EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 14 DAYS IN WELL DIFFERENTIATED, METASTATIC OR LOCALLY ADVANCED, UNRESECTABLE PANCREATIC OR MIDGUT NEUROENDOCRINE TUMOURS HAVING PROGRESSED RADIOLOGICALLY WHILE PREVIOUSLY TREATED WITH LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 28 DAYS

STUDY PROTOCOL
STUDY NUMBER: 8-79-52030-326 (CLARINET FORTE)

LANREOTIDE AUTOGEL®
EUDRACT NUMBER: 2014-005607-24

Final version (including Amendment 3) dated 09 January 2017

Sponsor's Medically Responsible Person:

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol 8-79-52030-326 entitled "Efficacy and safety of lanreotide Autogel® 120 mg administered every 14 days in well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut neuroendocrine tumours having progressed radiologically while previously treated with lanreotide Autogel® 120 mg administered every 28 days". 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

[redacted] [redacted] SIGNATURE: _____

DATE: _____

OFFICE: _____

COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol 8-79-52030-326 entitled "Efficacy and safety of lanreotide Autogel® 120 mg administered every 14 days in well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut neuroendocrine tumours having progressed radiologically while previously treated with lanreotide Autogel® 120 mg administered every 28 days". 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: _____

TITLE: Coordinating Investigator SIGNATURE: _____

DATE: _____

OFFICE: _____

SUMMARY OF CHANGES

The current version of the protocol was released on 09 January 2017 and includes Amendments 1, 2 and 3. Amendment forms were prepared and are provided in Appendix 2, Appendix 3 and Appendix 4, respectively (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	07 October 2015	Appendix 2
2	16 December 2015	Appendix 3
3	09 January 2017	Appendix 4

SYNOPSIS

Name of sponsor/company: Ipsen Innovation

Name of finished product: Lanreotide Autogel® 120 mg
Name of active ingredient(s): Lanreotide acetate

Title of study: Efficacy and safety of lanreotide Autogel® 120 mg administered every 14 days in well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut neuroendocrine tumours having progressed radiologically while previously treated with lanreotide Autogel® 120 mg administered every 28 days.
Study number: 8-79-52030-326 (CLARINET FORTE)

Number of planned centres: 30 to 35 centres in Belgium, France, Germany, Republic of Ireland, Italy, Spain, the United Kingdom (UK), the Netherlands, Denmark, and Poland.

Planned study period:	**Phase of development:**
First subject screened: Q4 2015 Last subject, last visit: Q3 2019	Phase II

Objectives:

Primary:

- To assess progression free survival (PFS) when treated with lanreotide Autogel® 120 mg administered every 14 days based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.0, and according to central review.

Secondary:

- To evaluate the clinical and biological safety profile.
- To evaluate time to progression.
- To evaluate PFS rate every 12 weeks.
- To evaluate overall survival at Week 48 and at the end of the study period in each cohort.
- To evaluate the objective response rate (ORR) as per RECIST v1.0 every 12 weeks.
- To evaluate the disease control rate (DCR) as per RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort.
- To evaluate the best overall response as per RECIST v1.0.
- To evaluate the duration of stable disease (SD) as per RECIST v1.0.
- To detect predictive factors of PFS.
- To evaluate the effect on symptoms (diarrhoea, flushing).
- To evaluate quality of life.
- To evaluate the changes in tumour biomarkers:
  - pNET cohort: nonspecific tumour biomarkers (Chromogranin A (CgA), neuron specific enolase (NSE) and 5-hydroxyindoleacetic acid (5-HIAA); 5-HIAA only in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above upper limit of normal (ULN)) at Baseline) and pancreatic neuroendocrine tumours (pNET)-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, somatostatin (SST), …; only for the tumour biomarkers above normal range at Baseline).
  - Midgut cohort: nonspecific tumour biomarkers (CgA, NSE and 5-HIAA).
- To evaluate the appearance of antilanreotide antibodies.
- To evaluate the pharmacokinetic (PK) profile of lanreotide and to evaluate, if any, the relationship between PK and pharmacodynamics (PD; PFS, tumour response or CgA).
- To evaluate, if any, the relationships between PK parameters and the safety outcomes.

Tertiary:

CCI [redacted]

Methodology:

This is a phase II, multicentre, prospective, open label, noncomparative, exploratory study. Subjects with well differentiated (grade 1 or 2 according to World Health Organisation (WHO) 2010 classification), metastatic or locally advanced, unresectable pNET or midgut neuroendocrine tumours (NET) with or without hormone related syndromes and who have had radiologically documented disease progression (as per RECIST v1.0) at least 24 weeks after their first injection of lanreotide Autogel® 120 mg at the standard dosing interval of every 28 days will be recruited to this study. Subjects will be recruited into one of two cohorts based on type of NET (i.e. pancreatic or midgut).

Following the Screening visit (Visit 1) and a Screening period of up to 28 days, where eligibility tests and assessments will be performed, eligible subjects will be treated with lanreotide Autogel® at a reduced dosing interval (i.e. 120 mg every 14 days) beginning at Baseline (Visit 2).

Study visits will be performed at Weeks 2, 4, 8, 12, 24, 36 and 48 (both cohorts), and Weeks 60, 72, 84 and 96 (midgut cohort only). An End of Study visit is scheduled approximately 2 weeks after the study visit at which progression is confirmed or after Weeks 48 (pNET cohort) or 96 (midgut cohort) for nonprogressive subjects, once central review of the radiological imaging is available.

As long as 25 events have not been observed in the respective cohorts, subjects who have not progressed at Week 48 (pNET cohort) or Week 96 (midgut cohort) will continue study treatment with lanreotide Autogel® 120 mg every 14 days and additional visits will be performed every 12 weeks until disease progression, death or unacceptable toxicity or tolerability.

Tumour response will be assessed every 12 weeks by tumour response evaluation according to RECIST v1.0, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study, and by independent central review. Additional efficacy assessments include symptom control (diarrhoea and flushing) and quality of life, as well as factors associated with PFS, and nonspecific (both cohorts) and pNET-specific (pNET cohort only) tumour biomarker concentrations. Safety evaluations will be performed throughout the study and will include the collection of clinical and biological safety data, including adverse events (AEs), vital signs, physical examination findings, serum haematology and biochemistry panels, urinalysis, and liver and pancreatic enzyme concentrations, as well as electrocardiogram (ECG) and gallbladder echography. PK evaluations will consist of lanreotide concentrations at selected timepoints throughout the study. CCI [redacted]

The overall duration of the study will be approximately 102 weeks assuming at least 25 subjects progress within 48 and 96 weeks in the 2 cohorts respectively.

Number of subjects planned:

It is planned to enrol a total of 100 subjects (50 subjects per cohort).

Diagnosis and criteria for inclusion:

Inclusion criteria:

1) Male or female subjects aged 18 years old or older.
2) Histopathologically confirmed well differentiated (grade 1 or grade 2 according to the WHO 2010 classification), metastatic or locally advanced, unresectable pNET (pNET cohort) or midgut NET (midgut cohort) with or without hormone related syndromes, with a proliferation index (Ki67) ≤20%.
3) Positive somatostatin receptors type 2 (SSTR2) as assessed by imaging (scintigraphy or positron emission tomography (PET) scan) in the organs of target lesions.
4) Progression as assessed by an independent central reviewer according to RECIST v1.0 from radiological imaging (CT scan or MRI) while receiving first line treatment with lanreotide Autogel® at a standard dose of 120 mg every 28 days for at least 24 weeks (6 injections). Progression must be radiologically documented using the same technique of images (CT scan or MRI) within 24 months prior to enrolment. Inclusion into the study must be within 28 days of the radiological imaging that is performed to document progression.
5) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2.
6) Provision of written informed consent prior to any study related procedures.
7) Female subjects of childbearing potential (not surgically sterile or 2 years postmenopausal) must provide a negative urine pregnancy test at Screening, and use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 2 months after participation in the study. Acceptable methods of contraception include double barrier method, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted and injected).
8) Subjects must be willing and able to comply with study restrictions and willing to return to the clinic for the follow up evaluation as specified in the protocol.

Exclusion criteria:

1) Has poorly differentiated grade 3 NET or rapidly progressive NET (within 12 weeks of initiation of lanreotide Autogel® 120 mg every 28 days) as per RECIST v1.0.
2) Has been diagnosed with VIPoma (i.e. Verner Morrison syndrome), insulinoma, foregut (except for pNET), hindgut NET, unknown primary NET or multiple endocrine neoplasms (MEN).
3) Has progressed during treatment with somatostatin analogues (SSAs) other than lanreotide Autogel® 120 mg.
4) Has been previously treated with any antitumour agent for NET other than lanreotide Autogel® 120 mg every 28 days: chemotherapy, molecular targeted therapy, peptide receptor radionuclide therapy (PRRT) or interferon. Exception made of prior treatment with Octreotide at standard dose stopped for other reason than disease progression.
5) Has had major surgery related to the studied disease within 3 months prior to entering the study. Previous debulking surgery and liver-directed therapies are acceptable as long as tumour burden is measurable (other target lesions).
6) Has symptomatic gallbladder lithiasis/sludge at Screening or a history of symptomatic cholelithiasis with no cholecystectomy since then.
7) Has had previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus if subjects treated with curative intent and free from disease for more than 5 years).

8) Was treated with any other investigational medicinal product (IMP) within the last 30 days before study entry.
9) Is pregnant or lactating.
10) Has abnormal findings at Screening, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety.
11) Has any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
12) Has been previously screened in this study, exception made of subjects who screen-failed following central reviewers eligibility assessment (ie non PD).
13) Has a history of hypersensitivity to lanreotide Autogel® or drugs with a similar chemical structure, or any excipient used in the formulation.
14) Is likely to require treatment during the study with drugs that are not permitted by the study protocol.
15) Has a history of, or known current, problems with substance or alcohol abuse.
16) Vulnerable subjects (i.e. subjects who are under legal protection, who are interned due to a mental disease and who are kept in detention).
17) Subjects who have a link with the sponsor, the clinical trial site or the investigator (medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the sponsor).

Test product, dose, mode of administration:
Lanreotide Autogel® will be administered by deep subcutaneous (s.c.) injection at a dose of 120 mg every 14 days.

Duration of treatment:
Up to 48 weeks for the pNET cohort or up to 96 weeks for the midgut NET cohort, or until disease progression, death or unacceptable toxicity or tolerability. Subjects in the pNET cohort who have not progressed at Week 48 will continue to receive lanreotide Autogel® every 14 days until 25 events have been observed. Similarly, subjects in the midgut cohort who have not progressed at Week 96 will continue to receive study treatment every 14 days until 25 events have been observed.

Reference therapy, dose and mode of administration:
Not applicable

Criteria for evaluation:
Efficacy:
Primary endpoint and evaluations:

- The primary endpoint is median PFS (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death). Disease progression will be assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study, and by independent central review to ensure intra and intersubject consistency and reliability.

Secondary endpoints and evaluations:

- Median time to progression (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression).
- Proportion of subjects alive and without progression every 12 weeks.
- Overall survival at Week 48 and at the end of the study for each cohort.
- ORR every 12 weeks as per RECIST v1.0. ORR is defined as the proportion of subjects who achieve either complete response (CR) or partial response (PR).

- DCR evaluated according to RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort. The DCR is defined as the rate of CR plus PR plus SD.
- Best overall response according to RECIST v1.0 (defined as the best response recorded from the initiation of treatment until disease progression).
- Median duration of SD according to RECIST v1.0 (defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days until the first occurrence of progressive disease by central assessment).
- Factors associated with PFS will include but will not be limited to: hepatic tumour volume ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (yes/no), Ki67 <10% versus ≥10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days.
- Symptom control (diarrhoea, flushing) at Baseline, Weeks 8 and 12 and every 12 weeks thereafter, and at the End of Study visit, as measured by the total number of stools and flushing episodes during the 7 days prior to the visit reported orally by the subject to the investigator.
- Quality of life measured at Baseline, Week 12 and every 12 weeks thereafter, and at the End of Study visit, after diagnosis of progression, using European Organisation into the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) v3.0 and Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21 (QLQ-GI.NET21; 2006), and the EuroQoL 5 dimensions, 5 levels (EQ-5D-5L) v1.0 questionnaires.
- pNET cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only). Note: at all scheduled visits, except Baseline, plasma/urinary 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.
  - pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …) at Baseline, every 12 weeks thereafter and at the End of Study visit: only for the tumour biomarkers above normal range at Baseline.
- Midgut cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only).

Tertiary endpoints and evaluations:

- CCI [redacted]

Safety:

- Clinical (AEs, vital signs, physical examination) and biological (serum haematology and biochemistry panels, liver and pancreatic enzymes, urinalysis) safety data collected at the timepoints specified in Table 2 (pNET cohort) and Table 3 (midgut cohort).
- ECG at Screening, Weeks 4, 24 and 48 (pNET cohort) or 96 (midgut cohort) and at End of Study.
- Gallbladder echography at Screening, and at Weeks 24 and 48 (pNET cohort) or 96 (midgut cohort) and at End of Study, or at any time if symptoms are thought to be related to gallbladder lithiasis.
- Potential relationships (if any) between PK parameters and safety outcomes.

Pharmacokinetic:

- Antilanreotide antibodies centrally analysed at Baseline and at the End of Study.
- Lanreotide serum concentration assessed at:
  - Baseline, prior to and 2 to 3 hours after the first injection at reduced dosing intervals;
  - Week 12, prior to injection
  - Week 24, prior to injection in all subjects, except in a subset of 30 subjects from selected sites, where a sample will be collected 1 to 3 days after the injection instead;
  - Week 48, prior to and 2 to 3 hours after injection;
  - Week 96, prior to injection (midgut cohort only);
  - End of Study, prior to any administration of commercial product (if applicable).

Statistical methods:

The sample size in this pilot study is 100 subjects in total (50 subjects per cohort). This should be sufficient to explore the efficacy of lanreotide Autogel® 120 mg at a reduced dosing interval. For the primary efficacy endpoint, data will be analysed for each cohort separately. The primary efficacy analysis on median PFS (measured using RECIST v1.0 and confirmed via centralised review) will be performed using the Kaplan Meier estimator. In addition, the median PFS, with associated 95% confidence intervals (CIs) will be presented.

All statistical analyses will be descriptive and p-values will be provided only for exploratory purposes. For descriptive analyses, summary statistics will be presented at each scheduled visit. Summary statistics will include sample size, number of available observations (N), number of missing observations (missing), mean, 95% CI of the mean, standard deviation (StD), number of nonmissing observations (n), median and range for continuous variables and scores. For categorical or discrete variables, the absolute and relative (percentage) numbers based on the nonmissing number of observations for each category will be presented, including 95% CIs.

The full analysis set (FAS) will consist of all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. The per protocol (PP) population will consist of all subjects in the FAS for whom no major protocol violations/deviations occurred. The PK endpoints will be analysed on the PK Valid population (i.e. all subjects who received at least one dose and who have at least one serum lanreotide concentration and no major protocol deviations affecting PK variables). Population PK (POPPK) modelling will be performed and a PK/PD relationship between lanreotide serum concentration and PD (PFS, tumour response or CgA) will be assessed, where possible. Exploratory graphs will be presented between PK parameters and safety outcomes. If a trend is detected, modelling analysis may be performed between PK and safety outcomes.

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
5-HIAA	5-hydroxyindoleacetic acid
βHCG	Beta human chorionic gonadotropin
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
CA(s)	Competent Authority(ies)
CFR	Code of Federal Regulations (United States of America)
CgA	Chromogranin A
CHDR	Centre for Human Drug Research
CI	Confidence interval
CLARINET	Controlled Study of Lanreotide Anti-proliferative Response in Neuroendocrine Tumours
C_{max}	Maximum concentration
CMC-SC	Chemistry, Manufacturing and Control Supply Chain
CR	Complete response
CRO	Contract research organisation
CSR	Clinical study report
CT	Computed tomography
DCR	Disease control rate
CCI	[redacted]
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC	European Organisation into the Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5 dimensions, 5 levels
EU	European Union
FAS	Full analysis set

LIST OF ABBREVIATIONS *(Cont.)*

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GEP NETs	Gastroenteropancreatic neuroendocrine tumours
GH	Growth hormone
GI	Gastrointestinal
HR	Hazard ratio
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IRB	Institutional review board
ISF	Interim Storage Facility
IUD	Intrauterine device
Ki67	Proliferation index
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEN	Multiple endocrine neoplasms
MRI	Magnetic resonance imaging
N	Number of available observations
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NET	Neuroendocrine tumours
NOS	Not otherwise specified
NSE	Neuron specific enolase
ORR	Objective response rate
PD	Pharmacodynamic
PDD	Protocol deviation document

LIST OF ABBREVIATIONS *(Cont.)*

PDM	Pharmacokinetics and Drug Metabolism
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
pNET	Pancreatic NET
POPPK	Population PK
PP	Per protocol
PR	Partial response
PRRT	Peptide receptor radionuclide therapy
PS	Performance Status
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-GI.NET21	Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
CCI	[redacted]
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
s.c.	Subcutaneous
SD	Stable disease
SOP	Standard Operating Procedure
SSA	Somatostatin analogue
SST	Somatostatin
SSTR	Somatostatin receptor
StD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment emergent adverse event
TFL	Tables, figures and listings
CCI	[redacted]
TMF	Trial master file
UK	United Kingdom

LIST OF ABBREVIATIONS *(Cont.)*

ULN	Upper limit of normal
USA	United States of America
WBC	White blood cell(s)
WHO	World Health Organisation
WHO-DD	World Health Organisation drug dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Neuroendocrine tumours (NETs) are a heterogeneous and rare group of malignancies originating from neural crest cells, endocrine glands, endocrine islets or in the diffuse neuroendocrine system. Although NETs may develop in almost any organ, they predominate within the pancreas and the gastrointestinal (GI) tract. Their incidence is increasing, approaching 5.25 cases per 100,000 per year [1, 2]. They are usually located in the GI tract (53%), but are also seen in the pancreas (7%) and pulmonary bronchii (27%).

Gastroenteropancreatic neuroendocrine tumours (GEP NETs) constitute a heterogeneous group which can be clinically divided into tumours producing hormone related syndromes and those not associated with hormonal syndromes.

Tumours within the GI tract are predominantly of enterochromaffin (Kulchitsky) cell origin. Tumours arising at diverse sites demonstrate a similar histological appearance, with numerous membrane bound secretory granules within the cell cytoplasm. These granules secrete neuroendocrine markers such as chromogranin A (CgA), neuron specific enolase (NSE) and synaptophysin. The majority of NETs demonstrate a low proliferation rate and evolve in an indolent fashion. Morphologic features suggesting malignancy (cellular pleomorphism, hyperchromatic nuclei, necrosis, and high mitotic activity) are not often seen. However, some studies have shown that these tumours result in significant morbidity and mortality by local disease progression, distant metastatic spread, most particularly to the liver, and the development of associated hormonal syndromes.

Surgery is the mainstay of treatment for resectable disease. However, since many of these patients have inoperable disease, medical therapy is often initiated to control disease progression. Therapeutic options for patients with advanced or metastatic GEP NETs have improved in recent years.

Somatostatin analogues (SSAs), such as lanreotide and octreotide, are considered the therapy of choice in controlling symptoms associated with NETs. With recent antitumour evidence, the role of SSAs has expanded from the treatment of the carcinoid syndrome's symptoms to control of tumour growth.

In the Controlled Study of Lanreotide Anti-proliferative Response in Neuroendocrine Tumors (CLARINET) [3], the antitumour effect of lanreotide 120 mg every 28 days was investigated in more than 200 patients with somatostatin receptor (SSTR) positive enteropancreatic NETs (including 45% of patients with pancreatic NET (pNET) and 36% with midgut), without hormonal symptoms and with proliferation index (Ki67) values of less than 10% (including 30% of patients with Ki67 between 3% and 10%). Progression free survival (PFS) was significantly prolonged with lanreotide as compared with placebo: median PFS, not reached at 24 months with lanreotide versus 18.0 months for placebo (95% confidence interval (CI), 12.1 to 24.0; $p<0.001$).

Based on the CLARINET results, lanreotide Autogel® 120 mg every 28 days is approved in the European Union (EU) for the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) GEP NETs of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease, as well as the treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours [4]. In the United States of America (USA), lanreotide Autogel® 120 mg every 28 days is approved for the treatment of patients with unresectable, well or moderately differentiated, locally advanced or metastatic GEP NETs to improve PFS [5].

However, patients treated at this standard dosing regimen may experience disease progression. Molecular targeted therapies sunitinib (Sutent®, multiple receptor kinases inhibitor) and everolimus (Affinitor®, mTOR inhibitor) have recently demonstrated their efficacy in progressive well differentiated pNET, leading to their authorisation in the EU and the USA. However, the safety profile of molecular targeted therapies is less favourable than the SSAs. In addition, molecular targeted therapies, such as everolimus or sunitinib, are currently indicated for pNET only, as they have not demonstrated so far any PFS benefit in GI NETs. Dose escalation of SSAs or reduced dosing interval of lanreotide could thus postpone the use of more aggressive therapies in progressive pNETs and represent an alternative for progressive GI NETs.

Increasing the dose of SSAs or reducing the interval between injections is a relatively common clinical practice in patients with NETs; however, no studies have yet been conducted with the primary objective of assessing efficacy and safety of such dose regimen modifications of lanreotide. The aim of this study is to explore the efficacy and safety of lanreotide Autogel® 120 mg when administered at a reduced dose interval (i.e. every 14 days) in subjects who progress while treated with lanreotide Autogel® at the approved dose interval of 120 mg every 28 days. A reduction in lanreotide Autogel® dosing interval may achieve radiological stabilisation, postpone the use of aggressive and less tolerated targeted and systemic therapies, and improve the quality of life of subjects with well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut NETs who have progressed on a standard dose of lanreotide Autogel® (i.e. 120 mg every 28 days).

1.2 Name and Description of Investigational Medicinal Product(s)

Lanreotide is a synthetic octapeptide analogue of somatostatin (SST) with a longer half life than the native molecule. Compared to SST, the biochemical stability, and thereby the half life of this synthetic molecule has been increased by the incorporation of modified amino acids. In the same way as the native hormone, lanreotide inhibits the secretion of a variety of hormones, including growth hormone (GH), and has direct and indirect antiproliferative activities (e.g. inhibition of growth factors and growth promoting hormones, antiangiogenic and immunomodulatory effects) [6, 7, 8, 9]. Lanreotide has a high affinity for human SST receptors 2 and 5. The presence of SST receptors in NETs and the suppressive effect of SST on the active substances secreted by these tumours (e.g. serotonin and tachykinins) provide the pharmacological rationale for using SSAs, such as lanreotide, to treat the symptoms associated with carcinoid syndrome. Furthermore, lanreotide has been shown to stabilise tumour size in patients with NETs.

Lanreotide Autogel® is a prolonged release, pharmaceutical form of lanreotide. The Autogel formulation has been developed for two main reasons. Firstly, its characteristics of a smoother and more extended release of lanreotide permit an injection interval of 28 days. Secondly, the formulation has the advantage of providing a ready to use deep subcutaneous (s.c.) injection. The formulation is a supersaturated solution for injection supplied as a prefilled polypropylene syringe with a stainless steel needle. Further details can be found in the current Investigator's Brochure (IB).

1.3 Findings from Nonclinical and Clinical Studies

The antiproliferative activity of SSAs has been reported both in vitro and in vivo. Several studies have shown a growth inhibiting effect of SSAs on tumour cells: activation of SSTRs, SSTR1, SSTR2 and SSTR5 induced antimitotic effects in most cell types [10, 11] whereas SSTR3 mediated apoptosis in endocrine cells [12, 13].

In patients with advanced neuroendocrine GI tumours, induction of apoptosis, determined by pre and post-treatment biopsy, was observed in patients who were treated with high doses of

lanreotide and who showed a biochemical response [14]. Tumour regression has been reported in 5% to 10% of patients with GEP NETs, while stabilisation of tumour size has been reported in 36% to 70% of patients [15]. Furthermore, lanreotide Autogel® has also been shown to be effective for symptom control, biochemical markers and tumour progression associated with NETs [16] (data on file).

In the phase III, double blind CLARINET study conducted in 204 subjects with enteropancreatic NETs not associated with hormonal syndromes, treatment with lanreotide Autogel® (120 mg every 28 days for up to 96 weeks) led to statistically significantly longer PFS than placebo treatment (not reached at 24 months for lanreotide versus 18 months for placebo; $p<0.001$). Based on Kaplan Meier estimates, 34.9% of subjects had progressed or died in the lanreotide Autogel® group compared with 77% of patients in the placebo group. Furthermore, treatment with lanreotide Autogel® reduced the risk of progression or death by 53% (hazard ratio (HR): 0.47; 95% CI: 0.30, 0.73; data on file).

1.4 Known and Potential Risks and Benefits to Human Subjects

1.4.1 Potential Benefits

Lanreotide Autogel® (120 mg every 28 days) has shown a positive effect in the relief of clinical symptoms associated with carcinoid syndrome and for tumour control of GEP NETs.

The main potential benefit of lanreotide Autogel® at a reduced dosing interval (120 mg every 14 days) is that radiological stabilisation may be achieved in participating subjects with GEP NETs who have progressed on a standard dose of lanreotide Autogel® 120 mg every 28 days, thereby postponing the use of aggressive and less tolerated systemic chemotherapy or molecular targeted therapies that may negatively impact on quality of life.

A pharmacokinetic (PK)/pharmacodynamic (PD) model generated from CLARINET data revealed a relationship between lanreotide concentrations and change in CgA. In addition, a quantitative model showed a relationship between change in CgA and PFS. Predictions from this PK/PD model showed that a reduction in the dosing interval of lanreotide may be of clinical benefit to the GEP NET population (data on file).

1.4.2 Potential Risks

1.4.2.1 Safety

Although reducing the dosing interval would not increase the dose of lanreotide administered at each injection, the safety profile of lanreotide Autogel® is not established for this regimen. Analyses looking at the relationship between lanreotide PK parameters (maximum concentration (C_{max}) and area under the curve (AUC)) and probability of occurrence of some adverse events (AEs; GI and injection site reactions) in lanreotide studies have been conducted. No relationship was observed between occurrence of AEs and exposure to lanreotide (data on file). In addition, no new safety signals have been reported in an ongoing externally sponsored study (EudraCT Number: 2012-005222-30 17]) assessing the antiproliferative effect of lanreotide Autogel® 180 mg administered every 28 days in a similar population. To date, 34 subjects with progressive GEP NETs and previously treated with octreotide LAR 30 mg every 28 days or lanreotide Autogel® 120 mg every 28 days have been enrolled in this ongoing study (EudraCT Number: 2012-005222-30 [17]).

For information on potential adverse effects of lanreotide on heart rate, injection site, gallbladder and pancreas, glycoregulation and thyroid function please refer to the current IB (Summary of Data and Guidance for the Investigator, Section 6.4).

1.4.2.2 Efficacy

Despite patients deriving initial clinical benefit from treatment with lanreotide Autogel® 120 mg every 28 days, it is not certain that further antitumoural effects will be achieved by reducing the dosing interval. The positive antitumour effect observed in the CLARINET study may have been maximal at a dose of 120 mg every 28 days and increasing the lanreotide exposure by reducing the dosing interval in patients progressing while being treated at the standard dose may not bring any further benefit.

Additionally, tachyphylaxis which may result from desensitisation or downregulation of SST receptors on the cell surface, resistance associated with the formation of antibodies to the SSA, or SST receptor gene mutations, have previously been reported on SSA treatment [18, 19, 20].

Additional information regarding risks and benefits to human subjects may be found in the current IB.

1.5 Selection of Investigational Medicinal Products and Dosages

The dosage to be evaluated in this multicentre, prospective, open label, noncomparative, two cohort study (i.e. 120 mg injected every 14 days for up to 48 weeks (pNET) cohort) or 96 weeks (midgut cohort)) was selected on the basis of data from the CLARINET study, and an ongoing externally sponsored study (EudraCT Number: 2012-005222-30 [17]). These studies demonstrated that doses of lanreotide Autogel® of 120 to 180 mg every 28 days were well tolerated. In addition, increasing the dose of SSAs or reducing the interval between injections is relatively common clinical practice in patients with progressive advanced NETs. The reduction in dosing interval, and consecutive increase in lanreotide concentration, was anticipated to achieve radiological stabilisation in subjects with pNETs or midgut NETs who have progressed on the standard dose of lanreotide Autogel®.

Increasing the exposure to lanreotide Autogel® 120 mg can be obtained either by administering two injections every 28 days, or by reducing the dosing interval to every 21 days or 14 days.

A simulation of the PK profile of lanreotide Autogel® 120 mg administered every 14 days showed a mean exposure (C_{max} at steady state) within the range of that observed in subjects with NET who received a dose of 120 mg every 28 days (19 ng/mL versus 14 ng/mL, respectively), whereas the simulated mean exposure of 240 mg every 28 days was much higher. In terms of exposure (i.e. lower C_{max}), administration of lanreotide Autogel® 120 mg every 14 days is thus preferable to 240 mg every 28 days.

Furthermore, a study in healthy volunteers evaluated the PK profile of a single administration of 240 mg lanreotide in a new Autogel® formulation [21]. Drug related AEs were experience by five of 16 subjects in the lanreotide group (including two serious AEs (SAEs)), compared with one subject in the placebo group. The type of AEs that occurred during the study was broadly consistent with the expected safety profile for lanreotide Autogel®. Some of the effects were exaggerated or of a higher incidence (GI disorders such as abdominal pain, indurations at site injection), and this is likely to be linked with the higher C_{max} observed after administration of the new lanreotide Autogel® 240 mg formulation. Five cases of gallbladder abnormalities (from sludge to cholelithiasis) were observed (four subjects treated with lanreotide Autogel®, one with placebo), including two subjects treated with lanreotide Autogel® who experienced cholelithiasis occurring more than 4 months after this single injection. These AEs/SAEs did not correlate with the C_{max} (mean C_{max} was around 25 ng/mL) or with the AUC. These safety signals also favoured reducing the dosing interval to 120 mg every 14 days rather than increasing the dose to 240 mg every 28 days.

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

1.6 Compliance Statement

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented. The electronic data capture (EDC) system will comply with the Food and Drug Administration (FDA), 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerised Systems Used in Clinical Trials. In addition, the study will adhere to all local regulatory requirements.

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

1.7 Population to be Studied

The study will enrol adult subjects with histopathologically confirmed well differentiated (grade 1 or 2 according to World Health Organisation (WHO) 2010 classification), metastatic or locally advanced, unresectable pancreatic or midgut NETs with or without hormone related syndromes and who have had radiologically documented (computed tomography (CT) scan or magnetic resonance imaging (MRI)) disease progression (as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.0) at least 24 weeks after their first injection of lanreotide Autogel® (120 mg every 28 days).

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

This study (CLARINET FORTE) aims to explore the efficacy and safety of a reduced lanreotide Autogel® dosing interval (120 mg every 14 days) in subjects with grade 1 or 2 (according to WHO 2010 classification), metastatic or locally advanced unresectable pancreatic or midgut NETs once they have progressed on the standard dose of lanreotide Autogel® (120 mg every 28 days).

Currently, patients with progressive disease after treatment with lanreotide Autogel® (120 mg every 28 days) have limited treatment options and receive aggressive and less tolerated systemic chemotherapy or molecular targeted therapies, such as everolimus or sunitinib. As lanreotide has a favourable tolerability profile, a reduced dosing interval might delay the need for such therapies and could potentially improve a patient's quality of life.

2.2 Study Objectives

The primary objective of the study is to assess PFS when treated with lanreotide Autogel® 120 mg administered every 14 days based on RECIST v1.0, and according to central review.

The secondary objectives of the study are as follows:

- To evaluate the clinical and biological safety profile.
- To evaluate time to progression.
- To evaluate PFS rate every 12 weeks.
- To evaluate overall survival at Week 48 and at the end of the study period in each cohort.
- To evaluate the objective response rate (ORR) as per RECIST v1.0 every 12 weeks.
- To evaluate the disease control rate (DCR) as per RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort.
- To evaluate the best overall response as per RECIST v1.0.
- To evaluate the duration of stable disease (SD) as per RECIST v1.0.
- To detect predictive factors of PFS.
- To evaluate the effect on symptoms (diarrhoea, flushing).
- To evaluate quality of life.
- To evaluate the changes in tumour biomarkers:
  - pNET cohort: nonspecific tumour biomarkers (CgA, NSE and 5-hydroxyindoleacetic acid (5-HIAA); 5-HIAA only in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above upper limit of normal (ULN)) at Baseline) and pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …; only for the tumour biomarkers above normal range at Baseline).
  - Midgut cohort: nonspecific tumour biomarkers (CgA, NSE and 5-HIAA).
- To evaluate the appearance of antilanreotide antibodies.
- To evaluate the PK profile of lanreotide and to evaluate, if any, the relationship between PK and PD (PFS, tumour response or CgA).
- To evaluate, if any, the relationships between PK parameters and the safety outcomes.

The tertiary objectives of the study are as follows:

- CCI [redacted]
- [redacted].

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a phase II, multicentre, prospective, open label, noncomparative, exploratory study to evaluate the efficacy and safety of lanreotide Autogel® at a reduced dosing interval of 120 mg every 14 days in adults with well differentiated (grade 1 or 2 according to WHO 2010 classification), metastatic or locally advanced, unresectable pNET or midgut NET with or without hormone related syndromes and who have had radiologically documented disease progression (as per RECIST v1.0) at least 24 weeks after their first injection of lanreotide Autogel® 120 mg at the standard dosing interval of every 28 days. Subjects will be recruited into one of two cohorts based on primary location of NET (i.e. pancreatic or midgut).

The study will consist of a Screening visit (Day -28), where informed consent will be taken, followed by a Screening period of up to 28 days, where eligibility tests and assessments will be performed. At Baseline (Visit 2), subject eligibility will be verified and Baseline assessments will be performed, followed by an open label treatment period. Eligible subjects will be treated with lanreotide Autogel® at a reduced dosing interval (i.e. 120 mg every 14 days) beginning at Visit 2. Subjects in the pNET cohort will be treated for up to 48 weeks and subjects in the midgut cohort will be treated for up to 96 weeks. In both cohorts, treatment will be discontinued at disease progression or death, or unacceptable toxicity or tolerability.

Study visits will be performed at Weeks 2, 4, 8, 12, 24, 36 and 48 (both cohorts), and Weeks 60, 72, 84 and 96 (midgut cohort only). As long as 25 events have not been observed in the respective cohorts, subjects who have not progressed at Week 48 (pNET cohort) or Week 96 (midgut cohort) will continue study treatment with lanreotide Autogel® 120 mg every 14 days and additional visits will be performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.

An End of Study visit is scheduled approximately 2 weeks after the study visit at which progression is confirmed or after Weeks 48 (pNET cohort) or 96 (midgut cohort) for nonprogressive subjects, once central review of the radiological imaging is available. Subjects still benefiting from treatment at the End of Study visit will have the option to continue on commercial product at the discretion of the investigator.

'Injection only' visits will not be considered as study visits; however, for subjects who will be administered the investigational medicinal product (IMP) at home, the date and time of injection will be recorded in a subject diary card by the healthcare professional administering the injection and will be returned to the investigational site and entered into the electronic case report form (eCRF). Any AEs reported at these visits will be transmitted by the healthcare professional administering the injection to the responsible investigational site staff on the same day to be recorded on the eCRF, reported to the sponsor (if a serious adverse event (SAE)), and followed up as appropriate by the responsible investigational site staff.

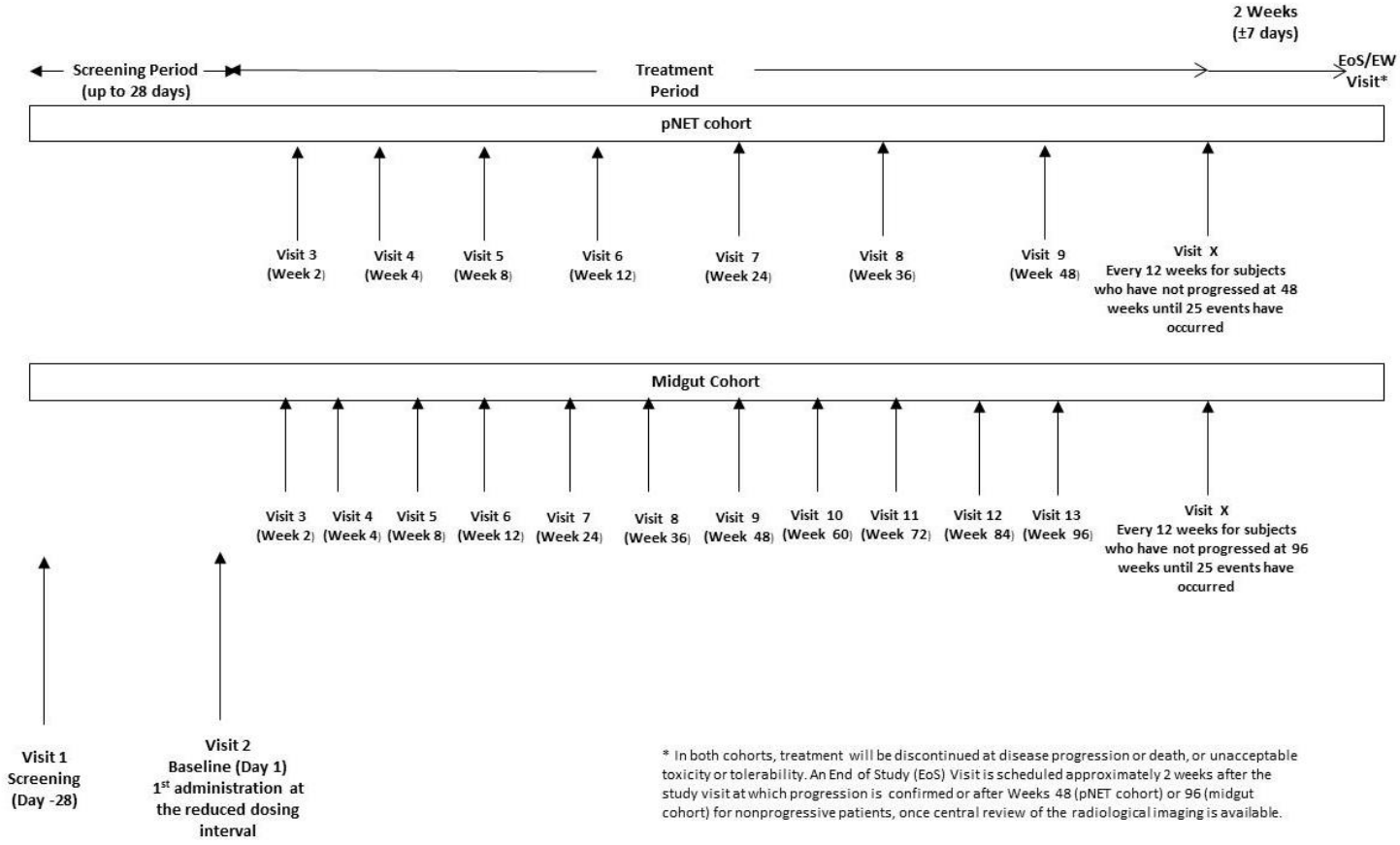
A data safety monitoring board (DSMB) covering both cohorts combined will be appointed to review data, as determined in the DSMB charter, at the following timepoints: (1) when 20 subjects from both cohorts have reached the Week 4 evaluation, (2) when 20 subjects from both cohorts have reached the Week 12 evaluation, and (3) when 50 subjects from both cohorts have reached the Week 12 evaluation.

Subjects who complete all scheduled visits or who have progressed or died will be considered to have completed the study.

For all subjects, with the exception of those who have died, final evaluations will be performed at the End of Study visit approximately 2 weeks (±7 days) after the subject's last treatment visit, once central review of radiological imaging data is available.

The study schema is provided in Figure 1.

Figure 1 Study Schema



3.2 Primary, Secondary and Tertiary Endpoints and Evaluations

3.2.1 Primary Efficacy Endpoint and Evaluation

The primary endpoint is median PFS (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death). Disease progression will be assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study, and by independent central review to ensure intra and intersubject consistency and reliability.

3.2.2 Secondary Efficacy Endpoints and Evaluations

- Median time to progression (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression).
- Proportion of subjects alive and without progression every 12 weeks.
- Overall survival at Week 48 and at the end of the study for each cohort.
- ORR every 12 weeks as per RECIST v1.0. ORR is defined as the proportion of subjects who achieve either complete response (CR) or partial response (PR).
- DCR evaluated according to RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort. The DCR is defined as the rate of CR plus PR plus SD.
- Best overall response according to RECIST v1.0 (defined as the best response recorded from the initiation of treatment until disease progression).
- Median duration of SD according to RECIST v1.0 (defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days until the first occurrence of progressive disease by central assessment).
- Factors associated with PFS will include but will not be limited to: hepatic tumour volume ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (yes/no), Ki67 <10% versus ≥10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days.
- Symptom control (diarrhoea, flushing) at Baseline, Weeks 8 and 12 and every 12 weeks thereafter, and at the End of Study visit, as measured by the total number of stools and flushing episodes during the 7 days prior to the visit reported orally by the subject to the investigator.
- Quality of life measured at Baseline, Week 12 and every 12 weeks thereafter, and at the End of Study visit, after diagnosis of progression, using European Organisation into the Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire Core 30 (QLQ-C30) v3.0 and Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21 (QLQ-GI.NET21; 2006), and EuroQoL 5 dimensions, 5 levels (EQ-5D-5L) v1.0 questionnaires.
- <u>pNET cohort</u>:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only). Note: at all scheduled visits, except Baseline, plasma/urinary 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.

- pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …) at Baseline, every 12 weeks thereafter and at the End of Study visit: only for the tumour biomarkers above normal range at Baseline.

- Midgut cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only).

3.2.3 Tertiary Efficacy Endpoints and Evaluations

- [redacted]

3.2.4 Safety Endpoints and Evaluations

- Clinical (AEs, vital signs, physical examination) and biological (serum haematology and biochemistry panels, liver and pancreatic enzymes, urinalysis) safety data collected at the timepoints specified in Table 2 (pNET cohort) and Table 3 (midgut cohort).
- Electrocardiogram (ECG) at Screening, Weeks 4, 24 and 48 (pNET cohort) or 96 (midgut cohort) and at End of Study.
- Gallbladder echography at Screening, and at Weeks 24 and 48 (pNET cohort) or 96 (midgut cohort) and at End of Study, or at any time if symptoms are thought to be related to gallbladder lithiasis.
- Potential relationships (if any) between PK parameters and safety outcomes.

3.2.5 Pharmacokinetic Endpoints and Evaluations

- Antilanreotide antibodies centrally analysed at Baseline and at the End of Study.
- Lanreotide serum concentration assessed at:
  - Baseline, prior to and 2 to 3 hours after the first injection at reduced dosing intervals;
  - Week 12, prior to injection
  - Week 24, prior to injection in all subjects, except in a subset of 30 subjects from selected sites, where a sample will be collected 1 to 3 days after the injection instead;
  - Week 48, prior to and 2 to 3 hours after injection;
  - Week 96 prior to injection (midgut cohort only);
  - End of Study, prior to any administration of commercial product (if applicable).

3.3 Randomisation and Blinding

This is a nonrandomised, single arm, two cohorts study.

3.4 Study Treatments and Dosage

The test product, lanreotide Autogel® 120 mg, will be administered as deep s.c. injections every 14 days starting at Visit 2 for up to 48 weeks (pNET cohort) or up to 96 weeks (midgut cohort) or until disease progression, death or unacceptable toxicity or tolerability.

Subjects in the pNET cohort who have not progressed at Week 48 will continue to receive lanreotide Autogel® every 14 days until 25 events in the pNET cohort have been observed. Similarly, subjects in the midgut cohort who have not progressed at Week 96 will continue to receive study treatment every 14 days until 25 events in the midgut cohort have been observed.

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

3.5 Study Treatment Supply, Packaging and Labelling

Lanreotide Autogel® will be packaged by the Chemistry, Manufacturing and Control Supply Chain (CMC-SC; CCI) and delivered to the investigational sites or deposited in an Interim Storage Facility (ISF). A sufficient quantity of lanreotide Autogel® 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 lanreotide Autogel® has been used under their study, Material Data Safety Sheet for lanreotide Autogel®, Packaging Order which reflects the product release statement.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages.

A description of the core text of the lanreotide Autogel® label is displayed below:

- Sponsor name
- Study Number
- Pharmaceutical dosage form
- Route of administration
- Quantity of dose units
- Batch number
- A treatment number
- A specific blank space to enter the subject ID
- "Keep out of reach of children"
- "For clinical study use only"
- "Caution: new drug limited by Federal Law to investigational use"
- Name, address and telephone number of the sponsor (the main contact for information on the product and clinical study)
- Storage conditions
- Expiry date

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

3.6 Study Duration

This study will consist of a Screening period of up to 28 days, a Baseline Visit (Visit 2), followed by an open label treatment period of up to 48 weeks (pNET cohort) or up to

96 weeks (midgut cohort), and a final End of Study visit approximately 2 weeks after the last treatment visit.

Each subject will participate in the study treatment phase for up to 48 weeks (pNET cohort) or up to 96 weeks (midgut cohort), or longer (i.e. until 25 events have been observed) for subjects who have not progressed within this time. The overall duration of the study will be approximately 102 weeks assuming at least 25 subjects progress within 48 and 96 weeks in the 2 cohorts respectively.

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

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 the End of Study visit.

3.7 Stopping Rules and Discontinuation Criteria

A DSMB covering both cohorts combined will review data in line with the DSMB charter at the following timepoints: (1) when 20 subjects from both cohorts have reached the Week 4 evaluation, (2) when 20 subjects from both cohorts have reached the Week 12 evaluation, and (3) when 50 subjects from both cohorts have reached the Week 12 evaluation. The purpose of the DSMB will be to evaluate safety early (Week 4) and at steady state (Week 12) of the reduced dosing interval, and to make recommendations to the sponsor as to whether the study should continue as planned or whether any changes are recommended to the trial conduct or protocol. The Chair of the DSMB will be responsible for communicating the DSMB's recommendations. Full details of the operating model for the DSMB will be provided in a DSMB charter.

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

The investigator should assess the ongoing benefit risk for each subject during their participation in the study, in consideration of any adverse events 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 (>2 x ULN) or lipase (>2 x ULN) with symptoms, or for >7 consecutive days without symptoms.
- Acute renal injury: NCI CTCAE grade ≥3; Creatinine >3x baseline or >4.0 mg/dL or hospitalization indicated.

- Hepatic impairment: NCI CTCAE grade ≥3 ALT (>5 x ULN) or AST (>5 x ULN) or Bilirubin (> 3 x ULN).
- 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. Subjects recommencing study drug may, if appropriate, re-start with an initial interval of 28 days between the first and second dose, before returning to the dosing interval of 14 days.

3.8 Investigational Medicinal Product Preparation Storage and Accountability

3.8.1 Investigational Medicinal Product Storage and Security

The investigator, or an approved representative (e.g. pharmacist), will ensure that all study drug is stored in a secured area, under recommended temperature monitored storage conditions (between +2°C and +8°C), in accordance with applicable regulatory requirements. Details of storage and distribution of study drug for injections performed at the subject's home are provided in Section 6.1.

3.8.2 Investigational Medicinal Product Preparation

Lanreotide Autogel® is supplied as a ready to use syringe, therefore no preparation is required. The investigator, or an approved representative (e.g. pharmacist), will ensure that all lanreotide Autogel® is dispensed by qualified staff members.

3.8.3 Investigational Medicinal Product Accountability

All study drug is to be accounted for on the accountability log provided by the sponsor. It is essential that all used and unused supplies are retained for safety and hygiene reasons and that syringes are eliminated in dedicated secure waste boxes, immediately after injection. These boxes will be destroyed according to normal practices for this category of injection waste. The destruction of unused study drugs and the outer boxes of the used study drugs should be performed by the sponsor or its representative. Study drug will be destroyed preferably on site or returned to CMC-SC ([redacted]).

3.9 Maintenance of Randomisation and Blinding

Not applicable as this is a nonrandomised, single arm, two cohorts study.

3.10 Source Data Recorded on the Electronic 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.

The items recorded directly on the eCRF and considered as source data will be described at each site in a site specific document signed by the investigator and filed in the investigator site file.

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 (for example 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 (CAs). This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

(1) Male or female subjects aged 18 years old or older.

(2) Histopathologically confirmed well differentiated (grade 1 or grade 2 according to the WHO 2010 classification), metastatic or locally advanced, unresectable pNET (pNET cohort) or midgut NET (midgut cohort) with or without hormone related syndromes, with a Ki67 ≤20%.

(3) Positive SSTR2 as assessed by imaging (scintigraphy or positron emission tomography (PET) scan) in the organs of target lesions.

(4) Progression as assessed by an independent central reviewer according to RECIST v1.0 from radiological imaging (CT scan or MRI) while receiving first line treatment with lanreotide Autogel® at a standard dose of 120 mg every 28 days for at least 24 weeks (6 injections). Progression must be radiologically documented using the same technique of images (CT scan or MRI) within 24 months prior to enrolment. Inclusion into the study must be within 28 days of the radiological imaging that is performed to document progression.

(5) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2.

(6) Provision of written informed consent prior to any study related procedures.

(7) Female subjects of childbearing potential (not surgically sterile or 2 years postmenopausal) must provide a negative urine pregnancy test at Screening, and use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 2 months after participation in the study. Acceptable methods of contraception include double barrier method, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted and injected).

(8) Subjects must be willing and able to comply with study restrictions and willing to return to the clinic for the follow up evaluation as specified in the protocol.

4.2 Exclusion Criteria

Subjects will not be included in the study if the subject:

(1) Has poorly differentiated grade 3 NET or rapidly progressive NET (within 12 weeks of initiation of lanreotide Autogel® 120 mg every 28 days) as per RECIST v1.0.

(2) Has been diagnosed with VIPoma (i.e. Verner Morrison syndrome), insulinoma, foregut (except for pNET), hindgut NET, unknown primary NET or multiple endocrine neoplasms (MEN).

(3) Has progressed during treatment with SSAs other than lanreotide Autogel® 120 mg.

(4) Has been previously treated with any antitumour agent for NET other than lanreotide Autogel® 120 mg every 28 days: chemotherapy, molecular targeted therapy, peptide receptor radionuclide therapy (PRRT) or interferon. Exception made of prior treatment with Octreotide at standard dose stopped for other reason than disease progression.

(5) Has had major surgery related to the studied disease within 3 months prior to entering the study. Previous debulking surgery and liver-directed therapies are acceptable as long as tumour burden is measurable (other target lesions).

(6) Has symptomatic gallbladder lithiasis/sludge at Screening echography or a history of symptomatic cholelithiasis with no cholecystectomy since then.

(7) Has had previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus if subjects treated with curative intent and free from disease for more than 5 years).

(8) Was treated with any other IMP within the last 30 days before study entry.

(9) Is pregnant or lactating.

(10) Has abnormal findings at Screening, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety.

(11) Has any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.

(12) Has been previously screened in this study, exception made of subjects who screen-failed following central reviewers eligibility assessment (ie non PD).

(13) Has a history of hypersensitivity to lanreotide Autogel® or drugs with a similar chemical structure, or any excipient used in the formulation.

(14) Is likely to require treatment during the study with drugs that are not permitted by the study protocol.

(15) Has a history of, or known current, problems with substance or alcohol abuse.

(16) Has a history of, or known current, problems with substance or alcohol abuse. Vulnerable subjects (i.e. subjects who are under legal protection, who are interned due to a mental disease and who are kept in detention).

(17) Subjects who have a link with the sponsor, the clinical trial site or the investigator (medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the sponsor).

4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, pregnancy (see Section 8.1.5), or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.7, 6.3, 8.1.7, 8.2.4 and 12.1.2.

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 5.2.4.1) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the 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, monitoring will continue until the event has resolved or stabilised, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol for the End of Study visit.

4.3.1 CCI

[redacted].

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study for the pNET and midgut cohorts is summarised in Table 2 and Table 3, respectively.

'Injection only' visits will not be considered as study visits; however, for subjects who will be administered the IMP at home, the date and time of injection will be recorded in a subject diary card by the healthcare professional administering the injection and will be returned to the investigational site and entered into the eCRF. Any AEs reported at these visits will be transmitted by the healthcare professional administering the injection to the responsible investigational site staff on the same day to be recorded on the eCRF, reported to the sponsor (if an SAE), and followed up as appropriate by the responsible investigational site staff.

Table 2 Study Procedures and Assessments (pNET Cohort)

Procedures and assessments	Screening period	Treatment period									End of Study/Early withdrawal[a]
	V1	V2	V3	V4	V5	V6	V7	V8	V9	VX[b]	EoS/EW
	-28 days	Baseline (Day 1)	W2	W4	W8	W12	W24	W36	W48	q12W	
Informed consent	X										
Demography	X										
Significant medical or surgical history	X										
NET history	X										
Prior treatments for study disease	X										
Inclusion and exclusion criteria	X	X									
Imaging assessment of SSTR2	X										
Urine pregnancy test	X										
Radiology imaging assessments (CT or MRI)[c]	X[d]					X	X	X	X	X	
Physical examination (including height (Screening only) and weight)	X		X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	X	X
Symptoms (diarrhoea, flushing)[e]		X			X	X	X	X	X	X	X
Prior and concomitant medication, and concomitant surgery and nondrug therapies	X	X	X	X	X	X	X	X	X	X	X
Quality of life questionnaires (QLQ-C30, QLQ-GI.NET21, EQ-5D-5L)		X				X	X	X	X	X	X
Study drug administration[f]		X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
ECG	X			X			X		X		X
Gallbladder echography[g]	X						X		X		X
Clinical laboratory tests (haematology and biochemistry panels, liver and pancreatic enzymes)	X	X		X	X	X	X	X	X	X	X
Urinalysis	X	X							X		X
Nonspecific tumour biomarkers: 5-HIAA, NSE and CgA[h]		X[i]				X[i]	X	X	X	X	X[i]
pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …,)[j]		X				X	X	X	X	X	X
PK samples		X[k]				X[l]	X[m]		X[n]		X[o]

Procedures and assessments	Screening period	Treatment period									End of Study/Early withdrawal[a]
	V1	V2	V3	V4	V5	V6	V7	V8	V9	VX[b]	EoS/EW
	-28 days	Baseline (Day 1)	W2	W4	W8	W12	W24	W36	W48	q12W	
Antilanreotide antibodies		X									X
CCI		X				X	X	X	X		

5-HIAA=5-hydroxyindoleacetic acid; CgA=chromogranin A; CT=computed tomography; CCI d; ECG=electrocardiogram; EoS=End of Study; EQ-5D-5L=EuroQoL 5 dimensions, 5 levels; EW=early withdrawal; MRI=magnetic resonance imaging; NET=neuroendocrine tumour; NSE=neuron specific enolase; PK=pharmacokinetic; pNET=pancreatic NET; q12w=every 12 weeks; QLQ-C30=Quality of Life Questionnaire Core 30; QLQ-GI.NET21=Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21; CCI ; SST=somatostatin; SSTR2=somatostatin receptor 2; ULN=upper limit of normal; V=Visit; W=Week.

Note: for study visits up to and including Week 4, visit windows are ±2 days and for visits after Week 4, visit windows are ±7 days.

a to be scheduled approximately 2 weeks after last treatment visit, once central review of radiological imaging is available.
b additional visits every 12 weeks: only for subjects not progressing within 48 weeks until 25 events have been observed in the pNET cohort.
c CT or MRI of the abdomen; additional scan of the pelvis and/or chest as deemed necessary or clinically indicated, or as per the centre's standard of care.
d radiology imaging assessments (CT or MRI) performed prior to signature of the informed consent form but within 28 days of the Baseline Visit (Visit 2; Day 1) do not need to be repeated as a screening procedure provided that the radiology imaging was performed at the centre's radiology facility or that the radiology imaging was deemed by the centre's radiologist to be of sufficient quality to be used as the reference screening assessment for the evaluation of response during the study.
e subjects will report the total number of stools and flushing episodes during the 7 days prior to the visit orally to the investigator.
f study drug will be administered every 14 days (±1day).
g may be performed at any time if symptoms are thought to be related to gallbladder lithiasis.
h at all scheduled visits, except Baseline, plasma/urinary 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.
i in addition to plasma 5-HIAA, urinary 5-HIAA will be assessed at Baseline, Week 12 and at the End of Study visit only.
j only for the tumour biomarkers above normal range at Baseline.
k collected prior to and 2 to 3 hours after the first injection (exact time to be recorded) at reduced dosing intervals.
l collected prior to injection.
m collected prior to injection in all subjects, except in a subset of 30 subjects from selected sites who provide additional informed consent, where a sample will be collected 1 to 3 days after the injection instead.
n collected prior to and 2 to 3 hours after the injection (exact time to be recorded).
o at End of Study only: prior to any administration of commercial product (if applicable).
p CCI .

Table 3 Study Procedures and Assessments (Midgut Cohort)

Procedures and assessments	Screening period	Treatment period													End of Study/Early withdrawal[a]
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	VX[b]	EoS/EW
	-28 days	Baseline (Day 1)	W2	W4	W8	W12	W24	W36	W48	W60	W72	W84	W96	q12W	
Informed consent	X														
Demography	X														
Significant medical or surgical history	X														
NET history	X														
Prior treatments for study disease	X														
Inclusion and exclusion criteria	X	X													
Imaging assessment of SSTR2	X														
Urine pregnancy test	X														
Radiology imaging assessments (CT or MRI)[c]	X[d]					X	X	X	X	X	X	X	X	X	
Physical examination (including height (Screening only) and weight)	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Symptoms (diarrhoea, flushing)[e]		X			X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medication, and concomitant surgery and nondrug therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life questionnaires (QLQ-C30, QLQ-GI.NET21, EQ-5D-5L)		X				X	X	X	X	X	X	X	X	X	X
Study drug administration[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X			X			X						X		X
Gallbladder echography[g]	X						X						X		X
Clinical laboratory tests (haematology and biochemistry panels, liver and pancreatic enzymes)	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X							X				X		X

Procedures and assessments	Screening period	Treatment period													End of Study/Early withdrawal[a]
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	VX[b]	EoS/EW
	-28 days	Baseline (Day 1)	W2	W4	W8	W12	W24	W36	W48	W60	W72	W84	W96	q12W	
Nonspecific tumour biomarkers: 5-HIAA, NSE and CgA		X[h]				X[h]	X	X	X	X	X	X	X	X	X[h]
PK samples		X[i]				X[j]	X[k]		X[l]				X[j]		X[m]
Antilanreotide antibodies		X													X
CCI [redacted]]		X				X		X		X		X			

5-HIAA=5-hydroxyindoleacetic acid; CgA=chromogranin A; CT=computed tomography; CCI [redacted]; ECG=electrocardiogram; EoS=End of Study; EQ-5D-5L=EuroQoL 5 dimensions, 5 levels; EW=early withdrawal; MRI=magnetic resonance imaging; NET=neuroendocrine tumour; NSE=neuron specific enolase; PK=pharmacokinetic; pNET=pancreatic NET; q12w=every 12 weeks; QLQ-C30=Quality of Life Questionnaire Core 30; QLQ-GI.NET21=Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21; CCI [redacted] SST=somatostatin; SSTR2=somatostatin receptor 2; V=Visit; W=Week.

Note: for study visits up to and including Week 4, visit windows are ±2 days and for visits after Week 4, visit windows are ±7 days.

a to be scheduled approximately 2 weeks after last treatment visit, once central review of radiological imaging is available.
b additional visits every 12 weeks: only for subjects not progressing within 96 weeks until 25 events have been observed in the midgut cohort.
c CT or MRI of the abdomen; additional scan of the pelvis and/or chest as deemed necessary or clinically indicated, or as per the centre's standard of care.
d radiology imaging assessments (CT or MRI) performed prior to signature of the informed consent form but within 28 days of the Baseline Visit (Visit 2; Day 1) do not need to be repeated as a screening procedure provided that the radiology imaging was performed at the centre's radiology facility or that the radiology imaging was deemed by the centre's radiologist to be of sufficient quality to be used as the reference screening assessment for the evaluation of response during the study.
e subjects will report the total number of stools and flushing episodes during the 7 days prior to the visit orally to the investigator.
f study drug will be administered every 14 days (±1day).
g may be performed at any time if symptoms are thought to be related to gallbladder lithiasis.
h in addition to plasma 5-HIAA, urinary 5-HIAA will be assessed at Baseline, Week 12 and at the End of Study visit only.
i collected prior to and 2 to 3 hours after the first injection (exact time to be recorded) at reduced dosing intervals.
j collected prior to injection.
k collected prior to injection in all subjects, except in a subset of 30 subjects from selected sites who provide additional informed consent, where a sample will be collected 1 to 3 days after the injection instead.
l collected prior to and 2 to 3 hours after the injection (exact time to be recorded).
m at End of Study only: prior to any administration of commercial product (if applicable).
n CCI [redacted]

The maximum volume of blood drawn for each subject who continues up to Week 48 (pNET cohort) or Week 96 (midgut cohort), including the End of Study/Early Withdrawal Visit, is 267 mL and 295 mL, respectively. For subjects who continue after 48 or 96 weeks until the 25 events have been observed, 15 mL of blood will be taken for clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes), 6 mL of blood will be taken for nonspecific tumour biomarkers and between 4 mL and 10 mL of blood will be taken for pNET-specific tumour biomarkers (depending on type) at each additional visit (where applicable).

CCI [redacted]

5.2 Study Visits

5.2.1 Procedures for Screening (Visit 1; Day -28)

The study will consist of a Screening visit (Day -28) followed by a Screening period of up to 28 days.

Signed and dated informed consent forms will be obtained at Screening (Day -28; Visit 1) before any study related procedures. CCI [redacted]

After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

The following assessments will be performed in both cohorts during the Screening period of up to 28 days, prior to administration of study treatment at Baseline (Visit 2; Day 1):

- Demographic data (date of birth, sex and race will be collected according to individual country requirements)
- Significant medical or surgical history
- NET history
- Prior treatments for the study disease
- Eligibility check (inclusion/exclusion criteria)
- Imaging assessment of SSTR2 (previous assessment within 24 months is acceptable)
- Urine pregnancy test
- Radiology imaging assessments (CT or MRI of the abdomen; additional scan of the pelvis and/or chest as deemed necessary or clinically indicated, or as per the centre's standard of care). Note: radiology imaging assessments (CT or MRI) performed prior to signature of the informed consent form but within 28 days of the Baseline Visit (Visit 2; Day 1) do not need to be repeated as a screening procedure provided that the radiology imaging was performed at the centre's radiology facility or that the radiology imaging was deemed by the centre's radiologist to be of sufficient quality to be used as the reference screening assessment for the evaluation of response during the study.
- Physical examination (including weight and height)

- Vital signs (body temperature, supine and standing blood pressure and heart rate)
- Prior and concomitant medications, and concomitant surgery and nondrug therapies
- Start of collection of AEs
- ECG
- Gallbladder echography
- Clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes)
- Urinalysis

Only subjects who screen-failed solely due to non-eligibility according to central review (ie non PD) can be screened more than once.

Each investigator will maintain a record of all subjects screened into the study (i.e. who signed the informed consent forms). Records up to the time of premature termination should be completed. In the event that the subject does not receive study drug the primary reason will be recorded on the eCRF.

5.2.2 Procedures for Baseline (Visit 2; Day 1)

The following Baseline assessments will be performed:

- Eligibility check (inclusion/exclusion criteria)
- Symptoms of diarrhoea and flushing (total number of stools/flushing episodes during previous 7 days)
- Concomitant medication, surgery and nondrug therapies
- Quality of life questionnaires
- Review of AEs since Screening
- Clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes)
- Urinalysis
- Nonspecific biomarkers: plasma and urinary 5-HIAA, NSE and CgA; both cohorts
- pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST,…,) for subjects in the pNET cohort only
- Blood sampling for PK and antilanreotide antibodies
- CCI

Study drug administration at the reduced dosing interval of every 14 days will commence at Visit 2 (Baseline) following completion of the Baseline assessments. Following the first injection of lanreotide Autogel® 120 mg at the reduced dosing interval, blood samples for PK analysis will be taken 2 to 3 hours post dose (exact time to be recorded).

5.2.3 Procedures During Study Treatment

Following the first dose at the reduced dosing interval at Visit 2 (Baseline), lanreotide Autogel® will be administered every 14 days (± 1 day) thereafter for up to 48 weeks (pNET cohort) and up to 96 weeks (midgut cohort), or until disease progression, death, or unacceptable toxicity or tolerability. For subjects who have not progressed at 48 weeks (pNET cohort) or 96 weeks (midgut cohort), study drug administration will continue and additional visits will be performed every 12 weeks after this time until 25 events have been observed in the respective cohort.

'Injection only' visits will not be considered as study visits; however, for subjects who will be administered the IMP at home, the date and time of injection will be recorded in a subject

diary card by the healthcare professional administering the injection and will be returned to the investigational site and entered into the eCRF. Any AEs reported at these visits will be transmitted by the healthcare professional administering the injection to the responsible investigational site staff on the same day to be recorded on the eCRF, reported to the sponsor (if an SAE), and followed up as appropriate by the responsible investigational site staff. At some sites and for some subjects, the injections at 'injection only' visits may be carried out by a "nurse service" at the subject's home rather than the subject attending the investigational site or a member of the investigational site personnel visiting the subject's home. In such cases, the subject will give their consent and the nurses will be qualified, trained in the study protocol and fully aware of the AE reporting procedure. In addition, they will be under the sponsor's responsibility and in contact with the investigational site.

5.2.3.1 Visits 3, 4 and 5 (Weeks 2, 4 (±2 Days) and 8 (±7 Days)): Both Cohorts

The following procedures will be performed in both cohorts prior to administration of lanreotide Autogel®:

- Physical examination (including weight)
- Vital signs (body temperature, supine and standing blood pressure and heart rate)
- Symptoms of diarrhoea and flushing (total number of stools/flushing episodes during previous 7 days; Visit 5 (Week 8) only)
- Concomitant medication, surgery and nondrug therapies
- Review of AEs
- ECG (Visit 4 (Week 4) only)
- Clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes; except Visit 3 (Week 2))

5.2.3.2 Visits 6, 7, 8 and 9 (Weeks 12, 24, 36 and 48 (±7 Days)): Both Cohorts

The following procedures will be performed in both cohorts prior to administration of lanreotide Autogel®:

- Radiology imaging assessments (CT or MRI of the abdomen; additional scan of the pelvis and/or chest as deemed necessary or clinically indicated, or as per the centre's standard of care; same technique as performed at Screening)
- Physical examination (including weight)
- Vital signs (body temperature, supine and standing blood pressure and heart rate)
- Symptoms of diarrhoea and flushing (total number of stools/flushing episodes during previous 7 days)
- Concomitant medication, surgery and nondrug therapies
- Quality of life questionnaires
- Review of AEs
- ECG and gallbladder echography (Visit 7 (Week 24) only both cohorts; Visit 9 (Week 48) only pNET cohort)
- Clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes)
- Urinalysis (Visit 9 (Week 48) only)
- Nonspecific biomarkers: plasma 5-HIAA, NSE and CgA; urinary 5-HIAA at Visit 6 (Week 12) only; both cohorts. Note: in the pNET cohort, plasma/urinary

5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline

- pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST,…,) for subjects in the pNET cohort only and only for the tumour biomarkers above normal range at Baseline
- Blood sampling for PK at:
  - Visit 6 (Week 12): prior to injection
  - Visit 7 (Week 24): prior to injection in all subjects, except in a subset of 30 subjects from selected sites who provide additional informed consent, where a sample will be collected 1 to 3 days after the injection instead
  - Visit 9 (Week 48): prior to injection and 2 to 3 hours after injection (exact time to be recorded)
- CCI [redacted]

5.2.3.3 Visits 10, 11, 12 and 13 (Weeks 60, 72, 84 and 96 (±7 Days)): Midgut Cohort Only

The following procedures will be performed in the midgut cohort only prior to administration of lanreotide Autogel®:

- Radiology imaging assessments (CT or MRI of the abdomen; additional scan of the pelvis and/or chest as deemed necessary or clinically indicated, or as per the centre's standard of care; same technique as performed at Screening)
- Physical examination (including weight)
- Vital signs (body temperature, supine and standing blood pressure and heart rate)
- Symptoms of diarrhoea and flushing (total number of stools/flushing episodes during previous 7 days)
- Concomitant medication, surgery and nondrug therapies
- Quality of life questionnaires
- Review of AEs
- ECG and gallbladder echography (Visit 13 (Week 96) only)
- Clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes)
- Urinalysis (Visit 13 (Week 96) only)
- Nonspecific biomarkers: plasma 5-HIAA, NSE and CgA
- Blood sampling for PK at:
  - Visit 13 (Week 96): prior to injection
- CCI [redacted]

5.2.3.4 Additional Visits Every 12 Weeks (±7 Days) for Subjects Who Have Not Progressed

Subjects in the pNET cohort who have not progressed at Week 48 will continue to receive lanreotide Autogel® every 14 days and be followed up every 12 weeks until progression, death, or unacceptable toxicity or tolerability or until 25 events have been observed in the pNET cohort. Similarly, subjects in the midgut cohort who have not progressed at Week 96 will continue to receive study treatment every 14 days after Week 96 and will also be followed up every 12 weeks until progression, death, unacceptable toxicity or tolerability or until 25 events have been observed in the midgut cohort.

The following procedures will be performed in both cohorts prior to administration of lanreotide Autogel®:

- Radiology imaging assessments (CT or MRI of the abdomen; additional scan of the pelvis and/or chest as deemed necessary or clinically indicated, or as per the centre's standard of care; same technique as performed at Screening)
- Physical examination (including weight)
- Vital signs (body temperature, supine and standing blood pressure and heart rate)
- Symptoms of diarrhoea and flushing (total number of stools/flushing episodes during previous 7 days)
- Concomitant medication, surgery and nondrug therapies
- Quality of life questionnaires
- Review of AEs
- Clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes)
- Nonspecific biomarkers: plasma 5-HIAA, NSE and CgA; both cohorts. Note: in the pNET cohort, plasma/urinary 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline
- pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST,…,) for subjects in the pNET cohort only and only for the tumour biomarkers above normal range at Baseline

5.2.4 Procedures After Study Treatment

5.2.4.1 End of Study/Early Withdrawal Visit

Subjects who complete all scheduled visits or who have progressed or died will be considered to have completed the study.

For all subjects, with the exception of those who have died, final evaluations will be performed at the End of Study visit approximately 2 weeks (±7 days) after the subject's last treatment visit, once central review of radiological imaging data is available. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.3 and Section 8.2, respectively.

The following procedures will be performed in both cohorts at the End of Study visit:

- Physical examination (including weight)
- Vital signs (body temperature, supine and standing blood pressure and heart rate)
- Symptoms of diarrhoea and flushing (total number of stools/flushing episodes during previous 7 days)
- Concomitant medication, surgery and nondrug therapies
- Quality of life questionnaires
- Review of AEs
- ECG and gallbladder echography
- Clinical laboratory tests (blood sampling for haematology and biochemistry panels, liver and pancreatic enzymes)
- Urinalysis
- Nonspecific biomarkers: plasma and urinary 5-HIAA, NSE and CgA; both cohorts. Note: in the pNET cohort, plasma/urinary 5-HIAA should only be performed in

subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline

- pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST,…,) for subjects in the pNET cohort only and only for the tumour biomarkers above normal range at Baseline
- Blood sampling for PK and antilanreotide antibodies

Subjects still benefiting from treatment at the End of Study visit will have the option to continue on commercial product at the discretion of the investigator once all study assessments have been performed.

6 TREATMENT OF SUBJECTS

6.1 Study Drugs Administered

All subjects will receive deep s.c. injections of lanreotide Autogel® 120 mg every 14 days for up to 48 weeks (pNET cohort) or up to 96 weeks (midgut cohort), or until disease progression, death, or unacceptable toxicity or tolerability. Subjects in the pNET cohort who have not progressed at Week 48 will continue to receive lanreotide Autogel® every 14 days until 25 events have been observed in the pNET cohort. Similarly, subjects in the midgut cohort who have not progressed at Week 96 will continue to receive study treatment every 14 days until 25 events have been observed in the midgut cohort. At some sites and for some subjects, the injections at 'injection only' visits may be carried out by a "nurse service" at the subject's home rather than the subject attending the investigational site or a member of the investigational site personnel visiting the subject's home (see Section 5.2.3).

Where administrations are to be performed at a subject's home, in order to comply with the storage requirements, study drug will be delivered directly to subject in due time, from the investigational sites, through a specific courier. This courier will act upon request of the investigators, according to applicable Good Distribution Practice (GDP). Traceability will be maintained throughout the product flows. Full logistics, including responsibilities of the courier, sponsor and investigators, will be detailed in a separate document agreed between sponsor and the courier.

6.1.1 Investigational Medicinal Product

Lanreotide Autogel® 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.

Lanreotide Autogel® will be administered by deep s.c. injection in the superior, external quadrant of the buttock at a dose of 120 mg, every 14 days.

6.2 Concomitant Medication/Therapy

All prior treatments for the study disease will be recorded on the eCRF. Any prior or concomitant therapy or medication given to a subject for another indication within 28 days before study drug administration or during study drug administration will be indicated on the eCRF. Dose and generic name or tradename will be indicated.

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

- chemotherapy, molecular targeted therapy, PRRT and interferon
- any SSAs other than lanreotide Autogel® 120 mg,
- GH antagonists,
- Cyclosporin
- tumour resection.

Previous debulking surgery and liver-directed therapies are acceptable as long as tumour burden is measurable (other target lesions).

All other concomitant treatments taken by the subject during the course of the study will be recorded on the eCRF. 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 (Section 6 Summary of Data and Guidance for the Investigator).

6.3 Procedures for Monitoring Subject Compliance

Study drug will be administered by a healthcare professional at each visit. 'Injection only' visits will not be considered as study visits; however, the date and time of injection will be recorded in a subject diary card by the healthcare professional administering the injection and will be returned to the investigational site and entered into the eCRF. At some sites and for some subjects, the 'injection only' visits may be carried out by a "nurse service" at the subject's home rather than the subject attending the investigational site or a member of the investigational site personnel visiting the subject's home. In such cases, the subject will give their consent and the nurses will be qualified, trained in the study protocol and fully aware of the AE reporting procedure. In addition, they will be under the sponsor's responsibility and in contact with the investigational site.

The investigator will be responsible for monitoring subject compliance. Subjects can be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol.

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 (pNET cohort) and Table 3 (midgut cohort).

7.1 Primary Efficacy Endpoint and Evaluation

The primary endpoint is median PFS (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death). Disease progression will be assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study, and by independent central review to ensure intra and intersubject consistency and reliability.

7.2 Secondary Efficacy Endpoints and Evaluations

- Median time to progression (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression).
- Proportion of subjects alive and without progression every 12 weeks.
- Overall survival at Week 48 and at the end of the study for each cohort.
- ORR every 12 weeks as per RECIST v1.0. ORR is defined as the proportion of subjects who achieve either CR or PR.
- DCR evaluated according to RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort. The DCR is defined as the rate of CR plus PR plus SD.
- Best overall response according to RECIST v1.0 (defined as the best response recorded from the initiation of treatment until disease progression).
- Median duration of SD according to RECIST v1.0 (defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days until the first occurrence of progressive disease by central assessment).
- Factors associated with PFS will include but will not be limited to: hepatic tumour volume ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (yes/no), Ki67 <10% versus ≥10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days.
- Symptom control (diarrhoea, flushing) at Baseline, Weeks 8 and 12 and every 12 weeks thereafter, and at the End of Study visit, as measured by the total number of stools and flushing episodes during the 7 days prior to the visit reported orally by the subject to the investigator.
- Quality of life measured at Baseline, Week 12 and every 12 weeks thereafter, and at the End of Study visit, after diagnosis of progression, using EORTC QLQ-C30 v3.0 and QLQ-GI.NET21 (2006), and EQ-5D-5L v1.0 questionnaires.
- pNET cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only). Note: at all scheduled visits, except Baseline, plasma/urinary 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.
  - pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …) at Baseline, every 12 weeks thereafter and at the End of Study visit: only for the tumour biomarkers above normal range at Baseline.

- Midgut cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only).

7.3 Tertiary Efficacy Endpoints and Evaluations

- CCI [redacted]

Primary, secondary and tertiary efficacy endpoints and evaluations are summarised in Table 4.

Table 4 Primary, Secondary and Tertiary Efficacy Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Disease progression or death	Screening and every 12 weeks or death date	PFS	Median PFS by centralised CT/MRI scan assessment (RECIST v1.0) or death.
Time to progression	Screening and every 12 weeks	Time to progression	Median time to progression
PFS	Screening and every 12 weeks	PFS rate	Proportion of subjects alive and without progression every 12 weeks
Overall survival	Week 48 and EoS	Overall survival	Overall survival
ORR	Screening and every 12 weeks	ORR	ORR every 12 weeks as per RECIST v1.0.
DCR	Weeks 24 and 48, and EoS	DCR	DCR evaluated according to RECIST v1.0.
Best overall response	Screening and then every 12 weeks until disease progression	Best overall response	Best overall response according to RECIST v1.0
Duration of SD	Screening and until the first occurrence of progressive disease by central assessment	Duration of SD	Median duration of SD by centralised CT/MRI scan assessment (RECIST v1.0)
Factors associated with PFS	Screening for all factors, every 12 weeks and death date	PFS and associated factors, to include: hepatic tumour volume, tumour severity, tumour functionality, previous surgery of the primary tumour, Ki67 level, prior duration of treatment with lanreotide Autogel®	Factors associated with PFS will include but will not be limited to: • hepatic tumour volume ≤25% versus >25%, • grade 1 versus grade 2, • previous surgery of the primary tumour (yes/no), • Ki67 <10% versus ≥10%, • duration of treatment with lanreotide Autogel® at standard dose every 28 days.

Measure	Timepoint	Variable	Endpoint
Symptom control	Baseline, Weeks 8 and 12, every 12 weeks thereafter, and at EoS	Total number of stools, total number of flushing episodes in previous 7 days (reported by subject)	Symptom control (diarrhoea and flushing) at Baseline, Weeks 8 and 12 and every 12 weeks thereafter, and at the End of Study visit, as measured by total number of stools and flushing episodes during the 7 days prior to the visit reported orally by the subject to the investigator.
Quality of life	Baseline, Week 12, every 12 weeks thereafter and at EoS	EORTC QLQ-C30 v3.0 and QLQ-GI.NET21 (2006), and EQ-5D-5L v1.0 questionnaires	Quality of life measured at Baseline, Week 12 and every 12 weeks thereafter, and at the EoS visit, after diagnosis of progression, using EORTC QLQ-C30 v3.0 and QLQ-GI.NET21 (2006), and EQ-5D-5L v1.0 questionnaires.
Tumour biomarkers (pNET cohort)	Baseline and every 12 weeks thereafter, and at EoS[a]	Concentrations of nonspecific and pNET-specific tumour biomarkers	• Nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only).[a] • pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …) at Baseline, every 12 weeks thereafter and at the End of Study visit: only for the tumour biomarkers above normal range at Baseline.
Tumour biomarkers (midgut cohort)	Baseline and every 12 weeks thereafter, and at EoS	Concentrations of nonspecific tumour biomarkers	Nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only).
CCI [redacted]	[redacted]	CCI [redacted]	[redacted]

Measure	Timepoint	Variable	Endpoint
CCI [redacted]	[redacted]	CCI [redacted]	[redacted]

5-HIAA=5-hydroxyindoleacetic acid; CgA=chromogranin A; CT=computed tomography; DCR=disease control rate; EORTC=European Organisation into the Research and Treatment of Cancer; EoS=End of Study; EQ-5D-5L=EuroQoL 5 dimensions, 5 levels; Ki67=proliferation index; MRI=magnetic resonance imaging; NSE=neuron specific enolase; ORR=objective response rate; PFS=progression free survival; pNET=pancreatic neuroendocrine tumour; QLQ-C30=Quality of Life Questionnaire-Core 30; QLQ-GI.NET21=Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease; SST=somatostatin; StD=standard deviation; CCI [redacted]; ULN=upper limit of normal.

CCI [redacted].

a at all scheduled visits, except Baseline, plasma/urinary 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.

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

Median PFS (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death) will be presented for each cohort. In addition, the proportion of subjects alive and without progression every 12 weeks will be estimated.

7.4.2 Tumour Response

Tumour assessments will be performed using the RECIST v1.0 criteria every 12 weeks throughout the study. The same imaging technique (CT scan or MRI) will be used for each subject throughout the study and assessments will be made by independent central review to ensure intra and intersubject consistency and reliability. In addition, at Screening, the Central Reading contract research organisation (CRO) will measure the hepatic tumour load. From the imaging data, median PFS and PFS rate (see Section 7.4.1), median time to progression, ORR, best overall response, DCR and median duration of SD will be estimated, along with CCI [redacted] CT or MRI.

Table 5 Overall Response

Target lesion	Nontarget lesion	New lesion	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non progressive disease	No	PR
SD	Non progressive disease	No	SD
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease

CR=complete response; PR=Partial response; SD=stable disease [23].

Median time to progression is defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression. The ORR, defined as the proportion of subjects who achieve either CR or a PR, will be assessed every 12 weeks. The best overall response is defined as the best response recorded from initiation of treatment until disease progression (Table 5). The DCR is defined as the rate of CR plus PR plus SD and will be presented at Weeks 24 and 48 and at the End of Study. Median duration of SD is defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days until the first occurrence of progressive disease by central assessment.

7.4.3 Factors Associated with PFS

Factors associated with PFS will include but will not be limited to: hepatic tumour volume ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (yes/no), Ki67 <10% versus ≥10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days). These factors are recorded at Screening, prior to dosing with lanreotide Autogel® at the reduced dosing interval.

7.4.4 Incidence of Stools and Flushing Episodes

The total number of stools and flushing events in the 7 days prior to each visit will be collected at each visit (except Screening, and Visits 3 and 4) based on information reported orally by the subject to the investigator.

7.4.5 Quality of Life

Quality of life will be assessed using the EORTC QLQ-C30 v3.0 and QLQ-GI.NET21 (2006), and EQ-5D-5L v1.0 questionnaires. The questionnaires will be completed at each visit (except Screening, and Visits 3, 4 and 5). The investigator or delegated personnel will explain the questions to the subject if necessary. The subject will complete the questionnaires in the same conditions throughout the study (i.e. prior to study medication administration).

7.4.6 Tumour Biomarkers

Blood samples will be taken for tumour biomarker analyses as follows:

- pNET cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit. At all scheduled visits, except Baseline, plasma 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.
  - pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …) at Baseline, every 12 weeks thereafter and at the End of Study visit: only for the tumour biomarkers above normal range at Baseline.
- Midgut cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit.

Samples will be taken, prepared and shipped as specified in the Central Laboratory Services Manual.

A 24-hour urine sample for 5-HIAA will also be taken at Baseline, Week 12, and at the End of Study visit for all subjects in the midgut cohort. For subjects in the pNET cohort, a 24-hour urine sample for 5-HIAA will be taken at Baseline for all subjects, and at Week 12 and the End of Study visit for subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or for those with elevated (above ULN) urinary 5-HIAA at Baseline. Each 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. 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 analysed in order to assess compliance with the 24-hour collection period.

8 ASSESSMENT OF SAFETY

For the timing of assessments in this study, refer to the schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort).

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study (see Section 3.6 for a definition of the study duration) and will be elicited by direct, nonleading questioning or if spontaneously reported by the subject. Further details for AE reporting can be found in Section 8.1.3.

Any AEs reported at 'injection only' visits will be transmitted by the healthcare professional administering the injection to the responsible investigational site staff on the same day to be recorded on the eCRF, reported to the sponsor (if an SAE), and followed up as appropriate by the responsible investigational site staff.

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, ECG). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no lanreotide Autogel® has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.6).

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

Death due to disease progression will be recorded as part of the efficacy evaluation and will not be regarded as an AE/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 disease under study.

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

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

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

Symptoms of diarrhoea and flushing will be collected as AEs and recorded on the eCRF.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

AEs will be recorded and graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) (Version 4.03, 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 wellbeing, significant impairment of function or incapacitation.
- **Life threatening:** any event that places the subject at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death (also see Section 8.1.4).

8.1.2.2 Causality Classification

The relationship of an AE to 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. ECG changes) that result in a change in study drug dosage or administration schedule, or in discontinuation of 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 study visit, the subject should be asked a nonleading question such as: "How have you felt since starting treatment at the reduced dosing interval?"

'Injection only' visits will not be considered as study visits; however, any AEs reported at these visits will be transmitted by the healthcare professional administering the injection to the responsible investigational site staff on the same day to 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 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 an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to make an assessment of 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 value 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 suspected relationship to study drug must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

An 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 inpatient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further),

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

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

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

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

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

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 study drug has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected (poststudy if necessary) and it may be necessary to discontinue administration of study drug.

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

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

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

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

8.1.6 Deaths

All AEs resulting in death during the study period or within 28 days after the last dose of lanreotide Autogel® must be reported as an SAE within 24 hours of the investigator's knowledge of the event, apart from death due to disease progression, which will not be regarded as an AE/SAE (see Section 8.1.1).

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 study drug.

If the study drug is discontinued due to an AE/SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.4). In all cases, the investigator must ensure the subject receives appropriate medical follow up (see Section 8.1.3).

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

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

8.2 Clinical Laboratory Tests

Blood and urine samples will be collected according to the study schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort) for the evaluation of haematology and biochemistry panels, liver and pancreatic enzymes, and urinalysis.

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

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

8.2.1 Haematology

The following parameters will be assessed: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others) and platelet count.

8.2.2 Blood Biochemistry

The following parameters will be assessed:

- urea, creatinine, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate
- alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase
- albumin, total protein, total cholesterol, triglycerides, fasting glucose (blood sample to be taken after at least 6 hours of fasting), amylase and lipase

Blood samples will be collected to assess HbA1c.

Any unscheduled test (indication and results) will be recorded on the dedicated page in the eCRF.

8.2.3 Urinalysis

Fresh urine samples (at least 10 mL) will be collected to assess the following parameters: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity.

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

8.2.4 Pregnancy Test

A urine pregnancy test will be performed for all female subjects of childbearing potential at Screening (Visit 1) and if clinically indicated thereafter. If this is found to be positive, it will be followed up with a beta human chorionic gonadotropin (βHCG) serum test. Any subject becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.5.

8.3 Physical Examination

Physical examinations, including body weight, will be conducted according to the study schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort), and height will be measured at Screening (Visit 1).

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at

the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4 Vital Signs

Vital signs will be recorded according to the study schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort). Blood pressure and heart rate will be recorded after 5 minutes rest in the supine position and after 1 minute standing.

Body temperature will also be recorded.

Any clinically significant abnormalities will be recorded as AEs.

8.5 Electrocardiography

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

The ECGs will be recorded according to the study schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort). Computerised standard 12 lead ECGs will be used so that the different ECG parameters (sinus rhythm, heart rate, RR interval, PR interval, QRS interval, QT and QTc) can be measured automatically. QTc will be calculated using Fridericia methodology. The ECG will be recorded with the subject in a supine position after 5 minutes of rest until four regular consecutive complexes are available. Automated ECG interval estimates taken from the ECG recorder will be used in this study.

Any clinically significant abnormalities will be recorded as AEs. A copy of the ECG trace and report will be retained.

8.6 Gallbladder Echography

Gallbladder echography will be conducted according to the study schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort), or at any time if symptoms are thought to be related to gallbladder lithiasis, as per study site procedures. The results will be recorded in the eCRF. The presence of lithiasis or sludge will be assessed and recorded (yes/no) on the eCRF. Any clinically significant abnormalities will be recorded as AEs.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Sample Collection

Blood samples (3 mL each) for determination of serum lanreotide concentrations will be collected according to the study schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort).

Lanreotide serum concentrations will be assessed in both cohorts at Baseline, prior to and 2 to 3 hours after the first injection at the reduced dosing interval; Week 12, prior to injection; Week 24, prior to injection in all subjects, except in a subset of 30 subjects from selected sites, where a sample will be collected 1 to 3 days after the injection instead; Week 48, prior to and 2 to 3 hours after the injection; and at the End of Study (prior to any administration of commercial product (if applicable)). In addition, in the midgut cohort, a blood sample will be collected at Week 96, prior to injection. During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection, and lanreotide Autogel® administration must be recorded on the eCRF.

The tubes will be left to stand for 30 minutes and will then be centrifuged at 1000 g to 1300 g for 10 minutes at 4ºC. For each analyte, the resulting serum will be stored as two 500 µL aliquots at 20°C in polypropylene tubes prior to shipment to the analysis laboratory. Each tube should be labelled in accordance with the sponsor's requirements. Aliquots will be shipped on dry ice and with a temperature tracker.

Details of the sample handling methodology will be provided in the Study Manual and archived in the TMF. Additionally, details will be included in the Pharmacokinetics and Drug Metabolism (PDM) Sample Management Plan.

9.1.2 Analytical Procedures

The determination of lanreotide serum concentrations will be performed using a validated assay by a bioanalytical CRO under Ipsen's PDM department supervision.

9.2 Putative Antibody Testing

Blood samples (3 mL) will be collected according to the study schedule in Table 2 (pNET cohort) and Table 3 (midgut cohort) for the assay of putative antibodies to lanreotide. The tubes should be left to stand for 30 minutes and then centrifuged at 1000 g to 1300 g for 10 minutes at 4°C. The resulting serum will be stored as two 500 µL aliquots at -20°C in polypropylene tubes prior to shipment to the analysis laboratory. Each tube should be labelled with the sample identification, study number, site number, subject number and initials, visit number (when applicable) and the planned time of collection.

Full details regarding the requirements for processing, labelling and shipment of these samples are provided in the Study Manual and archived in the trial master file (TMF). Additionally, details will be included in the PDM Sample Management Plan.

The determination of putative antibodies against lanreotide will be performed using a validated assay by a bioanalytical CRO under Ipsen's PDM department supervision.

9.3 Pharmacodynamics

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10 STATISTICS

10.1 Analyses Populations

The following populations will be used during statistical analyses:

- **Screened population:** All subjects screened (i.e. who signed the informed consent).
- **Full analysis set (FAS):** All subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study
- **Per protocol (PP) population:** All subjects in the FAS for whom no major protocol violations/deviations occurred.
- **Pharmacokinetics Valid (PK Valid) population:** All subjects who received at least one dose and who have at least one serum lanreotide concentration and no major protocol deviations affecting PK variables.

10.1.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint(s) will be performed on the FAS. All secondary and tertiary endpoints will be evaluated based on the FAS population. In addition, a PP population analysis will be performed on the primary and secondary endpoints of PFS, median time to progression, ORR, DCR, best overall response and median duration of SD.

The analyses of safety data will be performed on the FAS.

PK endpoints will be analysed and population PK (POPPK) modelling will be performed on the PK Valid population.

10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation will be described in the Protocol Deviation Document (PDD) and its impact on inclusion in each analysis population (FAS, PP, and PK Valid) for any subject will be specified. The final list of protocol deviations, including determination of those which are major, impacting the PP population will be reviewed during the data review meeting held prior to database lock.

10.2 Sample Size Determination

The sample size in this pilot study is 100 subjects in total (50 subjects per cohort). This should be sufficient to explore the efficacy of lanreotide Autogel® 120 mg at a reduced dosing interval.

10.3 Significance Testing and Estimations

Analyses will be descriptive and p-values will be provided only for descriptive exploratory purposes. All statistical tests will be two sided at the α 0.05 level.

10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's Speciality Franchise Clinical Operations Department.

A Statistical Analysis plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document. Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9).

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

categorical or discrete variables, the absolute and relative (percentage) numbers based on the nonmissing number of observations for each category will be presented, including 95% CIs.

10.4.1 Demographic and Other Baseline Characteristics

In order to characterise the pNET and midgut cohorts, descriptive summary statistics (n, mean, StD, median, minimum, maximum) or frequency counts of demographic and baseline data (significant medical history, concomitant disease (predosing AEs and ongoing medical history, prior medications and therapies, baseline symptoms, etc.) will be presented by cohort and both cohorts combined for the FAS population.

10.4.2 Homogeneity of Treatment Groups

In this nonrandomised exploratory study, all efficacy endpoints will be analysed by cohort and overall, with the exception of endpoints pertaining to disease progression and median duration of SD which will only be analysed by cohort. In addition, for the factors associated with the PFS endpoint, a model will be used for each cohort. Safety endpoints will be presented by cohort and overall, and PK endpoints will be evaluated for the overall population. It is not intended to compare the baseline characteristics of the cohorts.

10.4.3 Subject Disposition and Withdrawals

The number and percentage of subjects included in the FAS will be tabulated by cohort, country and centre. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the number of subjects who were treated, and who discontinued and completed the study will be tabulated by cohort. Primary reasons for discontinuation of study treatment will be tabulated.

10.4.4 Pharmacokinetic Data

The analysis of PK data will be performed by a CRO under the supervision of Ipsen's PDM department.

Individual serum concentrations for lanreotide will be listed and summarised by timepoint using descriptive statistics for continuous variables (N, mean, median, StD, minimum, maximum, geometric mean, and geometric coefficient of variation assuming log normally distributed data).

Population PK modelling will be performed for the PK Valid population, both cohorts combined, and a PK/PD relationship between lanreotide serum concentrations and PD (PFS, tumour response or CgA) will be assessed, where possible. Exploratory graphs will be presented between PK parameters and safety outcomes. If a trend is detected, modelling analysis may be performed between PK and safety outcomes.

The appearance of antilanreotide antibodies will be listed by cohort and overall, subject and visit and the percentage of subjects developing putative antidrug antibodies will be computed at Baseline and End of Study visits.

10.4.5 Efficacy Evaluation

10.4.5.1 Primary Efficacy Variable

The primary efficacy variable is median PFS (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death). Disease progression will be assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study, and by independent central review to ensure intra and intersubject consistency and reliability. Data will be analysed by cohort only.

PFS of subjects who are lost to follow up and those who are alive and without disease progression at the End of Study will be censored at the date of the last disease assessment subject to the rules summarised in Table 6.

Table 6 Censoring Rules for PFS

Reason for censoring	Rule
No Screening evaluable assessment	Date of first treatment administration
Two or more not evaluable (NE) assessments before progressive disease or death	Date of last evaluable disease assessment before the second NE assessment
No progressive disease	Date of last evaluable disease assessment
Treatment discontinuation for undocumented progression	Date of last evaluable disease assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable disease assessment

The distribution of PFS times will be estimated using the Kaplan Meier method for each cohort. The median PFS time will be presented with its associated 95% CI. The results will also be presented graphically in Kaplan Meier plots.

10.4.5.2 Secondary Efficacy Variables

Median time to progression

A similar analysis to the primary analysis will be performed. Time to progression is defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression. Data will be analysed by cohort only.

Subjects who are lost to follow up or who die during the study will be censored at the date of the last disease assessment subject to the rules summarised Table 7.

Table 7 Censoring Rules for Median Time to Progression

Reason for censoring	Rule
No Screening evaluable assessment	Date of first treatment administration
Two or more NE assessments before progressive disease	Date of last evaluable disease assessment before the second NE assessment
No progressive disease	Date of last evaluable disease assessment
Treatment discontinuation for undocumented progression	Date of last evaluable disease assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable disease assessment
Death	Date of last evaluable disease assessment

The distribution of time to progression will be estimated using the Kaplan Meier method for each cohort. The median time to progression will be presented with its associated 95% CI. The results will also be presented graphically in Kaplan Meier plots.

Proportion of subjects alive and without progression every 12 weeks

The proportion of subjects alive and without progression will be presented by cohort every 12 weeks with the corresponding 95% CIs. Data will be analysed by cohort only.

Overall survival at Week 48 and at the end of the study for each cohort

The overall survival rate will be presented at Visit 9 (Week 48) and at End of Study for both cohorts separately and overall, with the corresponding 95% CI.

Objective response rate (ORR)

The ORR is defined as the proportion of subjects who achieve either CR or PR according to centralised RECIST v1.0 criteria. The ORR will be computed every 12 weeks and presented by cohort and overall, with the corresponding 95% CI.

Disease control rate (DCR)

The DCR is defined as the rate of CR plus PR plus SD, evaluated according to RECIST v1.0. The DCR will be presented at Weeks 24 and 48 and End of Study by cohort and overall, with the corresponding 95% CI.

Best overall response

Best overall response is defined as the best response recorded from the initiation of treatment until disease progression, according to RECIST v1.0 evaluation. These data will be summarised descriptively by cohort and overall, using a frequency table.

Median duration of stable disease (SD)

Median duration of SD is the time from first injection of lanreotide Autogel® 120 mg every 14 days until the first occurrence of progressive disease by central assessment. Data will be analysed by cohort only.

A similar analysis to the primary analysis will be performed. Subjects who are lost to follow up or who die during the study will be censored at the date of the last disease assessment subject to the rules summarised Table 8.

Table 8 Censoring Rules for Median Duration of Stable Disease

Reason for censoring	Rule
No Screening evaluable assessment	Date of first treatment administration
Two or more NE assessments before progressive disease	Date of last evaluable disease assessment before the second NE assessment
No progressive disease	Date of last evaluable disease assessment
Treatment discontinuation for undocumented progression	Date of last evaluable disease assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable disease assessment
Death	Date of last evaluable disease assessment

The distribution of duration of SD will be estimated using the Kaplan Meier method for each cohort. The median duration of SD will be presented with its associated 95% CI. The results will also be presented graphically in Kaplan Meier plots.

Factors associated with PFS

A Cox proportional hazards model for each cohort will be used to estimate the stratified HR and its 2 sided 95% CI. The factors included in this analysis will include but will not be limited to: hepatic tumour volume ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (yes/no), Ki67 <10% versus ≥10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days. Each factor will be assessed for its importance in the model and further exploratory analyses may be carried out assessing interaction effects, where stratum sizes are sufficiently large.

Symptom control (diarrhoea, flushing) at each visit

Symptom control will be assessed by the total number of stools and flushing episodes during the 7 days prior to the visit reported orally by the subject to the investigator. The total number of stools and flushing episodes will be summarised by cohort and overall using summary statistics, including 95% CIs of the mean number of stools and flushing episodes, by visit.

Quality of life

Quality of life questionnaire overall and subscale scores will be derived according to the standard algorithms recommended for their derivation; full details of which will be provided in the SAP. Data will be summarised by cohort and overall every 12 weeks through summary statistics and 95% CIs of the mean values. Individual questionnaire responses will be listed only.

Tumour biomarkers

Tumour biomarker analyses will be summarised descriptively by cohort as follows:

- pNET cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only). Note: at all scheduled visits, except Baseline, plasma/urinary 5-HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.
  - pNET-specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, …) at Baseline, every 12 weeks thereafter and at the End of Study visit: only for the tumour biomarkers above normal range at Baseline.
- Midgut cohort:
  - nonspecific tumour biomarkers (CgA, NSE and 5-HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5-HIAA at all scheduled visits; urinary 5-HIAA at Baseline, Week 12 and at the End of Study visit only).

Changes from Baseline will be displayed for continuous variables and for categorical variables shift tables (above, within and below normal range) will be presented.

10.4.5.3 Tertiary Efficacy Variables

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10.4.6 Adjustment for Country/Centre Effect

In this noncomparative exploratory study, adjustments for country/centre effects are not applicable.

10.4.7 Safety Evaluation

All safety data will be included in the subject data listings. Analyses and summary tables will be based on the FAS and presented by cohort and overall.

All AEs will be recorded and graded by investigators using the NCI CTCAE classification and will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by cohort, subject, system organ class and preferred term.

Incidence of all reported treatment emergent AEs (TEAEs) and SAEs will be tabulated by cohort and overall, by associated NCI CTCAE worst grade and by drug relationship. In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum intensity (grade 5 >grade 4 >grade 3 >grade 2 >grade 1 >missing >not applicable) will be chosen. 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 will be listed by cohort, subject and visit. AEs resulting in dose delays, dose interruption and withdrawal will be listed and presented in summary tables.

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

- it was not present prior to receiving the first dose of lanreotide Autogel® 120 mg at a reduced dosing interval , or
- it was present prior to receiving the first dose of lanreotide Autogel® 120 mg at a reduced dosing interval but the intensity increased during the study, or
- it was present prior to receiving the first dose of lanreotide Autogel® 120 mg at a reduced dosing interval, the intensity is the same but the drug relationship became related during the study.

All TEAEs will be flagged in the AEs listings.

Prior and concomitant medication will be coded by using WHO drug dictionary (WHO-DD) and will be summarised by cohort and overall with the number and percentage of subjects receiving prior and concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, StD and range as appropriate) by cohort and overall will be presented for physical examination and vital signs (weight and height, body temperature, supine and standing blood pressure) and heart rate, ECG parameters, and clinical laboratory tests at each assessment (absolute values and change from Baseline). For gallbladder echography, the presence and/or absence of lithiasis and sludge will be presented at each visit. 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.

10.5 Subgroup Analyses

Descriptive statistics for the following efficacy endpoints will be presented by cohort (pNET and midgut) and overall: ORR, DCR, OS, best overall response, tumour biomarkers, symptoms (diarrhoea and flushing) and quality of life. In addition, safety analyses will be performed on the cohorts separately and on the overall population.

Survival rates, ORR and DCR will also be presented for hepatic tumour volume ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (yes/no) and Ki67 <10% versus ≥10.

10.6 Interim Analyses

No interim analysis will be performed. One final analysis will be performed at the end of the study, after database lock.

A DSMB covering both cohorts combined will be appointed to review data, as determined in a DSMB charter, at the following timepoints:

(1) when 20 subjects from both cohorts have reached the Week 4 evaluation,

(2) when 20 subjects from both cohorts have reached the Week 12 evaluation, and

(3) when 50 subjects from both cohorts have reached the Week 12 evaluation.

The DSMB will be composed of independent experts. The purpose of the DSMB will be to evaluate safety early (Week 4) and at steady state (Week 12) of the reduced dosing interval, and to make recommendations to the sponsor as to whether the study should continue as planned or whether any changes are recommended to the trial conduct or protocol. The Chair of the DSMB will be responsible for communicating the DSMB's recommendations. Full details of the operating model for the DSMB will be provided in a DSMB charter.

11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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

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

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

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

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

12.1.2 Protocol Deviations, Violations, and Exceptions

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

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

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

12.2 Information to Study Personnel

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

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

12.3 Study Monitoring

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

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

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

The site must complete the eCRFs according to the sponsor monitoring manual, of the subject's visit and on an ongoing basis (in a maximum 5 days) to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitors 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.

12.4 Audit and Inspection

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

12.5 Data Quality Assurance

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

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

13 ETHICS

13.1 Compliance with Good Clinical Practice and Ethical Considerations

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

The EDC system will comply with FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerised 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 IEC/IRB for the study protocol/amendment(s), written informed consent forms, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

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

13.2 Informed Consent

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

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

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

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

13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

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

13.4 Confidentiality Regarding Study Subjects

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

Personal medical information may be reviewed for the purpose of verifying data recorded on the 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, lanreotide Autogel® 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. Subject completed questionnaires will be printed.

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

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

14.2 Data Management

Electronic Data Capture 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 Specialty Franchise Clinical Operation Department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received inhouse at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Monitoring Procedures). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

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

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

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

The coding of AEs, medical history procedures, and therapies/medications will be performed by Medical Dictionaries and Coding specialist upon Sponsor supervision. Therapies/medications will be coded using WHO-DD and AEs/medical history procedure terms will be coded using MedDRA.

14.3 Record Archiving and Retention

During the prestudy 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.

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.

Analysis of the data and preparation of the final study report will be performed once all subjects have reached their End of Study Visit.

CCI

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