Extension ***OL Extension Treatment Period*** • Clinical evaluation • ECOG status • ECG, NYHA classification • CT or MRI (thorax & abdomen) using the same mode as per baseline, utilising the RECIST 1.1 • QoL rated by the EORTC QLQ-C30. • Hematology, biochemistry. • Urine 5-HIAA and plasma CgA. • Gallbladder echography, if biological and/or clinical inflammatory symptoms appear during the course of the study. • CCI [redacted] • CCI [redacted] • AEs/SAEs • Concomitant medications • Concomitant non-drug therapies • Concomitant surgical procedures • Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET ***OL Extension Follow-Up Period*** • Clinical evaluation • Survival status. • QoL rated by the EORTC QLQ C30. • Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET After approval of Protocol Amendment #5, the subjects will receive an addendum to Informed Consent Form (ICF) including changes in study rationale and explanations about the conduct of the study end. If the subject agrees to continue to participate to this study, this addendum to ICF will have to be signed.
Sample size justification	Due to the premature stop of the study recruitment, 77 subjects are enrolled.
Statistical analyses	Primary efficacy endpoint analysis: Progression-free survival (PFS) for subjects randomized in LAN group

	will be measured from the date of randomization to the documented date of centrally confirmed progressive disease (PD) or death (from any cause), whichever occurs first in either the double-blind phase, or in the OL period. Subjects who start a new cancer therapy, who are lost to follow-up, and those who are alive without documented PD will be censored at the date of the last evaluable response assessment (prior to initiation of a new cancer therapy. Distribution of PFS times on LAN plus BSC group will be estimated using the Kaplan-Meier product-limit method. As a sensitivity analysis of the primary endpoint, a similar PFS analysis will be performed using the local assessment of progression. <u>Secondary endpoint analyses:</u> • Progression-free survival (PFS) will be measured from the date of randomization every 12 weeks to the documented date of centrally confirmed progressive disease (PD) or death (from any cause) during the double-blind phase, whichever occurs first. Subjects who start a new cancer therapy, who are lost to follow-up, and those who are alive without documented PD during the double-blind phase will be censored at the date of the last evaluable response assessment during the double-blind phase (prior to initiation of a new cancer therapy). Distribution of PFS times for each treatment arm will be estimated using the Kaplan Meier method. A stratified Cox proportional hazards model will be used to estimate the hazard ratio, and its two-sided 95% confidence interval. • Progression-free survival (PFS) will be measured from the date of randomization every 12 weeks to the documented date of locally confirmed progressive disease (PD) or death (from any cause) during the double-blind phase, whichever occurs first. Subjects who start a new cancer therapy, who are lost to follow-up, and those who are alive without documented PD during the double-blind phase will be censored at the date of the last evaluable response assessment during the double-blind phase (prior to initiation of a new cancer therapy). Distribution of PFS times for each treatment arm will be estimated using the Kaplan Meier method. A stratified Cox proportional hazards model will be used to estimate the hazard ratio, and its two-sided 95% confidence interval. • The ORR in each treatment arm, with their corresponding exact 95% CIs, will be estimated. These analyses will be performed using data from local and central review of RECIST v1.1. • Treatment failure is defined as 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 LAR SSA), or initiation of anticancer treatment. Time to treatment failure will be defined as the time from randomization to treatment failure. The distribution of times to treatment failure for each treatment arm will be estimated using the Kaplan Meier method.

- Mean changes from Baseline in biomarker CgA will be presented descriptively by time point and treatment group, using summary statistics. Raw values and change from Baseline will be presented. The proportion of subjects with a decrease of CgA≥30% from baseline from Baseline to Week 8 will be estimated, with the corresponding 95% CI in each treatment arm.
- EORTC QLQ-C30 will be described at Baseline, and every 12 Weeks, for double blind and OL extension (both treatment and follow-up phases). Raw values and change from Baseline will be presented.
- Time to EORTC QLQ-C30 deterioration will be analyzed in a similar fashion to time to treatment failure. EORTC QLQ-C30 deterioration is defined as a reduction of at least 10 points between baseline and the given assessment.
- Mean changes from Baseline in urinary 5-HIAA levels in subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline will be presented descriptively by time point and treatment group, using summary statistics.

CCI [redacted]

Safety analyses:

The safety population comprises all subjects in the ITT Population who received at least one injection of the study drug. Safety analyses will be performed separately by study phase (DB, OL extension treatment and follow-up phases). All treatment emergent adverse events (TEAEs) reported from signature of the informed consent form up to the end of the study will be graded according to the NCI CTCAE, summarized according to the Medical Dictionary for Regulatory

	Activities (MedDRA, version 18.1 or later) System Organ Class (SOC) and Preferred Terms (PT), and classified by worst grade severity per subject by treatment group. Clinical laboratory results will be collected prior to each dose, up to 30 days post last administration of any study drug. Clinically significant laboratory abnormalities, namely tests that result in treatment modification and/or require intervention, will be recorded as AEs. Haematological and biochemistry toxicities will be recorded and graded according to the NCI CTCAE criteria. The NCI CTCAE grade 3 and 4 haematology and biochemistry parameters by subject and by visit will be listed.

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LIST OF ABBREVIATIONS

ABBREVIATION	WORDING DEFINITION
5-HIAA	5-hydroxyindoleacetic acid
βHCG	Beta human chorionic gonadotropin
AC	Atypical carcinoid
ACTH	Adrenocorticotropic hormone
AE	Adverse event
Alk Ph	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
CCI [redacted]	[redacted]
[redacted]	[redacted]
BSC	Best supportive care
BP-NET	Broncho-Pulmonary Endocrine Tumour
CA	Competent Authorities
CCI [redacted]	[redacted]
CFR	Code of Federal Regulations (United States of America)
CI	Confidence interval
CCI [redacted]	[redacted]
CMC-SC	Chemistry Manufacturing and Control Supply Chain
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CSR	Clinical study report
CRO	Contract research organisation
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computerized tomography
CTSU	Clinical Trial Supplies Unit (relates to sponsor)
DB	Double blind

DMC	Data Monitoring Committee
CCI	[redacted]
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
ENETS	European Neuroendocrine Tumor Society
EORTC QLQ-C30	Cancer Quality of Life Questionnaire Core-30
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GH	Growth Hormone
HbA1c	Hemoglobin A1c
HCG	Human chorionic gonadotropin
HIPAA	Health insurance portability and accountability
HPF	High Powered Field
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
i.m.	Intramuscular
IND	Investigational New Drug
INR	International normalised ratio
IRB	Institutional review board
ISF	Interim storage facility
ITT	Intention to treat
IUD	Intra-uterine device
IWRS	Interactive web response system
Ki 67	Proliferation index
LAN	Lanreotide autogel/depot 120 mg
LAR	Long acting release
LC-MS/MS	Liquid chromatography-mass spectrometry

MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEN 1	Multiple endocrine neoplasia type 1
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose (Dosage)
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NET	Neuroendocrine tumour
NOS	Not otherwise specified
NYHA	New York Heart Association
OL	Open label
OLITT	Open Label Intention to Treat
ORR	Objective Response Rate
OS	Overall Survival
PhD	Pharmacodynamics
PD	Progressive Disease
PET	Positron emission tomography
PFS	Progression Free Survival
PP	Per protocol
CCI	CCI [redacted]
PR	Partial response
PRRT	Peptide receptor radionuclide therapy
PT	Preferred term
PTT	Partial thromboplastin time
QoL	Quality of Life
RBC	Red blood cell(s)
RECIST	Response Evaluation Criteria In Solid Tumours
CCI	[redacted]
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SAS®	Statistical Analysis System®
s.c.	Subcutaneous
SCLC	Small-cell lung cancer
SPECT	Single photon emission computed tomography
SRI	Somatostatin receptor imaging
SRS	Somatostatin receptor scintigraphy
SSA	Somatostatin analogs
StD	Standard deviation
SD	Stable Disease
SDV	Source document verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSTR	Somatostatin receptors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Typical carcinoid
TEAE	Treatment emergent adverse event
TFLs	Tables, figures and listings
CCI	[redacted]
TMF	Trial master file
UDS	Urine drug screen
ULN	Upper limit of normal range
US(A)	United States (of America)
V/F	Apparent volume of distribution
WBC	White blood cell(s)
WHO	World Health Organisation
WHO-DD	World Health Organization (WHO) drug dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms originating from neural crest cells, endocrine glands, endocrine islets or the diffuse endocrine system. The majority of NETs are sporadic and little is known about their risk factors. In some cases NETs form part of heritable tumour syndromes such as multiple endocrine neoplasia type 1 or tuberous sclerosis [1].

Although considered rare malignancies, recent data suggest an increase in NETs incidence over the past 30 years, with 5.2 cases per 100,000 population per year [2]. NETs of pancreatic intestinal and bronchopulmonary origin are the most common, with the incidence of bronchopulmonary or bronchial NETs at 1.35 per 100,000 [2]; this is seemingly a drastic increase from the annual incidence of 0.3 per 100,000 of 1973 [2]. Bronchopulmonary NETs account for approximately 1 to 2 percent of all lung malignancies in adults and roughly 20 to 30 percent of all NETs [2, 3, 4, 5]. NETs of thorax include lung NETs and thymus NETs [5, 6].

Pulmonary NETs are classified in four categories, typical carcinoid, atypical carcinoid, large-cell NETs, and small-cell lung cancer (SCLC) [7]. Like neuroendocrine tumours at other body sites, bronchial NETs are thought to derive from peptide- and amine-producing neuroendocrine cells that have migrated from the embryologic neural crest.

While surgery remains the treatment of choice for patients with resectable tumours, there are limited options for those with advanced or metastatic disease with unresectable tumours [8, 5]. The primary goal in the treatment of unresectable, advanced NETs is to prevent tumour progression and reduce the symptoms related to carcinoid syndrome when present. Current treatment guidelines, including the 2015 National Comprehensive Cancer Network (NCCN) Guidelines for advanced lung NETs include observation or active surveillance as an option [9]. Typical and atypical carcinoid metastatic lung NETs are associated with poor prognosis; with median survival averaging 17 months and the 5-year survival rate approximately at 27% [2, 5]. However, recent studies dedicated to stage IV lung NETs suggest better median OS of 5 to 10 years for atypical and typical carcinoids [10, 11, 12]. There is a clear unmet need in patients with advanced lung NETs.

1.2 Compound Review

CCI [redacted]

INN: Lanreotide Autogel/Depot

Chemical formula: S----------S

D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH2

Empirical formula: C54H69N11O10S2

Molecular weight: 1096.34

Lanreotide is an octapeptide analogue of somatostatin. The depot formulation is a novel, prolonged release preparation of Lanreotide acetate and water for injection, which together

form a supersaturated solution of the peptide. Prolonged release of the peptide occurs by the physical nature of the supersaturated solution. The formulation enables active serum levels to be maintained for 1 to 2 months. The approved dosing regimen for gastroenteropancreatic neuroendocrine tumours is one deep subcutaneous (SC) injection of Lanreotide Autogel/Depot 120 mg (LAN), every 28 days in adults.

The most commonly reported side effects for Lanreotide Autogel/Depot are: diarrhea (or loose stools), abdominal pain, and cholelithiasis. Other common side effects are: pancreatic enzyme decrease, weight decrease, nervous system disorders, headache, lethargy, dizziness, nausea, vomiting, gas, bloating, constipation, fatty stool, heartburn, hair loss, low blood sugar, decreased appetite, diabetes mellitus, high blood sugar, injection site reactions (e.g. pain, mass, hardness, nodule, itching), fatigue, weakness, musculoskeletal pain, and muscle pain.

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

1.3 Clinical Trial Rationale

Limited data are available regarding treatment for advanced lung NETs due to the rarity of the disease. Cytotoxic chemotherapeutic agents have resulted in only minor activity in this disease and there is no standard therapeutic regimen. Participation in clinical trials testing new strategies is the preferred approach [13]. In most cases, treatment guidelines are extrapolated from the clinical experience with the more common gastrointestinal (GI) NETs or mixed retrospective studies. To date, available data on the application of Somatostatin analogs (SSAs) or other systemic intervention in lung NETs come from two prospective studies conducted in lung NETs progressive patients:

- In RADIANT 2 study, the median PFS (measured by local and central review in the lung NET subgroup), was 2.8 and 5.6 months, respectively, in the octreotide group (n=11) versus 8.8 and 13.6 months, respectively, in the everolimus plus octreotide group (n=33) [14].
- In RADIANT 4 study, conducted in patients with well-differentiated (G1/G2), advanced, progressive, non-functional NET of lung or GI origin, a reduction of 52% in the relative risk of progression or death with everolimus versus placebo (Hazard ratio = 0.48 (95% CI, 0.35-0.67); p<0.00001) was demonstrated in the overall population [15].

There are also some data reported from retrospective single centre study involving 61 patients with lung NET treated with SSAs, the estimated median PFS was 17.4 months (12.8 months in the AC subgroup and 24.8 months in the TC subgroup) [16]. In another study where nine patients were treated with octreotide and 13 patients were treated with lanreotide, a median PFS of 18.1 months was reported for 22 patients (32% of whom had AC) [17]. In a further study, a median PFS of 16.5 months was reported in 22 patients treated with SSAs [18].

Recently, the CLARINET study demonstrated that treatment with Lanreotide Autogel/Depot 120 mg, a somatostatin analogue (SSA), significantly prolonged PFS among subjects with metastatic enteropancreatic NETs of grade 1 or 2 (Ki-67 <10%) [19]. This is the first and only registration study of an SSA (Lanreotide Autogel/Depot 120 mg) demonstrating a tumour control benefit in this patient population. While, patients with bronchial neuroendocrine tumours (BPNETs) were not included in CLARINET, there is a well-established basis for the use of SSAs like Lanreotide Autogel/Depot 120 mg in the management of lung NETs the high expression of the somatostatin receptors SSTR2A and SSTR3 [20].

Besides their role in imaging for NETs (somatostatin receptor scintigraphy (SRS) such as octreotide scan), SSAs are also therapeutically used mainly to control hormone related symptoms, which occur in up to 40% of cases of hypersecretion in patients with advanced lung NET tumours [12].

Recent updates of NCCN & ENETs guidelines recommend SSA in first line for the treatment of locoregional unresectable or metastatic lung NETs as an option beyond 'observation' [21, 22]. Consequently, it was decided to prematurely stop the recruitment in the SPINET study and to transition subjects still treated in the double-blind phase to the OL treatment phase.

The new aim of this Phase 3, multicenter, prospective, randomized placebo controlled clinical study is to describe the antitumour efficacy and safety of Lanreotide Autogel/Depot 120 mg (LAN) plus Best Supportive Care (BSC) in subjects with well differentiated, metastatic and/or unresectable, typical or atypical, lung NETs. Placebo plus BSC/best supportive care was chosen as the control arm because there are no definitive, well-controlled studies demonstrating the efficacy and safety of SSAs in this setting. Current 2015 NCCN recommendations for Lung NET include observation for asymptomatic low-bulk typical pulmonary carcinoids. 2015 European Neuroendocrine Tumor Society (ENETS) guidance includes observation for asymptomatic pulmonary carcinoids of low proliferative index [9].

Further details can be found in the Investigator Brochure (IB).

1.4 Compliance Statement

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

This study will utilize Electronic Data Capture (EDC) which will be conducted in compliance with the following regulations: Food and Drug Administration (FDA), 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, this study will adhere to all USA FDA and other local regulatory requirements and relevant company policies.

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

1.5 Population to be Studied

The study enrolled adult subjects with well differentiated, metastatic and/or unresectable, typical or atypical lung NETs. These subjects must not require SSAs treatment for symptom control. It was planned to enrol 216 subjects at approximately 30 centers across the United States, 6 in Canada and 40 in Europe (including, but not limited to Austria, Denmark, France, Germany, Italy, Poland, Spain, Sweden and the United Kingdom). At time of Protocol Amendment #5, a total of 38 centers have actively recruited at least one subject in 10 countries.

Due to the premature stop of the recruitment, 77 subjects are enrolled.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

The purpose of this study is to describe the role of LAN plus BSC in the management of metastatic and/or unresectable, well differentiated, typical or atypical lung NETs. 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 SSAs like LAN plus BSC in advanced lung NETs [20].

2.2 Study Objectives

2.2.1 Primary Objective

- To describe the antitumour 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 Tumours (RECIST) v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung neuroendocrine tumoursin either the double blind phase, or in the OL period.

2.2.2 Secondary Efficacy Objectives

- To describe the antitumour efficacy during the double-blind phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of progression free survival (PFS), measured by central review using RECIST v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung NETs.
- To describe the antitumour efficacy during the double-blind phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of progression free survival (PFS), measured by local review using RECIST v1.1 criteria, 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 v 1.1criteria (proportion of subjects with an objective response of partial response (PR) or complete response (CR)) in the double blind phase,
- To describe time to treatment failure (Kaplan Meier estimates) of LAN monotherapy plus BSC every 28 days and placebo plus BSC in the double blind phase,
- To describe the changes from Baseline in the biomarker chromogranin A (CgA) during the double-blind 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 ULN) at Baseline during the double-blind and the OL treatment phases,
- To describe the change in Quality of Life (QoL) from baseline, as assessed by the EORTC QLQ-C30 questionnaire during the double-blind, the OL treatment and the follow-up phases,
- To describe the time to deterioration of QoL (using EORTC QLQ-C30) during the double-blind, 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 double-blind and the OL treatment phases.

2.2.3 Secondary Safety Objectives

- To evaluate the clinical and biological safety profile.

CCI [redacted]

3 STUDY DESIGN

3.1 General Design and Study Schema

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.

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), had to be randomized 2:1 to either LAN plus BSC (120mg/28 days) or placebo plus BSC following the stratification of 1) typical versus atypical and 2) prior chemotherapy versus no prior chemotherapy*. Due to the premature stop of the recruitment (as per Protocol Amendment #5), 77 subjects are enrolled. All subjects still treated in the DB Phase will enter into the OL Treatment Period (either for follow up or for OL treatment). The transition to the OL treatment 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 Period) 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 randomised. After disease progression subjects will be followed for survival, QoL and all subsequent anticancer treatments up to the end of the study.

** cytotoxic chemotherapy or molecular targeted therapy or interferon*.

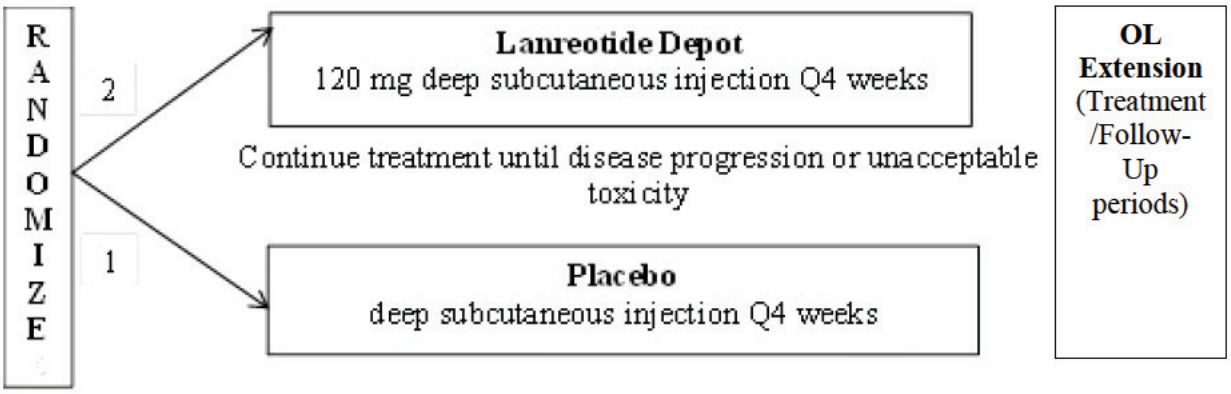
This study contains two phases: the Double-Blind (DB) Phase, and the Open Label (OL) Extension Phase. The DB Phase included: Screening, Baseline and Treatment period. The OL Extension Phase consists of two periods: Treatment Period and Follow-Up Period.

The DB Phase included a Screening Visit to establish protocol eligibility and disease characteristics. The Baseline Visit confirmed eligibility prior to randomization and treatment. The DB Phase of the study will end with Protocol Amendement #5 and will be followed by the OL Treatment Period.

At the end of the OL Extension Treatment period, if subjects are still benefiting from treatment (i.e. not progressing) and there is sufficient evidence of safety and efficacy of it, the subjects will have the option, to continue to receive lanreotide 120 mg every 28 days up to disease progression or unacceptable toxicity. In such a situation, as permitted by local regulations, lanreotide 120 mg 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.

Figure 1 Study Schema

Injection every 28 days (4 weeks)



Subjects will be stratified by:

1. Atypical (mitotic index ≤10 mitoses/2 mm^2 and/or foci of necrosis) vs. typical (mitotic index <2 mitoses/2 mm^2) and
2. prior chemotherapy* vs no prior chemotherapy* therapy

and randomized 2:1 (LAN plus BSC: placebo plus BSC).

** cytotoxic chemotherapy or molecular targeted therapy or interferon*

3.1.1 Double-Blind Phase

3.1.1.1 Screening Visit

Screening occured within 28 days prior to randomization (between Day -28 and Day -1.) The screening assessment could serve as the baseline assessment if performed within 3 days (72 hours) before randomization. The purpose of the Screening Period was to obtain informed consent and to establish protocol eligibility. Informed consent was obtained after the study had been fully explained to each subject and prior to the conduct of any screening procedures or assessments.

3.1.1.2 Baseline Visit

The Baseline Assessments were performed on Day 1 prior to randomization. Subjects who completed the Baseline Assessments and continued to meet the criteria for inclusion/exclusion criteria (Section 4.1 and Section 4.2) began the treatment of the DB Phase.

3.1.1.3 Randomization and Treatment Period

Subjects were randomized 2:1 to receive either LAN 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 or interferon*

Subjects underwent safety and efficacy assessment as defined in Table 2.

The DB Phase will end with Protocol Amendment #5 and will be followed by the OL Treatment Period.

Before approval of Protocol Amendment #5:

If a subject progresses during the DB phase, the subject will be proposed to enter the OL Extension phase:

- If the subject was on placebo and progressed during the DB phase, the subject will be 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 will enter the follow-up period of the OL extension phase and be followed for QoL/survival and all subsequent anticancer treatments received will be recorded.

The OL Treatment Period will stop once all subjects will have centrally progressed or 18 months after the last subject randomised (i.e. end of study).

After approval of Protocol Amendment #5:

- All ongoing subjects in the DB Phase, who have not yet progressed, 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 randomised.
- If a subject progresses during the DB phase, the subject will enter the OL follow-up period
- If a subject progresses during the OL Treatment Period, the subject will 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 randomised).

3.1.2 Open Label Extension Phase

The OL Extension Phase will consist of:

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

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

Before approval of Protocol Amendment #5, subjects will qualify for optional OL LAN plus BSC if they meet the following additional inclusion criteria:

(14) Subjects have central review confirmed/documented disease progression according to RECIST 1.1

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

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

The following inclusion criteria 9-11 and exclusion criteria 6, 9-15, 17-22 listed in Section 4.1 and Section 4.2 must continue to be satisfied.

After approval of Protocol Amendment #5, all ongoing subjects in the DB Phase who have not yet progressed (assessed locally and confirmed centrally), 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 randomised.

Please refer to Section 5.2.3 for more details.

Subjects who qualify to receive OL LAN plus BSC will receive LAN plus BSC via deep s.c. injection every 4 weeks (28 days) until documentation of disease progression (local review confirmed by the central review via RECIST 1.1) within the Extension Phase, development of intolerable toxicity, appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of any SSA (short acting and/or long acting release SSA), subject noncompliance with required safety and efficacy assessments, subject voluntary discontinuation, study termination by sponsor except those subjects who will continue in the study, or up to 18 months after the last subject randomised.

Subjects who discontinue OL LAN plus BSC during the Treatment Period of the Extension Phase will perform the Post Treatment/Early Withdrawal visit assessments as detailed in Table 4 and will enter the Follow-up period (except in case of consent withdrawal) for assessment of QoL and survival and all subsequent anticancer treatments received will be recorded up to the end of the study.

3.1.2.2 Follow-up Period of the Open Label Extension Phase

Subjects who experience disease progression during the DB Phase and do not enter or qualify for the optional OL Extension Treatment Period Phase will enter the Follow-up Period of the Extension Phase after completing the Post Treatment/Early Withdrawal Visit assessments listed in Table 2 and Table 5.

Subjects who have entered the optional OL LAN plus BSC Treatment Period of the Extension Phase and have progressed or subsequently discontinued OL LAN plus BSC administration will enter the Follow-up Period after completing the Post Treatment/Early Withdrawal Visit assessments listed in Table 4.

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

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 18 months after the last subject randomised.

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Endpoint

Progression-free survival (PFS) for subjects randomized in LAN group, assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes in either the double blind phase, or in the open label period.

3.2.2 Secondary Endpoints

- Progression-free survival (PFS), assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase.
- Progression-free survival (PFS), assessed by local review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase.
- ORR: objective response rate of CR or PR measured by RECIST v1.1 criteria every 12 weeks until the Post Treatment/Early Withdrawal Visit during the double-blind phase,
- Time to treatment failure during the double-blind 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 LAR SSA), or initiation of anticancer treatment,
- 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,
- 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 double-blind and the OL treatment phases,
- Change in QoL, as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (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,
- Time to QoL deterioration, defined by a decrease from baseline in EORTC QLQ-C30 score of at least 10 points during the double-blind, the OL treatment and the follow-up phases,
- Mean changes from Baseline in urinary 5-HIAA levels at Week 8, and 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.

3.2.3 Safety Endpoints

Safety and tolerability assessments throughout the study:

- Adverse events (AEs) grouped by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term, and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03,
- Clinical evaluations (medical and surgical history and physical evaluations, including biochemistry/hematology, ECG, CCI [redacted]),

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

CCI [redacted]

CCI [redacted]

3.3 Randomization and Blinding

The Ipsen Randomization manager who is a statistician independent from the study prepared two lists, which were performed in blocks and were based on computer-generated randomizations lists:

- List A: a list of randomization numbers stratified by 1) tumour subtype (typical versus atypical) and 2) prior chemotherapy* vs no prior chemotherapy* at baseline and generated with a 2:1 ratio LAN plus BSC: Placebo plus BSC.
- List B: a list of treatment numbers, which are specified on the treatment packs to be dispatched to the sites in order to dispense drug. This list was generated with a 2:1 ratio LAN plus BSC: Placebo plus BSC.

** cytotoxic chemotherapy or molecular targeted therapy or interferon*

The randomization, as well as the treatment numbers assignations at each drug dispensation, was managed by an Interactive Web response System (IWRS).

After eligibility was confirmed, subjects were randomized at baseline (Day 1), and were assigned to a randomization number and to the associated treatment arm, in sequential order within each study center and within each stratum.

Subjects meeting the randomization criteria were assigned to a randomization number and were allocated to the associated treatment arm, by the IWRS. An appropriate treatment number was allocated and will continue to be allocated by the IWRS at each drug dispensation, according to the allocated treatment group. The IWRS managed and continue to manage logistical aspects of treatment (e.g. drug supplies replacement of lost, damaged, quarantined, expiring and expired kits).

IWRS will continue to provide Investigators, site coordinators and project team members with a 24-hour per day, 7 day per week service, the details of which may be found in the IWRS reference manual). In case of medical or technical randomization or dispensation queries, a 24-hr helpline will continue to be available (see supporting information in the Investigator Site File).

The investigator under no circumstances changed (or will change) the Randomization number, the treatment numbers and the treatment arm allocated to the subject.

Recruitment was prematurely stopped and 77 subjects were randomized. Randomised subjects who terminated their study participation for any reason before starting the treatment retained their Randomization and treatment numbers (the treatment number was not [and will not be] reused). The next subject was given the next Randomization number and another treatment number even if they received the same treatment. Randomized subjects who left (or will leave) the study early were not (or will not be) replaced.

The sponsor's Randomization manager will continue to keep the master lists. A copy of the list of treatment numbers (list B) was confidentially supplied to the Chemistry Manufacturing and Control Supply Chain (CMC-SC; [redacted]) CE supply chain department in charge of study drug packaging, to the CRO in charge of IWRS. Similarly, a copy of the list of Randomization numbers (list A) was also confidentially supplied to the CRO in charge of IWRS. The master lists and the copies supplied to the CMCE supply chain department in charge of study drug packaging, to the CRO in charge of IWRS will continue to be kept confidential in a secure location. Access to the Randomization lists will continue to be restricted until authorisation is given to release them for final analysis.

3.4 Study Treatments and Dosage

The test product, Lanreotide Autogel/Depot 120 mg and placebo will be administered via deep subcutaneous injection, every 28 days until signs of tumour progression (assessed locally and centrally confirmed), development of unacceptable toxicity or withdrawal for any reason.

A more detailed description of administration procedures is given in Section 6.

The study drug will be packaged by Creapharm [[redacted]] and delivered to the interim storage facility (ISF) in the United States and directly to each investigational site in European countries. The ISF will send treatment kits to each investigational site in US and Canada.

A sufficient quantity of study drug will be supplied, as well as, an acknowledgement of receipt form.

The sponsor's representative will receive a Certificate of Analysis for which batch of study drug has been used under their study, Certificate of Compliance, Material Safety Data Sheet for study drug, which reflect the product release statement.

The core label texts for all packaging units will be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. A description of the core text of the study drug labels is displayed below:

- Name, address and telephone # of sponsor
- Study Number,
- Trial reference code,
- Product Name,
- Pharmaceutical dosage form,
- Route of administration,
- Quantity of dose units,
- Batch number,
- Treatment number,
- Randomization number/Blank space for subject number (this information will be completed by the investigator),
- "Caution: new drug limited by Federal Law to investigational use" for US only,
- 'For Clinical study use only',
- Storage Conditions,
- Expiry date.

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

Study treatment will be administered deep s.c. at the study center by an independent non-blinded representative designated by the Investigator. Drug accountability records will be maintained by the Investigator, documenting that subject received allocated drug.

3.5 Study Duration

This study will consist of a screening period of a maximum of 28 days, followed by a DB period and an OL extension. Subjects are expected to participate in the DB phase of the study until disease progression (assessed locally and confirmed centrally), death from any causes, premature withdrawal whatever the reason or up to approval of Protocol Amendment #5.

The subject's participation in the study will be considered to have ended at the time of their last study visit or death.

The overall duration of the study will be approximately 4 years (25 month duration of recruitment, approximately 36 month duration of DB treatment and an OL Extension Phase

which will end 18 months after the last subject randomised). The study will be considered to have started when the first subject has provided signed informed consent.

The study will be considered to have ended after the last subject has completed their last visit in the study, which will occur at the latest 18 months after the last subject randomised

The DB Phase of the study will end once protocol amendment #5 has been approved in all the countries and all subjects entered the OL Extension periods. All ongoing subjects in the DB Phase, who have not yet progressed, 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 randomised. If a subject progresses during the OL Treatment Period, the subject will enter the OL follow-up period. The follow-up period of the OL extension phase and the OL Treatment Phase will last up to 18 months after the last subject randomised.

3.6 Stopping Rules and Discontinuation Criteria

A subject may decide to discontinue participation in the study at any time for any reason (e.g. withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g. protocol violation or deviation as defined in Section 12.1.2, noncompliance with the protocol conditions or AE). In addition, a subject may be withdrawn from the study as described in Sections 4.3 and 8.1.7

During the conduct of the study, study drug can be temporarily discontinued (see Section 8.1.7).

Any change in the administration of study drug or its discontinuation will be documented in the eCRF.

During the conduct of the study, SAEs will be reviewed (see Section 8.1.4) as they are reported from the study centre to identify safety concerns. The study may be terminated by the sponsor at any time.

3.7 Early Study Termination

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

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

Due to the recruitment stop, all enrolled subjects will be followed up to disease progression or up to 18 months after the last subject randomised.

At the end of the OL Extension Treatment period, if subjects are still benefiting from treatment (i.e. not progressing) and there is sufficient evidence of the safety and efficacy of it, the subjects will have the option, to continue to receive lanreotide 120 mg every 28 days up to disease progression or unacceptable toxicity. In such a situation, as permitted by local

regulations, lanreotide 120 mg 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.

3.8 Study Drug Preparation Storage and Accountability

3.8.1 Study Drug Storage and Security

In order to maintain the blinded conditions of the study the investigator must assign an independent non-blinded representative (e.g. pharmacist), who will ensure that all study drug and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions (between +2°C and +8°C), in accordance with applicable regulatory requirements.

3.8.2 Study Drug Preparation and Accountability

The non-blinded qualified person will ensure that all study drugs are dispensed by qualified staff members.

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

Drug accountability will be performed by an unblinded monitor from the Sponsor of its representative. The unblinded monitor will ensure that study drug administration, study drug dispensing/accountability logs and the number of used/non used treatments are consistent.

Study drug will be destroyed preferably on site or returned to CMC-SC ([redacted]).

The destruction of used and unused study drugs should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted.

3.9 Maintenance of Randomization and blinding

All of the boxes of study treatments will be identical in appearance but the content of boxes will be different to each other. In addition, since LAN and placebo are not similar in appearance, an independent qualified person appointed by the investigator will be required to prepare and inject the study drug, allowing the blinded conditions of the study to be maintained. These unblinded individuals will be fully trained in the method of blinding for the subject, the investigator and the remainder of the project team and must not be involved in any of clinical or safety assessments.

In an emergency situation, which requires the identification of the study treatment group, the Investigator may break the treatment code immediately, or as quickly as possible if he/she finds it is in the best interest of the trial subject. The investigators have direct and immediate access to break the treatment code through the IWRS. At the earliest opportunity the

investigator is requested to inform the blinded monitor in charge of his/her centre that the blind has been broken for an emergency.

In addition, a set of hard copy sealed code break envelopes will be held by Global Patient Safety at Ipsen, in case of IWRS failure (this set will be prepared by Ipsen Randomization manager).

If the code-break was performed using the IWRS, the investigator must store the email notification revealing the unblinded treatment in a sealed envelope. The investigator will then sign, date and provide the reason for the code break on the emergency code break form, and on the sealed envelope. The date and reason for identifying the treatment group will be recorded in the eCRF.

The study treatment will be administered in double-blind fashion. Neither subjects nor staff site personnel in charge of the clinical and safety evaluations will know who is receiving placebo plus BSC or LAN plus BSC. If progression is confirmed by the central assessment, and the subject agrees to enter the OL Extension then the investigator will ask the IWRS whether the subject is eligible to enter the OL Treatment Extension Period.

- Subject assigned to **placebo plus BSC**: will be allowed to enter the OL Extension Treatment Period to receive OL LAN plus BSC
- Subject assigned to **LAN plus BSC**: will stop study treatment and attend the Post Treatment Visit and subsequently enter the Follow-Up Period of the Extension Phase

At time of Protocol Amendment #5, all subjects who are still treated in the DB Phase and who have not yet progressed will be moved to the OL Treatment Period without any unblinding.

3.10 Source Data Recorded on the Case Report Form

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

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

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

Definition for source data and source documents are given below:

- Source Data: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

- Source Documents: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

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

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion criteria

(1) Provision of written informed consent prior to any study related procedures,

(2) Subjects aged ≥ 18 years,

(3) Have metastasic and/or unresectable pathologically confirmed well-differentiated, typical or atypical neuroendocrine tumour of the lung,

(4) Histologic evidence of well differentiated NETs of the lung (typical and atypical according to the WHO criteria evaluated locally),

(5) Has a mitotic index < 2 mitoses/2 mm^2 for typical carcinoid (TC) and ≤ 10 mitoses/2 mm^2 and/or foci of necrosis for atypical carcinoid (AC),

(6) At least one measurable lesion of the disease on imaging (CT or MRI; RECIST v1.1),

(7) Positive somatostatin receptor imaging (SRI) (Octreoscan® ≥ grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background),

(8) ECOG performance status 0-1,

(9) Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required,

(10) Female subjects who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry,

(11) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use an effective method of contraception (see above). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration,

(12) Signed HIPAA authorization where required,

(13) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the study site for the follow-up evaluation as specified in the protocol.

4.2 Exclusion Criteria

(1) Poorly differentiated or high grade carcinoma, or neuroendocrine tumours not of lung origin,

(2) Subjects with multiple endocrine neoplasia type 1 (MEN 1),

(3) Has been treated with an SSA at any time prior to randomization, except if that treatment was for less than 15 days (e.g. peri-operatively) of short acting SSA or one dose of long acting SSA and the treatment was received more than 6 weeks prior to randomization,

(4) Has been treated with Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization,

(5) Has been treated for lung NET with chemotherapy* within 4 weeks of randomization (whatever the number of cycles),

(6) Has been treated with more than two lines of chemotherapy * for lung NET,

(* *cytotoxic chemotherapy or molecular targeted therapy or interferon*)

(7) Treated with surgery within 6 weeks prior to randomization,

(8) Previous local therapy (e.g. chemo-embolization, bland, or radio-embolization) is allowed if completed > 6 weeks prior to randomization. For subjects who received local therapy prior to randomization, there must be documented growth of measurable disease within the embolization field prior to study,

(9) Symptomatic subjects requiring SSA for symptom management (please also note the exclusion criteria No. 3),

(10) Subjects with known ectopic production of adrenocorticotropic hormone (ACTH) or other hormonal secreting subjects allowed ONLY if symptoms adequately controlled without SSAs,

(11) Subjects on concomitant Growth Hormone (GH) antagonist, cyclosporine or bromocriptine

(12) Inadequate bone marrow function as per investigator's judgement,

(13) Severe renal insufficiency as defined by a calculated creatinine clearance <30 mL/min,

(14) Total bilirubin >2 x ULN, AST, ALT or Alk Ph >5xULN, lipase, amylase >2xULN,

(15) Serum albumin <3.0 g/dL unless prothrombin time is within the normal range,

(16) Known hypersensitivity to the study drug,

(17) Present cholecystitis,

(18) Uncontrolled congestive heart failure

(19) Glycosylated hemoglobin (HbA1c) > 8.5%,

(20) Abnormal findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, would compromise the subject's safety or the outcome of the study,

(21) Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years,

(22) Pregnant or lactating women or those of childbearing potential age and not practicing a medically acceptable method for birth control,

(23) Subjects who have participated in any therapeutic clinical study/received any investigational agent within 30 days of randomization.

(24) Clinically significant cardiac arrhythmia, bradycardia, tachycardia that would compromise patient safety or the outcome of the study

(25) Uncontrolled hypothyroidism

4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or according to the investigator's clinical judgement.

All subjects will be asked to return to the sites for discontinuation or off-treatment assessments, if possible. If a subject fails to appear for a scheduled study visit, the investigator will make every attempt to contact the subject and determine the reason(s) for the missed visit as completely and accurately as possible. Subjects will only be judged as lost to follow-up if they cannot be reached following 3 documented attempts by the site to contact them (1 week apart).

Subjects will also be withdrawn from the study treatment should any of the following occur:

- 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 serious adverse event (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 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 (LAR) SSA).
- Appearance of biological and/or clinical symptoms for Gallbladder inflammation confirmed by an echography
- Pregnancy (see Section 8.1.5)
- Deviations from protocol
- Investigator's discretion

Subjects will also be withdrawn from the study should any of the following occur:

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

Should a subject decide to withdraw from the study after administration of study drug, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

During the conduct of the study, study drug can be temporarily discontinued (see Section 8.1.7).

Subjects will be considered for crossover to OL LAN after local documented progression has been confirmed centrally per RECIST 1.1. Progression will be assessed in-stream by an independent review, prior to crossover. Crossover is optional for subjects and at the discretion of the investigator.

The subject will enter the Follow-up Period of the Extension Phase (Section 3.1.2.2) after completing the Post Treatment Visit assessments as listed in Table 2 and be followed for survival and QoL **unless the subject withdraws consent**. If a subject withdraws consent, the

date will be documented in the source documents. Subjects who discontinue study treatment for reasons other than disease progression locally assessed and confirmed centrally will not be eligible to receive OL LAN but are eligible to enter the Follow-up Extension Period (Table 5).

All subjects will be followed for QoL, survival and all subsequent cancer treatments administered will be recorded until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up before the 18 month OL Extension Treatment and Follow-up Phases.

The Post Treatment Visit in the Double Blind Phase or OL Treatment Period should be performed within 30 days after the subject has received the last study drug injection.

Where the subject has withdrawn due to an AE the investigator should follow the procedures documented in Section 8.1.2 in order to assess the safety of the study drug.

The reason for and date of withdrawal from the study must be recorded on the eCRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality and the subject has not yet progressed on study treatment:

(1) the subject will be monitored for the given abnormality according to local standard of practice until event has resolved, or 30 days after the final administration of the study drug administration whichever occurs first.
(2) the subject should also continue to be assessed according to Table 5 (OL Extension Follow-up Period).

CCI [redacted]

5 STUDY PROCEDURES

5.1 Study Schedule for the DB phase

Table 2 presents the Schedule of Visits and Procedures for the DB Phase of this study.

Table 2 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 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 [redacted]																
[redacted] CCI	CCI [redacted]															
AEs/SAEs[q]	THROUGHOUT THE STUDY															
Prior and concomitant medications	THROUGHOUT THE STUDY															
Prior and concomitant non drug therapies	THROUGHOUT THE STUDY															
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 tumour; NYHA=New York Heart Association; OL=Open label; PET=positron emission tomography; CCI [redacted] QoL=Quality of Life; RECIST=Response Evaluation Criteria in Solid Tumours; SAE=serious adverse event; CCI [redacted] SPECT=single photon emission computed tomography; SRI= somatostatin receptor imaging; TNM=tumour-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 classification 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 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 tumour, 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, tumour assessments (by RECIST 1.1) 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 [23].
C [redacted]
CI
(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 e-CRF.

During the DB Phase and the OL Treatment phase, the volume of blood drawn for all haematology, serum chemistry, biomarkers CCI evaluations is around 16 mL. A further 16 mL will be taken at each subsequent study visit throughout the study.

CCI

CCI

CCI

The approximate total amount of blood to be collected from each subject is presented in Table 3.

Table 3 Blood Volume Calculation

Description	Approximate Volume (mL) per visit *(DB Phase + OL treatment Extension Phase)*
Haematology [a]	3 (EDTA tube) + (3 (SC tube) at Screening)
Serum chemistry [a]	5 (SST)
Biomarkers (CgA) [a]	5 (SST)
CCI	
Serum	5 (SST)
CCI	
Total volume (mL)	43.5 [b]

5-HIAA=5-hydroxyindoleacetic acid; CgA=chromogranin A; CCI EDTA=ethylenediamine tetraacetic acid; CCI SST=serum separator tube.

a additional samples will be taken every 12 weeks (±3 days) for subjects continuing to attend study visits after the 72 week treatment period.

b please note that not all samples are taken at every visit, therefore the subject does not always have 43.5 mL taken each time (eg CCI coagulations parameters at Screening)

5.2 Study Visits

5.2.1 Pre-Randomization

5.2.1.1 Screening Period Procedures

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial were explained to all subject candidates and written informed consent was obtained. CCI [redacted] Evaluations obtained as part of routine medical care and performed during the screening period might be used in place of the study specific evaluations. Subjects acknowledged and agreed to the possible use of this information for the study by giving informed consent.

After informed consent was obtained, subjects who were screened were allocated a subject number. All screened subjects had to be identifiable throughout the study. The investigator maintained a list of subject numbers and names to enable records to be found at a later date if required.

The screening visit took place between Day 28 and Day -1 of the study; if the screening assessments took place within 3 days (72 hours) of Day 1, the results could be accepted as Baseline values. The following screening assessments were performed: (Please see footnotes under Table 2 for details).

- Written informed consent (must be obtained before any screening assessments are performed)
- Verify inclusion/exclusion criteria as listed in Sections 4.1 and 4.2:
- Demographics data (year of birth, age, ethnicity and race (as per local regulations) and sex)
- Prior surgery, radiotherapy, chemotherapy and medications related to lung NETs
- Medical and surgical history, including ongoing medical history
- Disease history/diagnosis (mitotic count and foci of necrosis, KI67 value if available, tumour-node-metastasis (TNM) staging, location of primary tumour, number of metastatic organs, presence/absence of hormone related syndrome)
- Clinical evaluation (including physical examination and vital signs)
- ECOG status CCI [redacted]
- NYHA classification CCI [redacted] and ECG
- Hematology & Biochemistry
- Pregnancy test
  - Female subject of childbearing potential should have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
  - Female subject who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study

and for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry,

- CT scans/MRIs performed within 12 months of baseline collected if available (sent for analysis by central review as part of an ancillary study) - Refer to Section 5.2.1.2 for more details.
- SRI, if not available within the previous 6 months (Octreoscan® ≥ grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background),
- Gallbladder echography if biological and/or clinical symptoms of inflammation are present. If the gallbladder inflammation is confirmed, the subject failed the screening evaluation and should be excluded
- Start collection of AE's/SAE's
- Prior and concomitant medications/therapies (see Section 6.2)
- Prior and concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

Each investigator also maintained a record of all subjects screened into the study (i.e. who signed the informed consent form). Records up to the time of premature termination should have been completed. In the event that the subject was not receiving the study drug, the primary reason was recorded.

5.2.1.2 Baseline assessments and procedures on Day 1

The results of all screening assessments and evaluations had to be completed and reviewed by the investigator prior to the Baseline Visit. Baseline assessments should have been performed on Day1 prior to study treatment injection; however, screening assessment values could be used as Baseline values if done within 72 hours of Day1.

Only those subjects who continued to meet all of the inclusion and none of the exclusion criteria on Day1 were eligible to continue in the study.

At the Baseline Visit, the following evaluations were conducted, prior to the administration of study treatments:

- Verify inclusion/exclusion criteria
- QoL (EORTC QLQ-C30) CCI [redacted]
- Clinical evaluation
- ECOG status CCI [redacted]
- Hematology & Biochemistry
- Pregnancy test
  - Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study

medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

- Female subjects who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry,

- CgA and urinary 5-HIAA for all subjects
- CT scan or MRI:
  - Perform CT scan of thorax and abdomen, OR MRI of the abdomen with CT scan of the thorax
  - If available, collect CT scans/MRIs performed within 12 months of Baseline (for analysis as part of an ancillary study)
- Baseline value of hepatic and intrathoracic tumour load will be measured by the Central Reading CRO
- Gallbladder echography, if biological and/or clinical symptoms of inflammation are present
- CCI
- CCI
- CCI
- AE's/SAE's
- Concomitant medications
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET
- Randomization

Following confirmation of eligibility for the study, subjects were given a Randomization/treatment allocation number and allocated to either LAN plus BSC or placebo plus BSC (See Section 6.1). Administration of DB study treatment commenced at Baseline Visit following completion of the Baseline assessments. DB study treatment was administered every 28 days until centrally confirmed disease progression, development of unacceptable toxicity, premature withdrawal for any reason or up to approval of Protocol Amendment #5.

5.2.2 Double Blind Phase Assessments and Procedures

Efforts should have been made to conduct study visits at Week 8, Week 12 and then every 12 weeks, on the day scheduled (± 3 days). Clinical laboratory assessments might be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures. Whenever possible, subjects should have been evaluated at approximately the same time of the day (e.g., morning or afternoon) at each visit, and reasonable efforts should have been made to conduct all evaluations in the same test order at each visit and before the study drug injection.

Following the first dose at Baseline Visit, LAN/placebo will be administered every 28 days until centrally confirmed disease progression, development of unacceptable toxicity withdrawal for any reason or up to 18 months after the last subject randomised. The initial planned treatment period is estimated to last 72 weeks; however, after this time, if disease progression as assessed centrally or death from any causes have not occurred, subjects may continue to receive study drug in a double-blind fashion every 28 days until disease progression, development of unacceptable toxicity, withdrawal for any reason, or up to 18 months after the last subject randomised.

'Injection only' visits will not be considered as study visits; however, the date and time of injection will be recorded in the eCRF. Any AEs reported at these visits will also be recorded on the eCRF, reported to the sponsor (if an SAE), and followed up as appropriate by the responsible investigational site staff.

The following procedures will be performed every 12 weeks (or earlier if clinically indicated) and at the Post Treatment/Early Withdrawal Visit:

- QoL (EORTC QLQ-C30) CCI [redacted]
- ECOG status CCI [redacted]
- Hematology & Biochemistry
- Tumour response assessment by CT scan or MRI
- AE's/SAE's
- Concomitant medications/therapies
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

The following procedures will be performed according to the schedule in Table 2:

- Clinical evaluation at Week 8, Week 12 and every 12 weeks thereafter
- CgA will be measured for all subjects at Week 8, Week 12 and every 12 weeks thereafter.
- Urinary 5-HIAA will be measured at Week 8, Week 12 and every 12 weeks thereafter only for subjects with elevated urinary 5-HIAA (≥2 x ULN) at the Baseline Visit.
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- ECG and NYHA classification (at Week 24, Week 48 and then every 24 weeks)
- Gallbladder echography will be performed during the DB Study treatment period and at the Post Treatment/Early Withdrawal Visit, only if biological and/or clinical inflammatory symptoms appear.

5.2.2.1 Post Treatment Visit Assessments and Procedures

The following assessments should be performed at the Post Treatment/Early Withdrawal Visit, within 30 days after subjects have discontinued study treatment for any reason (including premature withdrawal please refer to Section 4.3):

- QoL (EORTC QLQ-C30)
- Clinical evaluation
- ECOG status,
- NYHA classification and ECG
- Hematology & Biochemistry
- Pregnancy test (urine; if positive with urine, confirm with serum)
- CgA
- Urinary 5-HIAA (only for subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline Visit)
- CT scan of the thorax and abdomen, OR MRI of the abdomen with a CT scan of the thorax
- Gallbladder echography if biological and/or clinical symptoms of inflammation are present
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- AE's/SAE's
- Concomitant medications
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

5.2.2.2 Post Treatment Visit Procedures for Subjects Not Receiving or Do Not Qualify for Open Label Lanreotide Autogel/Depot

For subjects who have discontinued study drug prior to disease progression, tumour assessment should be performed at the Post Treatment/Early Withdrawal Visit if not performed within the 4 previous weeks (Table 2) or sooner if clinically indicated until documentation of disease progression or start of another anticancer therapy.

The Post Treatment/Early Withdrawal Visit should be then performed within 30 days after the last study treatment injection, at which time subjects will enter the Follow-up Period of the OL Extension Phase.

Subjects who withdraw their consent will be asked to perform the Post Treatment/Early withdrawal Visit but will not enter the Extension Phase of the study, whatever the treatment or the Follow-up Periods.

The Post Treatment/Early Withdrawal Visit assessments in the DB Phase can be accepted as Baseline for the OL Extension Phase.

Before approval of Protocol Amendment #5, subjects who do not choose to receive or qualify for OL LAN plus BSC (those who were on LAN plus BSC during the DB phase) will enter the OL Extension Follow-up Period.

5.2.2.3 Post Treatment Visit Procedures for Subjects Receiving Open Label Lanreotide Autogel/Depot plus BSC (Extension Phase OL Lanreotide Autogel/Depot plus BSC Treatment Period)

Before approval of Protocol Amendment #5, subjects with locally documented and centrally confirmed disease progression and who were randomized in the placebo arm could choose to receive OL LAN. They will enter the OL Treatment Extension Period.

The OL Extension Phase is optional and subjects who qualify for OL LAN and choose to progress into this phase of the study will be assessed according to the procedures listed in Table 4.

For subjects treated with placebo plus BSC with confirmed and documented disease progression and who choose to receive and qualify for OL LAN,

- Establish new baseline tumour assessments (selection of target and non-target lesions) based upon scans taken that showed evidence of disease progression, or on new scans performed before beginning OL LAN.
- Assessments should be performed every 12 weeks according to Table 4.

All subjects who enter the OL Extension Phase must first complete the Post Treatment/Early Withdrawal Visit of the DB Phase within 30 days of the last study drug injection. The assessments from this visit can be accepted as Baseline for the OL Extension Phase if both visits are performed the same day.

After approval of Protocol Amendment #5, all ongoing subjects in DB Phase, who have not yet progressed, will enter the OL Treatment Period.

5.2.3 Open Label Extension Phase Assessments and Procedures

Table 4 presents the Schedule of Visits and Procedures for the Optional OL Extension Phase of the study.

Table 4 Schedule of Visits and Procedures in Open Label Treatment Extension 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 SYMPTOMS			
QoL (EORTC QLQ-C30)	X		X	X
LAN Injection Every 28 days	X	X	X	
CCI	CCI			
CCI	CCI			
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 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 tumour; NYHA=New York Heart Association; OL=Open label; PET=positron emission tomography; CCI QoL=Quality of Life; RECIST=Response Evaluation Criteria in Solid Tumours; SAE=serious adverse event; CCI

(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 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 (≥2xULN) 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),** 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
CI

C
CI

(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)

5.2.3.1 Open Label Extension Treatment Phase Baseline Procedures

Open label Extension Baseline assessments can be performed either on Day 1 of the OL Extension Treatment Phase prior to treatment, or value from the Post Treatment/Early Withdrawal Visit in the DB Phase can serve as the OL Extension Baseline values for the OL Extension Treatment Phase.

Before approval of Protocol Amendment #5, subjects were qualified for optional OL LAN plus BSC if they met the following additional inclusion criteria:

(14) Subjects have documented disease progression confirmed centrally 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

The following inclusion criteria 9-11 and exclusion criteria 6, 9-15, 17-22 listed in Section 4.1 and Section 4.2 must continue to be satisfied.

After approval of Protocol Amendment #5, subjects will be offered the option to move to the OL Treatment Period. The subjects will receive an addendum to Informed Consent Form (ICF) which details in study rationale and explanations about the conduct of the study end. If the subjects agree to continue to participate to this study this addendum to ICF will have to be signed.

At the OL Extension Baseline Visit, the following evaluations will be conducted:

- Reconfirm inclusion/exclusion criteria 9-11 and 6, 9-15, 17-22 eligibility criteria
- QoL (EORTC QLQ-C30)
- Clinical Evaluation (Physical Examination and vital signs)
- ECOG status
- NYHA classification and ECG
- Hematology & biochemistry
- Pregnancy test
  - Female subject of childbearing potential should have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
  - Female subject who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry,

- CgA will be measured for all the subjects at the OL Extension Baseline.
- Urinary 5-HIAA will be measured only for subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline of the DB Phase.
- CT/MRI (using the same mode as per baseline, utilizing RECIST 1.1); to be read locally by the same person to avoid bias); establish new baseline tumour assessments (selection of target and non-target lesions) based upon scans taken that showed evidence of disease progression according to central review, or on new scans performed before beginning OL LAN
- Gallbladder echography if biological and/or clinical symptoms of inflammation are present
- CCI [redacted]
- AE's/SAE's
- Concomitant medications
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET
- CCI [redacted]

5.2.3.2 Open Label Extension Treatment Phase Assessments and Procedures

The OL Extension Treatment Phase Visit assessments should be performed according to Table 4:

- QoL (EORTC QLQ-C30)
- Clinical Evaluation
- ECOG status,
- NYHA classification and ECG (every 6 months)
- Hematology and biochemistry
- CgA will be measured for all the subjects at OL Extension Baseline, and every 12 weeks thereafter and at the Post Treatment/Early Withdrawal Visit.
- Urinary 5-HIAA will be measured at the OL Extension Baseline 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 the OL Extension Baseline Visit, or if clinically indicated.
- CT/MRI: CT scan of thorax and abdomen, OR MRI of the abdomen with CT scan of the thorax
- Gallbladder echography if biological and/or clinical symptoms of inflammation are present
- CCI [redacted]
- CCI [redacted]
- AE's/SAE's reporting for the treatment part of this period only

- Concomitant medications
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

5.2.3.3 Post Treatment/Early Withdrawal Visit Procedures of OL Extension Treatment Phase

All subjects will be asked to return to the sites for discontinuation or off-treatment assessments, if possible. If a subject fails to appear for a scheduled study visit, the investigator will make every attempt to contact the subject and determine the reason(s) for the missed visit as completely and accurately as possible. Subjects will only be judged as lost to follow-up if they cannot be reached following three documented attempts by the site to contact them (1 week apart).

The Post Treatment/Early Withdrawal Visit assessments in the OL Extension Treatment Phase should be performed within 30 days after subjects have discontinued study treatment for any reason:

- QoL (EORTC QLQ-C30)
- Clinical Evaluation
- ECOG status
- NYHA classification and ECG
- Hematology and biochemistry
- Pregnancy test
  - Female subject of childbearing potential should have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
  - Female subject who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry
- CgA
- Urinary 5-HIAA (only for subjects with elevated urinary 5-HIAA (≥2 x ULN) at the OL Extension Baseline Visit)
- CT/MRI: CT scan of the thorax and abdomen, OR MRI of the abdomen with a CT scan of the thorax
- Gallbladder echography if biological and/or clinical symptoms of inflammation are present
- CCI [redacted]
- CCI [redacted]

- AE's/SAE's
- Concomitant medications
- Concomitant non drug therapies
- Concomitant surgical procedures
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

At the end of the OL Extension Treatment period, if subjects are still benefiting from treatment (i.e. not progressing) and there is sufficient evidence of the safety and efficacy of it, the subjects will have the option, to continue to receive lanreotide 120 mg every 28 days up to disease progression or unacceptable toxicity. In such a situation, if authorized by local regulations, lanreotide 120 mg 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.

5.2.3.4 Open Label Extension Follow-Up Phase Baseline Procedures

After study drug discontinuation, subjects will be followed for survival, QoL and all subsequent anticancer treatments during the OL Extension Follow-up Phase (Table 5). Survival data and other cancer treatments received will be collected every 12 weeks. The sponsor may elect to discontinue survival follow-up during the Extension Phase before the 18-month period.

Table 5 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 [23].

At the OL Extension Follow-up Baseline Visit, the following evaluations will be conducted:

- QoL (EORTC QLQ-C30)
- Clinical evaluation
- Survival status form

- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

5.2.3.5 Open Label Extension Follow-Up Phase and Post-Extension Follow-up Phase Visit Procedures

At the OL Extension Follow-up Visits and at the Post-Extension Follow-up Phase/Early Withdrawal Visit, the following evaluations will be conducted:

- QoL (EORTC QLQ-C30)
- Clinical evaluation
- Survival status form
- Concomitant medication/chemotherapy/molecular targeted therapy related to lung NET

6 TREATMENT OF SUBJECTS

6.1 Study drugs Administered

At Screening, subjects were allocated a subject number. Following confirmation of eligibility for the study, subjects were allocated to one of the following treatment groups:

- LAN, deep subcutaneous, every 28 days plus BSC

or

- Placebo, deep subcutaneous, every 28 days plus BSC

Subjects will receive injections of the study drug to which they are allocated by deep subcutaneous injection (in the superior external quadrant of the buttock) every 28 days thereafter. The first injection was administered during the baseline visit after randomization.

Subjects will receive study drug according to this schedule until locally documented and centrally confirmed disease progression, development of unacceptable toxicity, withdrawal for any reason or up to 18 months after the last subject randomised.

Because LAN and the placebo were not similar in colour and appearance, an independent qualified and unblinded person appointed by the investigator prepared and administered the injections, in order to maintain the blinded conditions of the study. All study drugs were administered at the study centres by these qualified persons. 'Injection only' visits were not considered as study visits; however, the date and time of injection were recorded in the eCRF.

There will be no dose modification as LAN administered at 120mg is well-tolerated, effective and has a safe AE profile. Based on our experience in subjects with Acromegaly, and in subjects with NETs in the CLARINET study, we do not anticipate toxicities that would require either discontinuation or dose modification (for more details, see Sections 6.2 and 8.1.7).

It is forbidden to use study drug for purposes other than as defined in this protocol.

6.1.1 Lanreotide Autogel/Depot

Lanreotide Autogel/Depot 120 mg will be administered by deep s.c. injection in the superior, external quadrant of the buttock at a dose of 120 mg, every 28 days.

Lanreotide Autogel/Depot 120 mg is a prolonged release, pharmaceutical form of lanreotide. It is a mixture of lanreotide acetate (0.246 mg/mg of product) and water (0.754 mg/mg of product) and is provided in a 0.5 mL prefilled syringe fitted with a 2 cm needle of 1.2 mm external diameter and an automatic safety system, sealed in a laminated bag.

It will be provided by the Sponsor (CMC SC (CMC Supply Chain), CCI [redacted]).

Lanreotide Autogel/Depot 120 mg will be stored at the recommended temperature (between +2°C and +8°C).

The procedures for drug administration are provided in the drug instructions leaflet and in the Study Manual.

6.1.2 Placebo

The placebo injection consisted of saline solution 0.9% and was provided as a vial with an empty syringe fitted with a 20 mm needle of 19 gauge external diameter, sealed in a laminated bag.

Placebo was provided by the sponsor and had to be stored under recommended temperature (between +2°C and +8°C).

An independent, non-blinded qualified person had to fill the empty syringe with the NaCl provided in order to administer the same volume as the active treatment.

The procedures for study drug administration are provided in the Study Manual.

6.2 Prior and Concomitant Medication/Therapy

Any medication and/or other therapy that the subject takes, other than the study investigational drug, is considered concomitant medication, whether or not it is targeting the studied tumour (Lung NET). Concomitant treatments are prescribed, modified or discontinued at the discretion of the investigator.

6.2.1 Prior Medication/Therapy

Any prior therapy or medication given to a subject within 6 months before entry into the study (Screening) will be indicated on the eCRF.

Forbidden prior therapies include:

- Surgery within 6 weeks prior to randomization,
- SSAs for more than 15 days (e.g. peri-operatively) of short acting SSA or one dose of long acting SSA and the treatment was received within 6 weeks prior to randomization,
- Cytotoxic chemotherapy, molecular targeted therapy, or interferon within 4 weeks prior to randomization
- More than one line of cytotoxic chemotherapy, molecular targeted therapy, and interferon
- Previous local therapy (e.g. chemo-embolization, bland, or radio-embolization) within 6 weeks prior to randomization
- Treatment with PRRT at any time prior to randomization

Dose and generic name or tradename will be indicated.

6.2.2 Concomitant Medication/Therapy

Any concomitant therapy or medication given to a subject during study drug administration will be indicated on the eCRF. Dose and generic name or tradename will be indicated.

The following concomitant medications, therapy and procedures are not permitted during this study:

- Cyclosporine,
- GH antagonists,
- Any SSAs (other than LAN used as study treatment), including rescue octreotide and/or LAR SSA,
- Bromocriptine
- Chemotherapy, molecular targeted therapy, chemoembolization, PRRT and interferon.

Radiation (radiotherapy) is allowed for lesions other than target lesions according to the RECIST analysis.

Rescue antidiarrheal medications (e.g., loperamide 2 mg tablets, and/or tincture of opium and/or pancreatic enzyme) are authorized.

If any of the medications/therapies prohibited by the study protocol are taken/performed during treatment with study drug, subjects must be withdrawn from the study and, when possible, followed up for further data collection. For information regarding the effects on blood glucose and the need for monitoring and adjustment of antidiabetic agents, as well as information about the possible effects on bioavailability of drugs mainly metabolised by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) and bradycardia inducing drugs (e.g. beta blockers) please refer to the current IB (Summary of Data and Guidance for the Investigator, Section 6.5.4 and Section 6.5.7).

6.3 Procedures for Monitoring Subject Compliance

Study treatment will be administered by an independent non-blinded representative assigned by the Investigator at the study center, thus subject compliance is not expected to be an issue. Drug accountability records will be maintained by the Investigator documenting that subject received allocated study drug. Any study drug administration issue should be explained on the eCRF.

'Injection only' visits will not be considered as study visits; however, the date and time of injection will be recorded in the eCRF.

A check system is included in the syringe to indicate that the whole dose has been administered.

Where a subject is consistently noncompliant with study drug intake they should be discontinued from study drug and entered into the OL Extension Follow-up Period. Please refer to Section 4.3 for the criteria for discontinuing the subject from study drug.

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 2 and Table 4, for the DB Phase and the OL Extension Treatment Period, respectively.

7.1 Primary Efficacy Endpoint and Evaluation

The primary endpoint will be the PFS for subjects randomized in LAN group, assessed by central review using the RECIST v1.1 criteria, every 12 weeks, defined as the time from randomization to disease progression or death from any causes in either the double-blind phase, or in the OL period.

Images centrally reviewed will be CT scan of thorax and abdomen, OR MRI of the abdomen with CT scan of thorax (using the same mode as per baseline).

7.2 Secondary Efficacy Endpoints and Evaluations

- Progression-free survival (PFS), assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase.
- Progression-free survival (PFS), assessed by local review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase.
- ORR: objective response rate of CR or PR measured by RECIST v1.1 criteria every 12 weeks until the Post Treatment/Early Withdrawal Visit during the double blind phase.
- Time to treatment failure during the double blind 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 LAR SSA), or initiation of anticancer treatment
- 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
- 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 double blind and the OL treatment phases.
- 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.
- Time to QoL deterioration, defined by a decrease from baseline in EORTC QLQ-C30 score of at least 10 points during the double blind, the OL treatment and the follow-up phases.
- 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]

Primary, secondary CCI [redacted] efficacy endpoints and evaluations are summarized in Table 6.

Table 6 Primary, Secondary CCI [redacted] Efficacy Endpoints and Evaluations

Measure	Time point	Variable	Endpoint
PFS assessed by central review using RECIST v1.1 criteria	Baseline and every 12 weeks or death date	PFS (central)	PFS
PFS assessed by local review using RECIST v1.1 criteria (sensitivity analysis of the primary endpoint)	Baseline and every 12 weeks or death date	PFS (local)	PFS
ORR: objective response rate of CR or PR, using RECIST v1.1 criteria	Baseline, and every 12 weeks until the Post treatment/Early Withdrawal Visit	Best Overall Response	ORR assessed by local and central review using RECIST v1.1 criteria
Time to treatment failure	Baseline, every 12 weeks, or death date, or date of consent withdrawn, date of withdrawal due to an AE, date of lost to follow-up, date of appearance of carcinoid syndrome or other hormone related syndrome necessitating initiation of SSAs (rescue octreotide and/or LAR SSA) or date of initiation of anticancer treatment.	Time to treatment failure	Time to treatment failure
Biomarker CgA level	Baseline, Week 8, Week 12 and every 12 weeks until the Post treatment/Early Withdrawal Visit	Biomarker CgA changes from Baseline	• Mean change from Baseline values at each post baseline time point • Proportion of subjects with decrease in CgA of ≥30% at Week 8

Measure	Time point	Variable	Endpoint
Change in QoL, as assessed by the EORTC QLQ-C30 questionnaire	Baseline, and every 12 weeks until the Post treatment/Early Withdrawal Visit	QoL change from Baseline	• Mean change from Baseline values at each post baseline time point. • Time to QoL deterioration
Mean change from Baseline in urinary 5-HIAA levels in subjects with elevated 5-HIAA (≥2xULN) at Baseline	Baseline, Week 8 and every 12 until the Post treatment/Early Withdrawal Visit	Urinary 5-HIAA levels change from Baseline	Mean change from Baseline values at each post baseline time point
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

5-HIAA=5-hydroxyindoleacetic acid; AE=adverse event; CgA=chromogranin A; CR=complete response, CCI [redacted] EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; LAR=long acting release; OS=overall survival; PFS=progression free survival; PR=partial response, QoL= quality of life; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease; SRI=somatostatin receptor imaging; SSA=somatostatin analogue; CCI [redacted] ULN=upper limit of normal.

CCI [redacted]

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

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

7.4.1 Time to Disease Progression or Death

PFS defined as time from randomization to the first documentation of progression according to RECIST v1.1 or death from any cause whichever occurs first, will be presented.

7.4.2 Tumour Response

All tumour assessments will be performed using the RECIST v1.1 criteria every 12 weeks throughout the study (Table 2 and Table 4). The same imaging technique will be used for each subject throughout the study, in order to ensure comparability between tumour assessments. Subjects will receive either CT scan of the thorax and abdomen, or an MRI 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 tumour assessments,
- that all scans will 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 will be 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 seven (7) weeks (49 days). If the subject is on study less than seven (7) weeks (49 days), any tumour assessment indicating stable disease before this time period will have a Best Response of "non evaluable" unless PD is identified.

In addition, at Baseline, the Central Reading CRO will measure the hepatic and intrathoracic tumour load. From the imaging data, PFS (see Section 7.4.1), ORR, time to treatment failure CCI .

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.

7.4.3 Biomarkers (Chromogranin A and 5-Hydroxyindoleacetic Acid)

7.4.3.1 Chromogranin A

Plasma CgA will be assessed according to the schedules in Table 2 and Table 4. At each time point a 5 mL blood sample for analysis of CgA will be taken, prepared and shipped as specified in the Central Laboratory Services Manual.

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

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

7.4.3.2 5-Hydroxyindoleacetic Acid

Urinary 5-HIAA will be assessed according to the schedules in Table 2 and Table 4.

At Baseline (Visit 2), urinary 5-HIAA levels will be assessed for all subjects. Urinary 5-HIAA levels will be 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 will require subjects to collect their urine for the 24 hour period prior to the study visit. Subjects will be provided with a receptacle for this purpose and will be 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 should be recorded on the receptacle.

The subject will be instructed to collect all their urine in the receptacle for a period of 24 hours. Due to the potential interference with the assay for 5-HIAA, subjects will be instructed not to eat bananas, pineapple, plums, walnuts, eggplant, tomatoes, chocolate or

avocado during the urine collection period and the 72 hours prior to the collection. At the study visits the investigator will question the subject about his/her diet over the collection period. At the end of the collection period the subject should empty his/her bladder as fully as possible into the collection receptacle, and record the time.

The collected urine will be given to the investigator (or designee), who will measure the volume of urine collected and record this, along with the start and stop times of the collection period, on the appropriate section of the eCRF. Intake of any prohibited food will also be recorded on the eCRF.

The sample of the collected urine should be prepared and shipped as specified in the Central Laboratory Services Manual.

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

7.4.4 Somatostatin Receptor Imaging

The following type of imaging can be used for SRI:

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 tumour.
      1 = uptake by tumour but < background liver.
      2 = uptake by tumour equal to background liver.
      3 = uptake by tumour greater than background liver.
      4 = very intense uptake by tumour.
   (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”

Somatostatin receptor imaging by Octreoscan or Ga-PET-scan performed within the last 6 months will be collected if available in the subject file and SRI positivity can be confirmed according to the rules described above. If not available in the subject file, a new SRI is required before inclusion.

7.4.5 Time to Treatment Failure

Treatment failure is defined as 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 LAR SSA), or initiation of anticancer treatment. Time to treatment failure will be defined as the time from randomization to treatment failure.

7.4.6 Quality of Life

Quality of life will be assessed using the EORTC QLQ-C30 v3.0 questionnaire. The questionnaire will be completed at Baseline (Visit 2), every 12 weeks (throughout the DB and both OL phases), at the Post treatment/Early Withdrawal Visit at the end of the DB and both OL Phases. If necessary, the investigator or delegated personnel will explain the questions, which will be provided in a paper format, to the subject. The subject will complete the questionnaire 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 have been answered.

7.4.7 Subsequent Therapies

Details of all new cancer therapies during the OL Extension Follow-up phase will be collected.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study and up to 30 days after the last study drug administration. They will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

8.1.1 Definition of an Adverse Event

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

This definition includes events occurring from the time of the subject giving informed consent up to 30 days after last study drug administration.

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

Death due to disease progression will be recorded as part of the efficacy evaluation and will not be regarded as an SAE.

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

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

- Judged by the investigator to be unusually severe or accelerated symptoms

or

- If the investigator considers the deterioration of signs and symptoms to be caused directly by the study drug.

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

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

Adverse events will be recorded and graded according to the current version of the NCI-CTCAE v4.03, dated 14 June 2010. In view of meta-analyses, and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

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

Where:

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

8.1.2.2 Causality Classification

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

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

8.1.2.3 Assessment of Expectedness

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

8.1.2.4 Laboratory Test Abnormalities

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

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

8.1.2.5 Abnormal Physical Examination Findings

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

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings as judged by the investigator as clinically significant (e.g. electrocardiogram changes, thyroid function disturbances) 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, should be recorded as AEs.

8.1.3 Recording and Follow up of Adverse Events

At each visit (during the DB and OL phase), the subject should 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 eCRF, reported to the sponsor (if an 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

exacerbation's of pre-existing illnesses should be recorded according to the National Cancer Institute (NCI) terminology if applicable.

Any AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

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

8.1.4 Reporting of Serious Adverse Events

All SAEs (as defined below) regardless of treatment group or suspected relationship to study drug must be reported immediately (within 24 hours of the investigator's knowledge of the event) via an SAE report form and sent immediately (within 24 hours of the treating physician's knowledge of the event) to the fax number specified at the beginning of this protocol.

A SAE is any AE that:

(1) Results in death,
(2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death,
(3) Results in in-subject hospitalization or prolongation of existing hospitalization, excluding admission for social or administrative reasons (see further),
(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,
(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the study drug,
(6) Is an important medical event that may not result in death, be life threatening, or require hospitalization when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse.

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

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

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

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

The following information is the minimum that must be provided to the sponsor Pharmacovigilance contact within 24 hours for each SAE:

- Study number
- Centre number
- Subject number
- AE
- Investigator's name and contact details
- Subject sex
- Nature and seriousness of the event
- Reason for the serious classification
- Causality (related, not related)
- Event Onset date
- Outcome of the event (if available) and any action taken

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the

sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

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

8.1.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug has interfered with a contraceptive method. If pregnancy occurs during the study, the subject will be immediately withdrawn from the study treatment. The outcome of the pregnancy will then need to be collected post study. Prior to withdrawal from the study, the pregnant subject will undergo either Post Treatment /Early Withdrawal Visit for the DB Phase or the OL Extension Phase, as applicable, within 30 days of last study drug administration.

Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor using the Standard Pregnancy Outcome Report Form. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

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

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

8.1.6 Deaths

All AEs resulting in death, except death due to disease progression, either during the study period or within 30 days after the last dose of study drug, must be reported within 24 hours of the investigator's knowledge of the event.

For AEs leading to death, NCI CTCAE Grade 5 is the only appropriate grade (see Section 8.1.2.1). Deaths that cannot be attributed to an NCI CTCAE term associated with Grade 5 or that cannot be reported within an NCI CTCAE category as 'Other' have to be reported as one of these four AE options:

- Death not otherwise specified (NOS),
- Disease progression NOS,
- Multi-organ failure,
- Sudden death.

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

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

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

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

The investigator should assess 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 should be temporary discontinued in case of:

- Severe unremitting gastrointestinal intolerance: NCI CTCAE 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 ADL) or vomiting (≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, 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 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 (>2x ULN) or lipase (>2x 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 ALT (>5xULN) or AST (>5xULN) or Bilirubin (>2xULN).
- Any other adverse event or lesser severity of the adverse events listed above that, in the opinion of the investigator, could jeopardise the subject's safety.

The Investigator should assess whether permanent discontinuation or reintroduction of study drug is appropriate in the event of recovery from any such adverse event, 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.

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

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

It is the investigators' responsibility to notify their IRB/IEC in a timely manner.

8.2 Clinical Laboratory Tests

During the DB Phase and OL Extension Treatment Period, blood samples will be collected at Screening, Baseline, Week 12 and then every 12 weeks until the Post Treatment/Early Withdrawal Visit (see Table 2 and Table 4).

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

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they 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.

8.2.1 Hematology

Blood samples (3 mL+3 mL) will be 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.

8.2.2 Blood Biochemistry

Blood samples (5mL) will be 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
- glycated haemoglobin (HbA1c)

Blood samples will be 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 normalised ratio (INR).

Detailed requirements for blood collection will be provided in the laboratory manual.

8.2.3 Pregnancy Test

Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours; if positive with urine, confirm with serum prior to receiving the first dose of study medication and at Baseline of the Post OL Extension Treatment Phase. A urinary test should also be performed at the Post Treatment/Early Withdrawal Visit and confirm with serum if positive with urine.

If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Female subjects who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry. Any subject becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.5.

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8.3 Physical Examination

Physical examinations will be assessed at Screening, Baseline, and every 12 weeks thereafter until the last study Visit. Please see Table 2, Table 4 and Table 5 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.

8.4 Vital Signs

Vital signs will be assessed at Screening, Baseline, and every 12 weeks thereafter until the last study Visit. Please see Table 2, Table 4 and Table 5.

Blood pressure (SBP/DBP) and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after five minutes rest in supine and standing position and after 1 minute of standing. Absolute values and change from Baseline will be analyzed.

Weight will be recorded, and height will be measured at Screening (Visit 1) only.

9 ASSESSMENTS OF CCI [redacted] PHARMACODYNAMICS

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[redacted]

9.1.2 Analytical Procedures

The concentrations of lanreotide in serum will be analyzed by COVANCE (Harrogate, UK) using a validated LC-MS/MS method.

A detailed description of the analytical procedures and validation methods will be provided in the Trial Master File (TMF).

At the end of the study when all serum samples are analysed, the bioanalytical report will be appended to the clinical study report.

Details of sample handling will be provided in the laboratory manual.

9.2 Pharmacodynamics

For subjects participating in the optional research programme, serum and whole blood samples will be taken for further potential analyses, aimed at:

- Exploring the association of biomarkers with drug activity (clinical benefit and mechanisms of action).
- Exploring the association of biomarkers with AEs, or other effects associated with LAN treatment.
- Exploring biomarkers of diagnostic assays and establishing the performance characteristics of these assays.

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Samples will be archived in a central biorepository designated by the sponsor and according to local administration regulations, and/or the European Medicines Agency and will not carry personal identification (e.g. Social Security number or name). The samples will be destroyed no more than 15 years after the end of the main study or at the subject's request.

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Only people designated by the sponsor will be allowed access to the samples. All information collected will be kept strictly confidential and all clinical information will be anonymous.

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10 STATISTICS

10.1 Analyses Populations

The following populations will be used for the statistical analyses:

- **Screened population**: All subjects screened (i.e. who signed informed consent).
- **Intention to treat (ITT) population**: All randomized subjects. Subjects will be analyzed as randomized, regardless of the treatment received.
- **Per protocol (PP) population**: All subjects in the ITT population with no major protocol violations/deviations.
- **Safety population**: All subjects in the ITT population who received at least one injection of study treatment. Subjects will be analyzed as treated.
- **Open Label Intention to Treat (OLITT) population**: All subjects entering the LAN OL Extension Treatment Phase who have signed an informed consent.
- **Follow-up population**: All OLITT subjects entering the Follow-up Extension Phase.

10.1.1 Populations Analyzed

The primary analysis of efficacy will be performed on the ITT population. The PP population will be used for secondary efficacy analyses of the primary endpoints as well as all PFS derived endpoints. All other secondary endpoints will be analyzed only on the ITT. All safety data related to the DB phase will be analyzed on the safety population according to the treatment received. All safety data related to the OL extension treatment period will be analyzed on the OLITT population. All safety data related to the OL extension follow-up period will be analyzed on the Follow-up population.

10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation will be described in the Protocol-Deviation Specification Document. The final list of protocol deviations impacting inclusion in all populations will be reviewed during the data review meeting held prior to database lock.

10.2 Sample Size Determination

Eligible subjects are stratified by

- Typical versus atypical tumour characteristics, and
- Prior chemotherapy (cytotoxic chemotherapy or molecular targeted therapy 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 is clinically meaningful.

The following assumptions are used to derive the 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 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
- A 2:1 random assignment ratio

Under these assumptions, using SAS procedure POWER, a total of 201 randomized subjects were initially necessary to observe an estimated 175 disease progression as assessed centrally or death events in both treatment groups, and detect a statistically significant treatment effect. Taking into account 5% of subjects lost to follow up, and the stratification factors, 216 subjects had to be randomized initially (144 subjects in the LAN plus BSC group and 72 subjects in the placebo plus BSC group).

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

Due to the premature stop of the 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 were included in this study. Assuming a theoretical 2:1 randomization, 52 subjects are included in experimental arm and 25 in placebo arm. It will ensure an estimation accuracy of 13% for an expected median PFS of 10 months.

10.3 Significance Testing and Estimations

All statistical analyses will be descriptive.

10.4 Statistical/Analytical Methods

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

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

Statistical analyses will be performed using Statistical Analysis System® (SAS)® (version 9.3 or higher).

10.4.1 Demographic and Other Baseline Characteristics

In order to evaluate balance of treatment groups, descriptive summary statistics (n, mean, standard deviation (StD), 95% CI of the mean, median, minimum, maximum) or frequency counts of demographic (age, ethnicity and race (as per local regulations) and sex) and baseline data (medical and surgical history, concomitant disease (predosing AEs and ongoing medical history), disease history/diagnosis (mitotic count and foci of necrosis, Ki67 value if available, TNM staging, location of primary tumour, number of metastatic organs, hepatic and intrathoracic tumour load, presence/absence of hormone related syndrome), ECOG status and subject status in terms of somatostatin receptors (Krenning scale) will be presented by treatment group and overall for the ITT. 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.

10.4.2 Homogeneity of Treatment Groups

Homogeneity of treatment groups at Baseline will be explored for selected parameters such as age, sex, performance status, and other known risk factors using 95% CI.

10.4.3 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each population will be summarized. The reasons for subject exclusions from each of the populations will be tabulated. In addition, the number of subjects who were randomized, treated, discontinued and completed at each of the study periods will be summarized by treatment group for the DB phase (as randomized), the OL Treatment Period (per status at the end of the DB phase), the OL Extension Follow-up Period and overall. Primary reasons for discontinuation of study treatment will be tabulated for each study phase.

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10.4.5 Efficacy Evaluation

10.4.5.1 Primary Efficacy Variable

As indicated in Section 7.1, the primary efficacy endpoint is PFS for subjects randomized in LAN group assessed by central review using RECIST v1.1 criteria every 12 weeks. PFS is defined as the time from randomization to the first documentation of progression according to RECIST v1.1 in assessments every 12 weeks, or death from any cause, whichever occurs first in either the double-blind phase or in the OL period.

Table 7 summarizes the rules for determination of the date and assignment of the outcome [26].

Table 7 Progression Free Survival Rules (Centrally Assessed Using RECIST v1.1 Criteria)

Situation	Date of progression or censoring	Outcome
No baseline tumour assessment	Randomization	Censored
Progression documented (centrally)	Date of radiological assessment of measured lesions showing progression	Event
Progression documented (locally) and withdrawal from DB phase	Date of radiological assessment of measured lesions showing progression	Censored
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of measured lesions prior to initiation of an anti-cancer 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 measured lesions	Censored
Prohibited medication/therapy	Date of last evaluable assessment prior to initiation of prohibited medication/therapy	Censored

PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumours.

The distribution of PFS times in the LAN plus BSC group will be estimated using the Kaplan Meier product limit method. The median PFS times with 2-sided 95% confidence intervals will be estimated in the LAN plus BSC group, together with the estimates of PFS rates at 6, 12, 18, and 24 months interval after randomization. The results of the analyses will be presented both in summary tables and graphically in Kaplan Meier plots.

As a sensitivity analysis to the primary endpoint, the analysis of PFS according to local review will include investigator assessed PD and deaths. Other data will be censored.

Clinical progression (i.e., locally assessed documented progression when 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 progression in this analysis.

Table 8 summarizes the rules for determination of the date and assignment of the outcome [26].

Table 8 Censoring Rules for PFS via Local Review

Situation	Date of progression or censoring	Outcome
No baseline tumor assessment	Randomization for subjects randomized in LAN group	Censored
Progression documented (locally)	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	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of measured lesions prior to initiation of an anti-cancer 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 measured lesions	Censored
Prohibited medication/therapy	Date of last evaluable assessment prior to initiation of prohibited medication/therapy	Censored

PD=progressive disease.

Similar analyses to those employed for the primary efficacy endpoint will be performed.

10.4.5.2 Secondary Efficacy Variables

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

Progression-free survival (PFS) assessed by central review using RECIST v1.1 criteria every 12 weeks during the double-blind phase:

PFS is defined as the time from randomization to the first documentation of progression according to RECIST v1.1 in assessments every 12 weeks, or death from any cause during the double-blind phase, whichever occurs first. The rules for determination of the date and assignment of the outcome will be described in the SAP.

The distribution of PFS times for each treatment group will be estimated using the Kaplan Meier product limit method. The median PFS times with 2-sided 95% confidence intervals will be estimated for each treatment group, together with the estimates of PFS rates at 6, 12, 18, and 24 months interval after randomization. The results of the analyses will be presented both in summary tables and graphically in Kaplan Meier plots. A stratified Cox proportional hazards model will be used to estimate the HR, and its two sided 95% CI. If the assumption of the proportionality of hazards is not satisfied, an appropriate model will be used (with time varying covariate or by using a parametric model).

Progression-free survival (PFS) assessed by local review using RECIST v1.1 criteria every 12 weeks during the double-blind phase:

PFS is defined as the time from randomization to the first documentation of progression according to RECIST v1.1 in assessments every 12 weeks, or death from any cause during the double-blind phase, whichever occurs first. The rules for determination of the date and assignment of the outcome will be described in the SAP.

The distribution of PFS times for each treatment group will be estimated using the Kaplan Meier product limit method. The median PFS times with 2-sided 95% confidence intervals will be estimated for each treatment group, together with the estimates of PFS rates at 6, 12, 18, and 24 months interval after randomization. The results of the analyses will be presented both in summary tables and graphically in Kaplan Meier plots. A stratified Cox proportional hazards model will be used to estimate the HR, and its two sided 95% CI. If the assumption of the proportionality of hazards is not satisfied, an appropriate model will be used (with time varying covariate or by using a parametric model).

ORR: Proportion of subjects with the best overall response of CR or PR using RECIST v1.1 criteria.

The ORR in each treatment arm, with the corresponding exact 95% CIs, will be estimated. In addition, the difference in rates, together with a 95% CI, will be calculated. ORR will be performed for the DB phase.

Time to treatment failure, 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 LAR SSA), or initiation of anticancer treatment

Treatment failure is defined as 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 LAR SSA), or initiation of anticancer treatment. Time to treatment failure (TTF) will be performed for the DB phase. The distribution of times to treatment failure for each treatment arm will be estimated using the Kaplan Meier method. The median time to treatment failure and associated 95% CI will be computed for each treatment arm. The results will be presented both in summary tables and graphically in Kaplan Meier plots.

Mean changes from Baseline in biomarker CgA at Week 8, Week 12 and every 12 weeks thereafter until the Post Treatment/Early Withdrawal visit

Mean changes from Baseline in biomarker CgA will be presented descriptively by time point and treatment group in the DB phase and in OL treatment phase, using summary statistics. Raw values and change from Baseline will be presented.

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

The proportion of subjects with a 30% or more decrease in CgA from Baseline to Week 8 during the double-blind phase and the OL treatment phase will be estimated (in the population of subjects with an elevated CgA (≥2 x ULN) at Baseline), with the corresponding 95% CI in each treatment arm.

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

EORTC QLQ-30 will be described at each time point, by treatment arm. Both raw values and change from Baseline will be presented in the DB phase, in the OL treatment phase and in the follow-up treatment phase.

Time to QoL deterioration, defined by a decrease from baseline in EORTC QLQ-30 score of at least 10 points.

Time to QoL deterioration will be analyzed in a similar fashion to time to treatment failure during the double-blind phase, during the OL treatment phase and during the follow-up treatment phase.

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

Mean changes from Baseline in 5-HIAA urinary levels will be presented descriptively for subjects with elevated urinary 5-HIAA (≥2 x ULN) at Baseline, by time point and treatment group in the DB phase and in the OL treatment phase, using summary statistics.

For all RECIST 1.1 based efficacy endpoints, the analyses will be performed using data from local and central review.

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10.4.6 Adjustment for Country/Center Effect

No adjustment for country/center effect is planned.

10.4.7 Safety Evaluation

All safety data will be included in the subject data listings.

All safety data related to the DB phase will be analyzed on the Safety Population according to the treatment received.

All safety data related to the OL extension treatment period will be analyzed on the OLITT Population.

All safety data related to the OL extension follow-up period will be analyzed on the Follow-up Population.

All treatment emergent adverse events (TEAEs) will be reported and graded by investigators using the NCI CTCAE classification (Version 4.03, dated 14 June 2010). All AEs will also be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 18.1or later).

Summary incidence tables will be provided, classified by body system, System Organ Class (SOC), Preferred Term (PT) and associated NCI CTCAE worst grade. In the event of multiple occurrences of the same AEs (same PT term) being reported by the same subject, the maximum intensity (grade 5>grade 4>grade 3>grade 2>grade 1> missing>not applicable) will be chosen. AEs resulting in dose delays, dose interruptions and study drug withdrawal will be listed and presented in summary tables.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI CTCAE criteria. The NCI CTCAE grade 3 and 4 haematology and biochemistry parameters by subject and by visit will be listed.

Incidence of all reported TEAEs and SAEs will be tabulated by treatment group and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs associated with premature withdrawal of study medication.

A TEAE is defined as any AE that occurs from receiving the first dose of study drug to End of Study/withdrawal if:

- it was not present prior to receiving the first dose of study drug, or
- it was present prior to receiving the first dose of study drug but the intensity increased at or after receiving the first dose of study drug.

All TEAEs will be flagged in the AEs listings.

Prior and concomitant medication will be coded by using the WHO Drug Dictionary (version 2 (June 2015) or later) and will be summarized by treatment group and overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name. Concomitant therapies and surgical procedures will be summarized separately. Prior medications/therapies are all those stopped at the Screening visit (Visit 1) and concomitant medications/therapies are defined as all those ongoing or started within 28 days before the study drug administration/after the first dose of study drug.

For the DB phase, summary statistics (mean, 95% CI of the mean, median, StD and range as appropriate) by treatment group and overall will be presented for vital signs, clinical laboratory tests, physical exam, NYHA, ECG, ECOG, and gallbladder at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and

normal or abnormal physical examinations between Baseline and the Post Treatment/Early Withdrawal Visit in the DB Phase.

For the OL Extension Treatment phase, similar analyses will be performed on the OLITT population according to the status at the end of the DB phase.

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10.5 Subgroup Analyses

No subgroup analyses will be performed.

10.6 Interim Analyses

No interim analyses are planned.

11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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

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

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

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

12.1.2 Protocol Deviations, Violations, and Exceptions

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

A protocol violation is any significant divergence from the protocol, i.e. non-adherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study centre personnel, on the eCRF. In addition, protocol violations will be reported by the monitor in the monitoring reports and any other related study documents, as detailed in the monitoring manual.

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

12.2 Information to Study Personnel

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

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

12.3 Study Monitoring

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

The sponsor is responsible for monitoring these data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements. Monitoring will be conducted by a CRO, directed by the sponsor's Specialty Franchise Clinical Operations department.

Contracted CRO assigned monitors will conduct regular site visits. As the active treatment and placebo are not similar in appearance (see Section 6.1) two monitors will be assigned to each site. One monitor will be dedicated to conducting study treatment checks and accountability and will have no access to the subject's data, files or assessments. The other monitor will be responsible for all other monitoring activities.

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

Electronic data capture (EDC) will be utilized for collecting subject data. The site must complete the eCRFs according to the subject’s visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor and/or at the assigned CRO(s) will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

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

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

12.4 Audit and Inspection

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

12.5 Data Quality Assurance

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

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

13 ETHICS

13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IRBs/IECs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1.4).

For electronic data capture (EDC) studies the following regulations must be included: Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

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

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

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

13.2 Informed Consent

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

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

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

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

CCI [redacted]

13.3 Health Authorities and Institutional Review Boards/Independent Ethics Committees

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

13.4 Confidentiality Regarding Study Subjects

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

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

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Recording of Study Data

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

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

QoL questionnaires will be presented to the subjects in paper format. Once completed, the original copy will be sent to the designated CRO in charge of data management.

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

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

14.2 Data Management

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

Data management will be conducted by a CRO, directed by the sponsor's Specialty Franchise Clinical Operation Biometry department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Study Monitoring). The paper subject questionnaires and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor. A hard copy should be retained at site in the subject file.

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

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

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

The coding of AE, medical and surgical history, prior/concomitant medication/chemotherapy/molecular targeted therapy/radiotherapy related to lung NETs and general prior/concomitant medication/non drug therapies/surgical procedures will be performed by the Sponsor's specialised Medical Coding Group.

Coding will be performed with WHODRUG and MedDRA dictionaries as appropriate.

14.3 Record Archiving and Retention

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

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

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

15 FINANCING AND INSURANCE

15.1 Contractual and Financial Details

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

Financial Disclosure Statements will need to be completed, as requested by FDA 21 CFR Part 54.

15.2 Insurance, Indemnity and Compensation

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

16 REPORTING AND PUBLICATIONS OF RESULTS

16.1 Publication Policy

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

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

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors (ICMJE) guidelines [26]. In particular, those named as authors, whether employed by an Ipsen Affiliate or sponsor, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'.

Authorship credit should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a manuscript should meet all four criteria. Each author must agree to their inclusion in the list of authors.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

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

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

16.2 Clinical Study Report

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

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