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STATISTICAL AND ANALYSIS PLAN

PROTOCOL TITLE 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

PROTOCOL VERSION AND DATE: 2.0 – 15 DECEMBER 2015
PROTOCOL AMENDEMENT 1: 07 OCTOBER 2015
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PROTOCOL AMENDEMENT 3: 09 JANUARY 2017

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Final Version 1.0	22 January 2019
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STUDY NUMBER:	8 79 52030 326 (CLARINET FORTE)
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PROTOCOL TITLE:	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
SAP VERSION:	Final Version 2.0
SAP DATE:	13 January 2020

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

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Clinical Statistics Manager or designee	PPD Boulogne Billancourt		
Medical Development Director	PPD Rare Diseases		

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Statistician	PPD Covance Clinical Development SARL		
Manager Statistician	PPD Covance Clinical Development SARL		

IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical and Analysis Plan version became the Final Statistical and Analysis Plan

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
		22 Jan 2019	13 Jan 2020	Updates post baseline analysis. Addition of sections 3.2.2.7 and 3.2.9. Updates in list of TFLs. Change name of SAP approvers (Covance)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HIAA:	5 Hydroxyindoleacetic Acid
AE:	Adverse Event
ALP:	Alkaline phosphatase
ALT (SGPT):	Alanine aminotransferase
ANCOVA:	Analysis of Covariance
AST (SGOT):	Aspartate aminotransferase
ATC:	Anatomic Therapeutic Chemical
AUC:	Area Under the Curve
BMI:	Body Mass Index
CgA:	Chromogranin A
CI:	Confidence interval
CLARINET:	Controlled Study of Lanreotide Anti proliferative Response in Neuroendocrine Tumours
CR:	Complete response
CRF:	Case Report Form
CRO:	Contract Research Organisation
CSR:	Clinical Study Report
CT:	Computed Tomography
DCR:	Disease Control Rate
DSMB:	Data Safety Monitoring Board
e:	Electronic
ECG:	Electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
EORTC:	European Organisation for Research and Treatment of Cancer
EQ-5D-5L:	EuroQoL 5 dimensions, 5 levels
FAS:	Full analysis set
FDA:	Food and Drug Administration
GGT:	Gamma-Glutamyl Transferase
GI:	Gastrointestinal
HbA1c	Haemoglobin A1C
HR:	Hazard Ratio
ICH:	International Conference on Harmonisation

IMP:	Investigational Medicinal Product
Ki67:	Proliferation index
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA:	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI-CTC:	National Cancer Institute - Common Toxicity Criteria
NCI-CTCAE:	National Cancer Institute - Common Terminology Criteria for Aes
NET:	Neuroendocrine Tumours
NSE:	Neuron Specific Enolase
ORR:	Objective Response Rate
OS:	Overall Survival
PD:	Progressive Disease
PDD:	Protocol Deviation Document
PH:	Proportional Hazards
PhD:	Pharmacodynamics
PK:	Pharmacokinetic
PFS:	Progression Free Survival
pNET:	Pancreatic Neuroendocrine Tumours
POPPK:	Population PK
PP:	Per Protocol
PR:	Partial response
PV:	Pharmacovigilance
QLQ C30:	Quality of Life Questionnaire Core 30
QLQ GI.NET21:	Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21
QRS:	QRS interval duration
QT:	Time interval for ventricular depolarisation and repolarisation
QTc:	Corrected QT interval
SAP:	Statistical and Analysis Plan
SD:	Stable Disease
Se:	Sensitivity
SoD:	Sum of Diameter
Sp:	Specificity

RBC:	Red blood cell
RECIST:	Response Evaluation Criteria in Solid Tumours
ROC:	Receiver Operating Characteristics
SAE:	Serious Adverse Event/Experience
SAS®:	Statistical Analysis System®
s.c.:	Subcutaneous
SI:	Standard International
SOP:	Standard Operating Procedure
SSTR	Somatostatin receptor
StD:	Standard Deviation
TEAE:	Treatment Emergent Adverse Event
TFLs:	Tables, Figures and Listings
CCI	CCI
UK	United Kingdom
ULN	Upper Limit of Normal
WBC:	White blood cell
WHO- DD:	World Health Organization – Drug dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

The primary objective of the study is 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 [1], and according to central review.

1.1.2 Secondary objectives

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 (OS) 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 (PhD) (PFS, tumour response or CgA).
- To evaluate, if any, the relationships between PK parameters and the safety outcomes.

1.1.3 Tertiary objectives

- CCI [redacted]

[redacted]

1.2 Study design

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 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.

Subjects will be recruited into one of two cohorts based on their primary location of NET (i.e. pNET cohort and midgut cohort).

The study consists of a Screening visit (Visit 1, Day -28 / Day -1), where informed consent is taken, followed by a Screening period of up to 28 days, where eligibility tests and assessments are performed.

At Baseline (Visit 2), subject eligibility is verified and Baseline assessments are performed, followed by an open label treatment period. Eligible subjects are 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 are treated for up to 48 weeks and subjects in the midgut cohort are treated for up to 96 weeks. In both cohorts, treatment will be discontinued at disease progression or death, or unacceptable toxicity or tolerability.

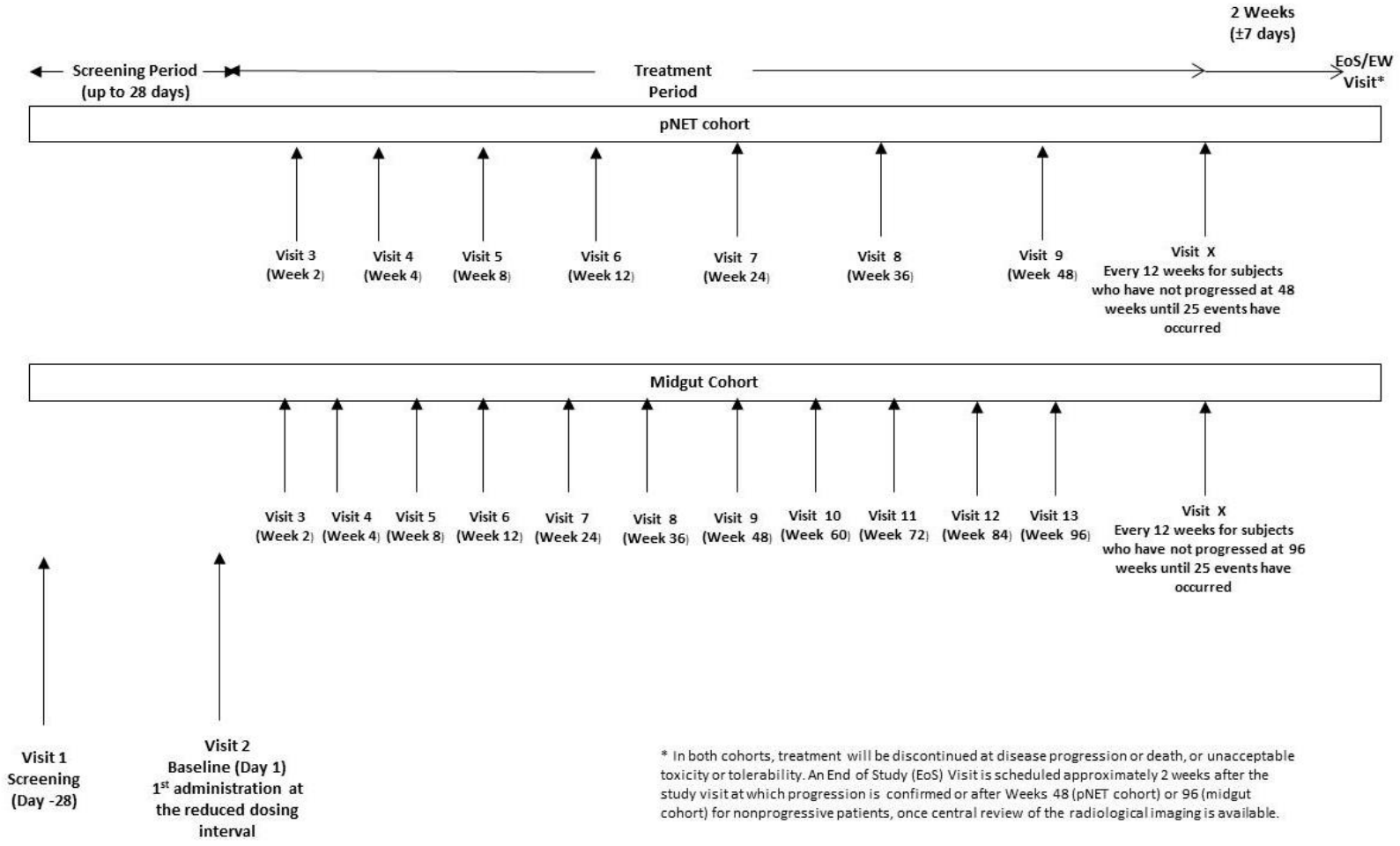
Study visits are performed at Weeks 2, 4, 8, 12, 24, 36 and 48 (both cohorts), and Weeks 60, 72, 84 and 96 (midgut cohort only). As long as 25 events, i.e. either progressions (assessed centrally) or deaths, have not been observed in the respective cohorts, subjects who have not progressed at Week 48 (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.

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

Figure 1 Study Schema



1.2.1 Study population

It is planned to enrol a total of 100 subjects (50 subjects per cohort), in 30 to 35 centres in Belgium, France, Germany, Republic of Ireland, Italy, Spain, the United Kingdom (UK), the Netherlands, Denmark and Poland.

Adults with well differentiated (grade 1 or 2 according to WHO 2010 classification), metastatic or locally advanced, unresectable pancreatic neuroendocrine tumours (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 in this study.

1.2.2 Study exposure

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 i.e. either progressions assessed centrally or deaths, 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.

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 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.

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

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.

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

- Tumour assessments

Tumour assessments will be performed using the RECIST v1.0 criteria every 12 weeks throughout the study:

- at screening (Visit 1),

- Visit 6 (Week 12), Visit 7 (Week 24), Visit 8 (Week 36), Visit 9 (Week 48) for both cohorts,

- Visit 10 (Week 60), Visit 11 (Week 72), Visit 12 (Week 84), Visit 13 (Week 96) for midgut cohort only, and,

- additionally every 12 weeks 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 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, or unacceptable toxicity or tolerability until 25 events have been observed in the midgut cohort.

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.

From the imaging data, median PFS and PFS rate, median time to progression, objective response rate, best overall response, disease control rate and median duration of stable disease will be estimated, CCI [redacted] on CT or MRI.

In addition, at Screening, the Central Reading Contract Research Organisation (CRO) will measure the hepatic tumour load.

- Symptoms of diarrhoea and flushing

Symptom control (diarrhoea, flushing) at Baseline, Visit 5 (Weeks 8), Visit 6 (Week 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 questionnaires (QLQ-C30, QLQ-GI.NET21, EQ-5D-5L)

The questionnaires will be completed at Baseline, Visit 6 (Week 12), Visit 7 (week 24), Visit 8 (Week 36), Visit 9 (Week 48) for both cohorts, Visit 10 (Week 60), Visit 11 (Week 72), Visit 12 (Week 84), Visit 13 (Week 96) for midgut cohort only, and then every 12 weeks until progression, death, or unacceptable toxicity or tolerability until 25 events have been observed in each cohort.

- Tumour biomarkers concentration 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 (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).

1.3.2.2 Safety assessments

- Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study. AEs will be elicited by direct, nonleading questioning or by spontaneous reports.

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).

- Vital signs

Blood pressure and heart rate will be collected at each visit (except baseline).

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.

- Physical Examination

Physical examinations, including body weight and height (screening only) will be conducted at each visit (except baseline).

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.

- Electrocardiography

The Electrocardiograms (ECGs) will be recorded at Screening (Visit 1), Visit 4 (Week 4), Visit 7 (Week 24), for both cohorts, at Visit 9 (Week 48) for pNET cohort, and Visit 13 (Week 96) for midgut cohort, and at the end of study/early withdrawal visit for both cohorts. 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.

- Gallbladder echography

Gallbladder echography will be conducted at Screening (Visit 1), Visit 7 (Week 24), for both cohorts, at Visit 9 (Week 48) for pNET cohort, and Visit 13 (Week 96) for midgut cohort, and at the end of study/early withdrawal visit for both cohorts, or at any time if symptoms are thought to be related to gallbladder lithiasis, as per study site procedures. 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.

- Clinical Laboratory Tests

Blood samples will be collected at all visits (except V3) for the evaluation of haematology and biochemistry panels, liver and pancreatic enzymes. Urine samples will be collected at screening (Visit 1), baseline (Visit 2), Visit 9 (Week 48) for both cohorts, Visit 13 (Week 96) for midgut cohort only, and at end of study/early withdrawal visit (for both cohorts).

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

Blood Biochemistry – the following parameters will be assessed:

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

Blood samples will be collected to assess Haemoglobin A1C (HbA1c).

Urinalysis – the following parameters will be assessed: pH, urine color, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity.

Microscopic urine - the following parameters will be assessed if clinically indicated: Urine White Blood Cells (WBC Cells), Urine Red Blood Count (RBC Cells), Squamous Epithelial Cells, Mucous Fibers Urine, Bacteria, U Amorphous, Crystals, Sperm Urine, Urine Waxy Casts, Granular Cast, Hyaline Cast, RBC Cast, WBC Cast, Trichomonas Vaginalis Urine, Glitter Cells, Renal Epithelial Cells and Transitional Epithelial Cells.

1.3.2.3 Other assessments

The following parameters will be assessed at Screening (Visit 1) or prior to administration of study treatment at Baseline (Visit 2; Day 1):

- Demographic data (country, age, sex and race),
- Significant medical or surgical history,
- All prior medications or therapies: prior surgical procedures for pancreatic/midgut NETs, prior radiotherapy for pancreatic/midgut NETs, prior therapies given to a subject for another indication than study disease (within 28 days before study drug administration), prior medications (within 28 days before study drug administration), prior non-drug therapies, prior medications for pancreatic/midgut NETs
- NET diagnosis (location of primary tumour, histopathological type for pancreatic/midgut, tumour grading (according to WHO 2010 classification), proliferation index KI67, date of NET diagnostic),
- SSTR2 assessment /Krenning Scale,
- ECOG performance Status Scale.

- **Pharmacokinetic (PK) and Pharmacodynamic (PhD) analyses**

PK and PK/PhD analyses will be described in a separate Data Analysis Plan.

1.3.2.4 Withdrawal/discontinuation

A subject may discontinue participation in the study at any time for any reason (for example lost to follow-up, 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 of the protocol, noncompliance with the protocol conditions or AE).

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

1.3.3 Schedule of assessments

The schedule of procedures and assessments during the study for the pNET and midgut cohorts is summarised in Table 1 and Table 2, respectively.

Table 1 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]

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	
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]
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; 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 [redacted]

Table 2 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].

1.3.4 Planned sample size

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.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

The following populations will be used during statistical analyses:

The ***Screened population*****,** i.e. all subjects screened (i.e. who signed the informed consent), the enrolled subjects, i.e the screened subjects included in the study and the Full analysis set (FAS), Per protocol (PP) population, the Pharmacokinetics Valid (PK Valid) population, as described below.

2.1 Efficacy

2.1.1 Full analysis set (FAS)

The FAS includes all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

2.1.2 Per Protocol population (PP)

The Per Protocol population includes all subjects in the FAS for whom no major protocol violations/deviations occurred.

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

Reasons for exclusion from Per Protocol population will be presented in a summary table by cohort.

2.2 Safety

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

2.3 Pharmacokinetics

2.3.1 Pharmacokinetics Valid (PK Valid) population

Pharmacokinetics Valid (PK Valid) population will consist of all subjects who received at least one dose and who have at least one serum lanreotide concentration. A subject having at least one valid PK concentration (including PK sampling with minor deviation) among other major deviations should be kept in the PK valid population. In case of a single major deviation, the corresponding timepoints are discarded but the subject is still included in the PK valid population.

2.4 Primary population

The primary analysis based on the primary efficacy endpoint 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 (i.e. median PFS and PFS rate), median time to progression, ORR, DCR, best overall response and median duration of SD, if the difference in number of subjects between FAS and PP population is > 10%, based on subjects in FAS.

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.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guidelines [2] and will be based on the pooled data from the individual study sites, unless otherwise stated.

When overall statistics are provided in addition to the statistics by cohort, it is for descriptive purpose only and not for inferential purpose to any population.

Statistical analyses will be performed by Chiltern.

3.1.1 Primary efficacy endpoint(s)

The primary endpoint is median PFS, where PFS is defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death (whichever occurs first). 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.

3.1.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoint(s) are:

(a) Median time to progression
Time to progression is defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days to progression.

(b) Proportion of subjects alive and without progression every 12 weeks.

(c) Overall survival (OS) at Week 48 and at the end of the study for each cohort.
The overall survival is defined as the time in months from the first injection of lanreotide Autogel® 120 mg every 14 days to death due to any cause.

(d) Objective response rate (ORR) every 12 weeks as per RECIST v1.0.
The ORR is defined as the proportion of subjects who achieve either CR or PR according to centralised RECIST v1.0 criteria. A responder is defined as a subject experiencing either a CR or PR by these criteria.

(e) Disease control rate (DCR) at Weeks 24, 48 and End of study.
The DCR is defined as the rate of CR plus PR plus SD, evaluated according to RECIST v1.0.

(f) Best overall response
The best overall response according to RECIST v1.0 is defined as the best response recorded from the initiation of lanreotide Autogel® 120 mg every 14 days until disease progression (Table 3).

Table 3 Overall Response

Target lesion	Non target 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 [1].

(g) Median duration of stable disease (SD)
Duration of SD according to RECIST v1.0 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 (in months).

(h) Factors associated with PFS
To detect prognostic factors of PFS, the effects of the following factors will be explored simultaneously on PFS: hepatic tumour load ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (Yes versus No), Ki67 <10% versus ≥10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days by category (≥ median value versus < median value) , age by category (≥65 years, <65 years), time from diagnostic to study entry (by category: ≥3 years versus < 3 years), Time interval between the 2 CT scans (pre-screening / screening) <12 months / >=12 months) and symptoms (diarrhoea or flushing at baseline: Yes / No). Other potential factors to consider will be discussed during the Blind Review Meeting.

(i) Symptom control (diarrhoea, flushing), as measured by presence/absence of each symptom and 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.

(j) 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.

EORTC QLQ-C30 v3.0

The European Organisation for Research and Treatment of Cancer (EORTC) score questionnaire (QLQ-C30) will be used for quality of life (QoL) evaluation.

Following the EORTC recommendations, fifteen scales can be derived from the initial 30 questions:

- A global health status/QoL scale,
- Five functional, scales (physical, role, cognitive, emotional and social),
- Nine "symptoms" scales /items (nausea and vomiting, pain, fatigue, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

Of note, for functional scales, a higher value reflects a better level of function, but for symptoms scales /items a higher value reflects worse symptoms; moreover high score for the global health status represents a high QoL.

Each scale in the questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-C30 Scoring Manual. The scoring method is summarized below. In this summary, Qi refers to the i^{th} question on the EORTC QLQ-C30.

Scoring and scale dimension:

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

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

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

$$RawScore\ RS = \left(I_1 + I_2 + ... + I_n\right)/n$$

Then for **Functional scales**:

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

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

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

Missing value (item) consideration for scoring:

The scale scores will only be calculated if at least half of the items from the scale have been answered. Otherwise, no score will be calculated and the scale score will be set to missing.

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

EORTC QLQ-GI.NET21 (2006)

The QLQ-GI.NET21 module is intended for use among subjects with gastro-intestinal-related (G.I.-related) neuroendocrine tumours, who vary in disease stage and treatments.

The module comprises 21 questions, consisting of 5 scales and 4 single items, assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality. The module has been developed according to the EORTC guidelines. The QLQ-GI.NET21 has been translated into several European languages.

Each question is quoted from 1 (Not at all) to 4 (very much). The scoring algorithm for the scales and single items is described below:

	Number of items (range*)	**Item number**
Scales		
Endocrine symptoms scale	3 (3)	31, 32, 33
G.I. symptoms scale	5 (3)	34 to 38
Treatment related symptom scale	3 (3)	39, 40, 46
Social function scale	3 (3)	42, 44, 49
Disease related worries scale	3 (3)	41, 43, 47
Single items		
Muscle /bone pain symptom	1 (3)	48
Sexual function	1 (3)	51
Information/communication function	1 (3)	50
Body Image	1 (3)	45

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

For all scales, a high score is equivalent to worse or more problems.

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

$$RawScore\ RS = \left(I_1 + I_2 + ... + I_n\right)/n$$

Then for each of the five **scales** and for each **single item**:

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

Missing value (item) considerations for scoring are the same as for the QLQ-C30 questionnaire presented above.

EQ-5D-5L v1.0

The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (VAS).

The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort and anxiety / depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems.

The EQ-5D-5L was created based on the EQ-5D-3L, questionnaire with the same dimensions but 3 levels only (no problem, some problems, extreme problems) to improve its sensitivity and reliability.

With the EQ-5D-5L, a unique health state is defined by combining 1 level from each of the 5 dimensions. There are 3125 possible health states defined in this way. Each state is referred to in terms of a 5 digit code.

For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression

Any missing values will be set to missing (and hence no health state value will be calculated).

Ambiguous values (e.g., 2 boxes ticked for a single dimension) should be treated as missing values.

The EQ VAS records the subject's self-rated health on a 20 cm vertical, visual analogue scale where the endpoints are 'the best health you can imagine' and 'the worst health you can imagine'. The subject has to mark an X on the scale to indicate how his health is today, and then has to write the number marked on the scale in a box.

Missing values will be set to missing.

If there is a discrepancy between where the subject has placed the X and the number he/she has written in the box, the number in the box should be used.

The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, can be converted into a single index value.

A crosswalk link function between the EQ-5D-3L descriptive systems and the EQ-5D-5L descriptive systems has been developed and can be used to calculate index values for EQ-5D-5L, based on the existing value sets for the EQ-5D-3L.

By using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, index values for the EQ-5D-5L can be calculated.

Documents containing information on the crosswalk project, tables of values for all 3125 health states and the 'EQ-5D-5L Crosswalk Index Value Calculator' can be downloaded from the EuroQol website.

The SAS syntax files were received from the EuroQol Office for Denmark, France, Germany, Italy, Netherlands, Spain, UK. It is not available for Poland.

Of note, for Ireland, the SAS syntax crosswalk values EQ-5D-5L United Kingdom will be used ; for Belgium, the one for France, and for Poland, the one for Germany.

(a) Biomarkers

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).

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 load, tumour severity, tumour functionality, 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 • time from diagnosis to progressive disease during the study (≥3 years; < 3 years). • Time interval between the 2 CT scans (pre-screening / screening) <12 months / >=12 months) • Symptoms (diarrhoea or flushing at baseline: Yes / No)
Symptom control	Baseline, Weeks 8 and 12, every 12 weeks thereafter, and at EoS	Presence/ absence of diarrhoea and flushing, 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	CCI dosing interval CCI	CCI	
	g CCI		

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.

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 ; ULN=upper limit of normal.

CCI .

3.1.3 Safety endpoint(s)

- Clinical (AEs, vital signs, physical examination)
- Biological (serum haematology and biochemistry panels, liver and pancreatic enzymes, urinalysis) safety data
- ECG
- Gallbladder echography
- Potential relationships (if any) between PK parameters and safety outcomes.

3.1.4 Multiplicity

No multiple testing will be performed in this study.

3.1.5 Significance testing and estimation

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.

3.2 Analysis methods

3.2.1 Efficacy

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

3.2.1.1 Primary efficacy analysis

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.

Event dates are assigned to:

- The first time when progressive disease was noted, or
- Date of death.

In case of progressive disease followed by death, the first event will be considered in the analysis.

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

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

Censoring dates are defined in subjects with no progressive disease or death before end of study or withdrawal. In these subjects, the censoring date is defined as the last date on which progression status was ‘adequately’ assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by central review (see Table 5).

Table 5 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
Initiation of medications or therapy not permitted during the study	Date of initiation of non permitted medication or therapy

* An assessment is considered NE when no imaging/measurement is done at all at a particular time point, or only a subset of lesion measurements are made at the time point. The subject is considered NE at that time point.

The PFS time will be calculated as the time from first injection of lanreotide Autogel® 120 mg every 14 days to either progressive disease or death.

PFS time (in months) = [(Date of event – date of first injection of lanreotide Autogel® 120 mg every 14 days) + 1] / 30.4375

Data will be analysed by cohort only. 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.

Completely missing tumour data:

When tumour assessment visits are completely missing, FDA Guidance “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” [4] states that "events occurring after two or more missed radiological assessments will be censored in the analysis at the last adequate assessment’.

This will be implemented as follows:

PDs occurring after two or more missed radiological assessments will be censored in the analysis at the last adequate* assessment before the missing assessments: If a subject has one missed radiological assessment before a PD the event will be analysed as an event (i.e. a PD is analysed as an event if the previous radiological assessment was performed within approximately the last 6 months).

The following table shows the event status for various scenarios with missing data:

Scan Time	Visit 6 (V6)	Visit 7 (V7)	Visit 8 (V8)	Visit 9 (V9)	Event status
Scenario 1	missing	PD			Censored at V2 if (V7 – Screening) >= 26 weeks
Scenario 2	missing	PD			Event at V7.if (V7 – screening) < 26 weeks
Scenario 3	missing	missing	PD		Censored at V2
Scenario 4	missing	SD	PD		Event at V8

Scenario 5	missing	missing	SD	PD	Event at V9
Scenario 6	SD	SD	missing	PD	Event at V9
Scenario 7	SD	missing	missing	PD	Censored at V6

The following SAS® code will be used:

CCI [redacted]

3.2.1.2 Secondary efficacy analysis

(a) 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 6.

Table 6 Censoring Rules for 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
Initiation of medications or therapy not permitted during the study	Date of initiation of non permitted medication or therapy

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.

(b) Proportion of subjects alive and without progression every 12 weeks

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

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

The overall survival, defined as the time in months from the first injection of lanreotide Autogel® 120 mg every 14 days to death due to any cause, will be analysed similarly to the primary efficacy endpoint.

Subjects without death date will be censored at the date the subject was last known to be alive.

OS time (in months)= [(date of death/date subject last known to be alive - date of first injection of lanreotide Autogel® every 14 days)+ 1]/30.4375.

Kaplan-Meier curves and estimates including survival rates at Visit 9 (Week 48) and at End of Study and the associated 95% CIs will be provided for each cohort separately and overall. If the median is not reached, the first quartile (i.e. 25 % percentile) will be provided instead.

(d) Objective response rate (ORR)

For analysis of the ORR, summary tables will be generated, presenting the number and proportion of responders and non-responders every 12 weeks in each cohort and overall, together with two-sided 95% Pearson-Clopper CIs. Subjects with no tumour assessment after the start of study treatment will be considered as non-responders. The denominator at each timepoint will be all subjects in the population regardless whether they are still in the study at that timepoint or not.

Responses for each subject will be listed at each visit. Responders will be identified.

The following SAS® code will be used for tables that need exact 95% Pearson-Clopper CIs:

CCI [redacted]

(e) Disease control rate (DCR)

The number and proportion of subjects with disease control and with no disease control at Weeks 24, Week 48 and End of Study will be presented by cohort and overall, together with two-sided 95% Pearson-Clopper CIs. Subjects with no tumour assessment after the start of study treatment will be considered as with no disease control. The denominator at each timepoint will be all subjects in the population regardless whether they are still in the study at that timepoint or not.

(f) Best overall response

The number and percentage of subjects with each best overall response and those who were non-evaluable (i.e. with no tumour assessment after the start of study treatment) will also be tabulated with two-sided 95% Pearson-Clopper CIs.

(g) Median duration of stable disease (SD)

A similar analysis to the primary analysis will be performed for the median duration of stable disease. Duration of SD, according to the central assessment, will be analysed in subjects who experienced stable disease until the first occurrence of progressive disease. 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 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
Initiation of medications or therapy not permitted during the study	Date of initiation of non permitted medication or therapy

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.

(h) Factors associated with PFS

A multivariate analysis of the progression free survival will be performed in order to take into account prognostic factors. These analyses will be conducted on the FAS. A Cox proportional hazards model for PFS will be performed for each cohort, to estimate the Hazard Ratio (HR) and its two-sided 95% CI.

The factors included in this analysis will include: hepatic tumour load ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (Yes versus No), Ki67 <10% versus ≥10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days by category (≥ median value versus < median value), age by category (≥65 years, <65 years), time from diagnostic to study entry (by category: ≥3 years versus < 3 years), Time interval between the 2 CT scans (pre-screening / screening) <12 months / >=12 months) and symptoms (diarrhoea or flushing at baseline: Yes / No).

In a first step, each factor will be assessed for its importance in the Cox model for PFS in a univariate fashion. All variables associated with PFS with a p-value < 0.20 will be pre-selected to be entered in the multivariate model.

The following SAS® code will be used

CCI [redacted]

In a second step, each pre-selected parameter will be tested with the other retained parameters at the 0.001 level to confirm that there is no strong link between them. For continuous variables the Pearson correlation will be tested. For a mix of categorical and continuous variables Kendall's tau (τ) correlation coefficient will be used and for categorical variables a Chi^2 test will be used. If the independence is not met for two parameters ($p < 0.001$) and/or the correlation coefficient is moderate or high (i.e. ≥ 0.5), the choice will be done according to clinical and statistical relevance.

A multivariate Cox regression model will then be run with the selected variables remaining after first and second steps.

The stepwise variable selection method in the SAS® procedure CCI will be performed with p=0.20 to enter variables in the model, and p=0.05 to remove variables from the model, to select the best model.

The following SAS® code will be used

CCI

The stepwise regression analysis will be composed of different steps:

- Individual score tests will be used to determine which of the explanatory variables has to be first selected into the model. In this case, the score test for each variable is the global score test for the model containing that variable as the only explanatory variable. The variable with the largest chi-square value significant at the CCI level will be selected first to enter the best model.

- The next step will consist of selecting another variable to add to the model. Chi-square statistics and p-values of individual score tests (adjusted for the first variable selected) for the remaining variables will be calculated. The second variable to be selected will be the one with the highest chi-square value and significant at the CCI level.
- This step will be repeated until a variable has to be removed from the model at the CCI. The best model will be the model with this last variable tested removed.

Tied events will be handled with the Exact approximation.

When the stepwise selection process will result in a best model, further exploratory analyses may be carried out assessing interaction effects, where stratum sizes are sufficiently large.

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

The graphical methods used will be:

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

The following SAS® code will be used with the best model retained (with CCI

.The second method to check the proportional hazards assumption will be using the time-dependent covariates, i.e. time*covariate interactions will be added to the model.

The following SAS® code will be used

CCI

;

CCI

If an added interaction is not statistically significant at the level of 0.10, this indicates that proportional hazard assumption is satisfied for the concerned variable.

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

If PH fails for a covariate x_i, previously checked covariates will be re-check after adjusting for the non-PH of x_i.

The second method used to handle non-PH will be to enter the covariate xi as a stratification variable in the model to have the estimation for each level of the covariate.

Therefore, the model with interaction and stratified model will be run, and the model with best fit statistics (AIC criterion) will be chosen.

Finally the estimation of the best model (selected with the stepwise procedure) will be presented, as well as the best model adjusted for non-PH and a graph of HR over time will be provided for non-PH variable(s) based on the best model adjusted for non-PH, if applicable.

(i) Symptom control (diarrhoea, flushing) at each visit

Symptom control will be assessed by presence/absence of each symptom and 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 presence/absence of each symptom will be presented as a frequency table per visit, as well as a shift table. The total number of stools episodes and the total number of flushing episodes by visit as well as the change from baseline will be summarised by cohort and overall using summary statistics, including 95% CIs of the mean.

Incidence of symptoms (presence/absence) and number of episodes will be listed, along with urinary 5-HIAA level (xULN) and plasma 5-HIAA level (ng/ml).

(j) Quality of life

Quality of life questionnaire overall and subscale scores will be derived according to the standard algorithms recommended for their derivation. Data will be summarised by cohort and overall every 12 weeks through summary statistics and 95% CIs of the mean values.

For subject reported outcomes, descriptive statistics will be presented for the raw data and for the changes from baseline during treatment.

Individual responses to each question will be listed. For each question the number and percentage of subjects who recorded each response will be presented by cohort and visit. For the EQ-5D-5L questionnaire, levels will also be dichotomised into “no problems” (i.e level 1) and 'problems' (i.e. levels 2 to 5) and tabulated.

Raw scores and transformed scores will be listed. Transformed scores (i.e. scales) will be summarised by cohort, scale (as defined in section 3.1.2) and visit. Changes from baseline in transformed scale scores will be calculated, listed and summarised by cohort, scale and visit.

An analysis of covariance (ANCOVA) will be performed using a SAS® PROC mixed procedure for each scale of the three questionnaires, in overall:

For each visit, an ANCOVA mixed model will be fitted with the change from baseline results as dependant variable; including cohort group as fixed effect; subject as random effect; and baseline QoL score as a covariate (fixed effect).

Least squares (LS) means (with 95% CIs) will be presented.

Calculations will be performed using REML (restricted maximum likelihood) estimation.
Type III tests will be used for the differences in least-square means.

The following SAS® code will be used for the model run for each visit:

CCI [redacted]

In this model, the overall cohort effect (i.e. the average cohort effect over the whole study period) will be tested (at the 0.05 level).

Normality assumption checking:

Based on the fitted ANCOVA model for each QoL scale score, the Shapiro-Wilk test statistic, (W), for testing the hypothesis of normality will be calculated for the Studentised residuals. The test statistic, W, and plots of the studentised residuals will be visually checked for the assumption of normality. In the event that normality is revealed to be unreasonable, the data will be log transformed. Again using the Shapiro-Wilk test statistic, if the assumptions of normality are revealed still to be unreasonable then the SAS® procedure CCI [redacted] will be considered.

CCI [redacted]

Original data will be presented in all tables and will be used in analysis unless log transformation is necessary. If log-transformation is used, results will be back transformed and will be presented in the tables in the original scale.

In SAS®, validity assumptions for the ANCOVA mixed model will be explored using the option CCI [redacted]

For each questionnaire, the score values for each visit will be plotted against time (by cohort).

(k) Tumour biomarkers

Nonspecific tumour peptide biomarkers (CgA, NSE and plasma/urinary 5-HIAA) will be summarised descriptively at Baseline (Visit 2) and Week 12 and every 12 weeks thereafter by cohort and overall. Changes from Baseline will be displayed for continuous variables and for categorical variables shift tables (above, within and below normal range) will be presented.

pNET-specific tumour peptide biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, where above normal range at Baseline) will be summarised descriptively at Baseline (Visit 2) and Week 12 and every 12 weeks thereafter for the pNET cohort. Changes from Baseline will be displayed for continuous variables and for categorical variables shift tables (above, within and below normal range) will be presented.

All data will be analysed and listed regardless of the timing of the assessment with regards to the injection.

3.2.2 Safety

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

3.2.2.1 Adverse events

All AEs will be recorded and graded by investigators using the NCI-CTCAE classification (Version 4.03, dated 14 June 2010) and will be coded using MedDRA Version 20.0 or higher, and will be classified by MedDRA preferred term and system organ class.

Listings will be presented and sorted by cohort, center, subject, system organ class and preferred term for all adverse events recorded during the study.

Listings of serious adverse events (SAE), adverse events leading to study treatment withdrawal and listings of deaths will also be presented.

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

(1) it was not present prior to receiving the first dose of lanreotide Autogel® 120 mg at a reduced dosing interval, i.e every 14 days, or

(2) it was present prior to receiving the first dose of lanreotide Autogel® 120 mg at a reduced dosing interval, i.e every 14 days but the intensity increased during the study, or

(3) it was present prior to receiving the first dose of lanreotide Autogel® 120 mg at a reduced dosing interval, i.e every 14 days the intensity is the same but the drug relationship became related during the study.

(4) AEs starting > 28 days after last treatment intake will not be considered as TEAEs.

All TEAEs will be flagged (*) in the AEs listings.

An overall summary table of all adverse events will be presented by cohort and overall.

TEAEs will be summarised by cohort and overall with the number and percentage of subjects with adverse events classified by primary system organ class and preferred term. The number of occurrences of a TEAE will also be presented.

Incidence of all reported treatment emergent AEs (TEAEs), SAEs, non SAEs, TEAEs by associated NCI-CTCAE worst grade and by causality, TEAEs by decreasing frequency will be tabulated by cohort and overall. For these incidence tables by primary system organ class and preferred term, in the event of multiple occurrences of the same AEs (same PT term) being reported by the same subject, the maximum intensity (grade 5> grade 4> grade 3> grade 2> grade 1 > missing> not applicable) and the most serious causality (related> missing> not related) will be chosen. For intensity*causality combined description, the most serious causality prevails. All occurrences of this worst grade, causality, intensity*causality by PT term will be taken into account in the number of occurrences (m). Nonetheless, for the overall summary of events, in the cross classification of causality and intensity, any subject experiencing multiple AEs with different intensities for each causality category will be counted for each intensity.

AEs resulting in dose interruptions and withdrawal will be listed and presented in summary tables by worst grade.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTCAE criteria (Version 4.03, dated 14 June 2010). The NCI-CTCAE grade 3 and 4 haematology and biochemistry parameters will be listed by cohort, subject and visit.

3.2.2.2 Laboratory data

Laboratory data (serum haematology and biochemistry panels, liver and pancreatic enzymes, urinalysis) will be listed in SI units in individual data listings by cohort, center, subject id and visit and abnormal values will be flagged (High, [H], Low [L], clinically significant [C], NCI-CTC grade (G)) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings. A list of clinically significant abnormal values will be presented.

A listing of microscopic urine parameters will be provided.

Baseline values will be defined as the last measurement of the specific laboratory parameter collected prior to the first dose of study drug (Day 1).

Since all samples will be analysed by a central laboratory, the same reference value ranges apply to subjects from all study centres. A separate listing of normal ranges for SI units will be provided by gender and age where appropriate.

Summary tables with actual values and changes from Baseline to each post-baseline visit will be presented for each cohort and overall.

Shift tables will be presented of the number and percentage of subjects with low, normal or high values.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTC criteria (Version 4.03, dated 14 June 2010). The NCI-CTC grade (0 to 4) of haematology and biochemistry by visit and by subject will be listed in the Section 16.2.8. Listings of the laboratory parameters in section 14.3.4 & 14.3.5 will include listings of NCI-CTC Grade 3 and 4 haematological toxicities, listings of NCI-CTC Grade 3 and 4 biochemical toxicities and listings of out of range biochemistry parameters that could not be graded using NCI-CTC grade (below LLN – normal – above ULN).

Also, listing of lipase increased (any grade) and listing of hypocalcemia (any grade) will be provided.

Diarrhoea status at baseline (presence/absence) will be summarised by baseline urinary and plasma 5-HIAA level (≤ULN, >ULN, missing) overall and by cohort.

Baseline level of urinary and plasma 5-HIAA (raw and in xULN) will be analysed according to baseline diarrhoea status (presence/absence) overall and by cohort.

3.2.2.3 Vital signs

Vital signs (body temperature, supine and standing blood pressure and heart rate) will be listed at each assessment by cohort and subject. Any unscheduled vital signs will be flagged [U] in the listing.

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

Summary tables with actual values and changes from Baseline to each post-baseline visit will be presented for each cohort and overall.

3.2.2.4 Physical examination

Physical examination and weight will be listed by cohort, subject identifier and visit. Any unscheduled physical examination will be flagged [U] in the listings.

Baseline values will be defined as the last physical examination performed prior to the first dose of study drug.

A summary table of weight and BMI with actual values and changes from Baseline to each post-baseline visit will be presented for each cohort and overall.

3.2.2.5 ECG

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

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

For continuous ECG parameters, summary statistics, by cohort and overall, will be presented at each scheduled assessment for actual values and changes from baseline.

For sinus rhythm, a frequency table by cohort and overall, will be presented at each scheduled assessment.

For interpretation of clinical significance (within normal limits / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented, by cohort and overall, at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable > within normal limits) as well as a shift table between baseline and each of the visits with the following categories: improved, stable, worsened, clinically significant worsening.

3.2.2.6 Gallbladder Echography

Gallbladder echography will be listed. Any unscheduled visits will be flagged [U] in the listings. A frequency table of the presence and/or absence of lithiasis and sludge will be presented at each assessment by cohort and overall.

A shift table from the screening period with number and percentage of subjects with presence and absence of lithiasis and sludge will be presented at each visit by cohort and overall.

3.2.2.7 Specific analysis of cholecystectomy, gallbladder surgery, lithiasis or sludge during the study

The following analyses will be provided, based on occurrence of cholecystectomy, gallbladder surgery, lithiasis or sludge during the study (source data will be concomitant surgical procedures for cholecystectomy or gallbladder surgery, and post-screening gallbladder echography for lithiasis and sludge):

- The number and percentage of subjects with cholecystectomy or gallbladder surgery or lithiasis or sludge during the study will be calculated, among subjects in the FAS population. Among the subpopulation of subjects having presented at least one of the four events during the study, the number and percentage of subjects having presented each of the four events will be displayed in the same table.
- In addition, shift tables of those four events will be provided, displaying the prior occurrence (ie during their treatment with lanreotide Autogel® 120 mg administered every 28 days, see section 3.2.9) versus the occurrence during the study as defined above. Five shift tables will be provided: “cholecystectomy, gallbladder surgery, lithiasis or sludge”, “cholecystectomy”,”gallbladder surgery”, “lithiasis”, “sludge”.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

- Efficacy endpoints

When tumour assessment visits are completely missing, rules from FDA Guidance “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” [4] will be implemented as described in section 3.2.1.1.

Any missing QoL data (EORTC QLQ-C30, QLQ-GI.NET21 and EQ-5D-5L questionnaires) will be handled as described in section 3.1.2.j.

- Safety endpoints

If a value requires a retest (for laboratory values, vital signs, ECG, gallbladder echography), the closest non-missing reliable value to the scheduled visit is used in the summary tables. An assessment is considered reliable if it is performed without any technical problem or altered blood samples and if the result is within the range of plausible values.

For adverse events with missing information for the intensity and causality, the value will not be replaced and will be summarized as a separate category.

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

3.2.3.2 Missing or incomplete dates

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

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

For partially missing dates for efficacy endpoints derived using tumour assessments, the following imputation rules will be used: if the day of the month is missing, but month and year are known (UN-MMM-YYYY), it will be imputed by the 1st of the month (01-MMM-YYYY). If this implementation rule produces a date before the first injection of lanreotide Autogel® 120 mg every 14 days, then the date of start of study treatment is used.

A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment. The imputation rules described for efficacy endpoints will be applied.

If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly a medication with partial start and stop dates could be considered as prior and concomitant treatment. However if the medication is lanreotide Autogel® 120 mg every 28 days with partial stop date and month and year are the same as month and year of the first study drug administration every 14 days (within the study) then the medication would be considered as ended prior to the start of study treatment.).

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

3.2.3.3 Outliers

A search of outliers should be performed before the database lock and the impact may be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect. The decision of how to handle these outliers will be made during the Data Review Meeting and documented.

3.2.4 Subject disposition

The number and percentage of subjects included in each of the FAS and PP population will be tabulated by cohort, country and centre.

The numbers and percentages of subjects screened, enrolled and included in each of the FAS, PP and PK population will be tabulated in total and by cohort. The reasons for subject exclusions from FAS and PP population will also be tabulated.

A summary table and a flow chart will be presented for each subject population presenting the number of subjects in each cohort at each visit and identifying the number of subjects who withdrew over time.

A summary table will present the study drug exposure in the study for each cohort and in overall. Study drug exposure (days) is defined as last drug intake - date of first drug intake +28 (c.f. in Section 6 Appendix 1 Derived Data).

A listing of dates of assessments (relative day) and their study exposure will be presented by subject for each cohort.

3.2.5 Withdrawals

The number of subjects who were treated, who discontinued and completed the study will be tabulated by cohort and listed. Primary reasons for discontinuation of study treatment will first be tabulated by cohort and overall, then by visit, by cohort and overall.

3.2.6 Demographic and baseline characteristics

In order to characterise the pNET and midgut cohorts, descriptive summary statistics (n, mean, StD, median, minimum, maximum, 95% Confidence Interval [CI] of the mean) or frequency counts of demographic and baseline data will be presented by cohort and overall for the FAS and the PP population (on PP if difference in number of subjects enrolled between FAS and PP is >10%)

All demographic and baseline characteristics will be listed by cohort and subject.

Summary statistics will be provided for demographic and baseline characteristics (sex, race, age, height, weight and BMI in categories at screening, ECOG performance status).

Summary statistics of the tumour characteristics will be provided: histopathological type of the tumour, proliferation Index Ki67, categories of proliferation Index Ki67: <10% (with details for categories ≤ 2,]2; 10[) versus ≥10%, tumour grade according to World Health Organisation (WHO) 2010 classification, time since diagnostic (see refer to section 6, Appendix 1, Derived data), time since diagnostic by category (≥3 years versus < 3 years), hepatic tumour load ≤25% (with details for categories ≤ 10, >10%) versus >25%, previous surgery of the primary tumour (Yes versus No).

Summary statistics of the duration of treatment with lanreotide Autogel® 120 mg every 28 days by category (<6 months [should be 0 as per inclusion criterion 4]; [6- 12[; [12-24[; ≥24) will also be provided by cohort and overall, as well as summary statistics of the Krenning scale (grade 0 to 4).

Presence/absence of symptoms at baseline will be summarised overall and by cohort. A description of the frequency of the symptoms (over the last 7 days (prior to baseline)) will also be provided.

3.2.7 Medical and surgical history

Medical and surgical history will be coded using MedDRA Version 19.1 or higher.

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

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

3.2.8 Prior Surgical Procedures for Pancreatic/Midgut NETs

Prior Surgical Procedures for Pancreatic/Midgut NETs will be tabulated and listed in a similar way to medical and surgical history.

3.2.9 Specific analysis of prior cholecystectomy, gallbladder surgery, lithiasis or sludge

The following analysis will be provided, based on the medical and surgical history and prior surgical procedures for Pancreatic/Midgut NETs:

- The number and percentage of subjects with prior cholecystectomy or gallbladder surgery or lithiasis or sludge during their treatment with lanreotide Autogel® 120 mg administered every 28 days will be calculated, among subjects in the FAS population. Among the subpopulation of subjects having presented at least one of the four events during their treatment with lanreotide Autogel® 120 mg administered every 28 days, the number and percentage of subjects having presented each of the four events will be displayed in the same table.

3.2.10 Radiotherapy for Pancreatic/Midgut NETs

Prior Radiotherapy for Pancreatic/Midgut NETs will be tabulated and listed in a similar way to medical and surgical history.

3.2.11 Subject compliance

A listing will be presented for drug administration (all captured data in the eCRF) by subject for each cohort. Deviations from observed and scheduled times will be presented (with tables and listings displaying anticipation/delayed injections/missed injections).

The compliance (%) will be calculated as the ratio of the actual number of injections according to eCRF over the planned number of injections, then multiplied by 100 (c.f. in Section 6 Appendix 1 Derived Data).

A summary table of compliance by cohort and overall will be presented on the FAS. Additionally, the number and percentage of subjects with a compliance in the categories <70%, [70%; 100% [, 100%,]100%; 130% [and ≥130% will be provided by cohort and overall.

Moreover, a listing of subjects with difficulties during drug administration will be provided.

3.2.12 Prior and concomitant therapies

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.

All recorded data will be included in data listings.

3.2.12.1 Prior and concomitant medication

Prior and concomitant medications will be coded using WHO Drug Dictionary, version June 2016 or higher. Medications which started and stopped before start of study treatment are considered as prior medications.

Medications which started before start of study treatment but are continuing will be considered as both prior and concomitant medications.

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term and verbatim text. The listings will be sorted by cohort, subject id, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior medications and concomitant medications by therapeutic class and preferred name for each cohort and overall on the FAS population.

3.2.12.2 Prior and concomitant non-drug therapies

Concomitant non-drug therapies will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher. Therapies which started and stopped before start of study treatment are considered as prior therapies.

Therapies which started before start of study treatment but are continuing will be considered as both prior and concomitant therapies.

Listings will include the system organ class, preferred term and verbatim text. The listings will be sorted by cohort, subject id, chronological start date, stop date, system organ class, preferred term and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior therapies and concomitant therapies by system organ class and preferred term for each cohort and overall on the FAS population.

3.2.12.3 Prior and concomitant medications for Pancreatic/Midgut Neuroendocrine Tumours

Prior and concomitant medications for Pancreatic/Midgut Neuroendocrine Tumours will be coded using WHO Drug Dictionary, version June 2016 or higher. Medications which started and stopped before start of study treatment are considered as prior medications.

Medications which started before start of study treatment but are continuing will be considered as both prior and concomitant medications.

Listings will include the therapeutic class (i.e., the second level of ATC classification system code, that is, corresponding to the first 3 figures), preferred term and verbatim text. The listings will be sorted by cohort, subject id, start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior medications and concomitant medications by therapeutic class and preferred name for each cohort and overall on the FAS population.

3.2.12.4 Concomitant surgical procedures

Concomitant surgical procedures will be coded using the MedDRA Dictionary, Version 19.1 or higher. Surgical procedures which started after start of study treatment will be considered as concomitant surgical procedures.

Listings will include the system organ class, preferred term and verbatim text. The listings will be sorted by cohort, subject id, chronological start date, stop date, system organ class, preferred term and verbatim name.

A frequency table of the number and percentage of subjects will be provided for concomitant surgical procedures by system organ class and preferred term for each cohort and overall for FAS population.

3.2.13 Pharmacokinetics

Analysis of pharmacokinetic (PK) and PK/PhD data will be performed by a Contract Research Organisation (CRO) under IPSEN supervision (Clinical PK and Pharmacometry department).

A listing of PK and antibodies sampling time and any deviation from the scheduled time will be provided. A listing of individual lanreotide concentrations per timepoint will be provided. A listing of individual antibodies results will also be provided as well as three tables including:

- the percentage of subjects developing anti-lanreotide antibodies at baseline and at the EOS,
- descriptive statistics on anti-lanreotide antibodies titer.
- descriptive statistics on individual lanreotide concentrations per timepoint.

Further details of the PK analysis will be provided in a separate document.

3.2.14 Derived data

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

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

3.2.15 Visit windows

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

Reallocation of a visit to a time window for the FAS and PP analyses will be as follows:

Study phase	Scheduled visit	Time interval (days)
Pre treatment	Screening (visit 1)*	-28 to -1
Treatment period	Baseline (visit 2)* 1	Day 1 Study drug administration commences at Visit 2 (Baseline) following completion of the Baseline assessments
	Visit 3 (Week 2)*	2 to 21
	Visit 4 (Week 4)*	22 to 42
	Visit 5 (Week 8)*	43 to 70
	Visit 6 (Week 12)*	71 to 126
	Visit 7 (Week 24)*	127 to 210
	Visit 8 (Week 36)*	211 to 294
	Visit 9 (Week 48)*	295 to 378
	Visit 10 (Week 60)	379 to 462
	Visit 11 (Week 72)	463 to 546
	Visit 12 (Week 84)	547 to 630
	Visit 13 (Week 96)	631 to 714
	Visit X	Every 12 weeks
After study treatment	End of Study/Early Withdrawal Visit	Last visit + 1 day to Last visit + 30.4375 days

*Common visit for pNEt cohort and Midgut cohort (up to Week 96)

[1] When Visit 2 (Day 1) is missing, baseline value is based on screening value for change from baseline analysis.

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.

3.2.16 Rules and data formats

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

For descriptive analyses, summary statistics will be presented at each scheduled visit. Summary statistics will include sample size, number of available observations (N), number of missing observations (missing), mean, 95% CI of the mean, 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.

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

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of non-missing observations. The denominator will be specified in a footnote to the tables for clarification if necessary.

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

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

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

3.2.17 Pooling of Centres

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

3.2.18 Interim analysis

A baseline analysis will be performed on all subjects enrolled until data extraction. This interim analysis (descriptive analysis of baseline data) was planned and Agencies/Committees were informed in October 2018. Visit 1 and Visit 2 only will be used for this interim analysis. The following baseline assessments will be described on the FAS population :

- Subjection disposition
- Demographic data (country, center, age, sex, height, weight, race, BMI, ECOG performance status),
- Tumours characteristics,
- Significant medical or surgical history,
- Presence/absence of symptoms at baseline
- Prior surgical procedures for pancreatic/midgut NETs, prior radiotherapy for pancreatic/midgut NETs, prior medications for pancreatic/midgut NETs,
- SSTR2 assessment /Krenning Scale,
- Quality of life questionnaires (QLQ C30, QLQ GI.NET21, EQ-5D-5L), Visit 2 day 1 only,
- Concentrations of nonspecific tumour peptide biomarkers, Visit 2 day 1 only,
- Gallbladder echography, Screening only
- Progression at pre-screening and screening as assessed by an independent central reviewer (only listed).

3.2.19 Role of the Data Safety Monitoring Board (DSMB)

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, and details of the data analysis (e.g. parameters, frequency, stopping rules) will be provided in a separate DSMB SAP.

3.2.20 Covariates and analysis of subgroups

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 load ≤25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour and Ki67 <10% versus ≥10, Time interval between the 2 CT scans (pre-screening / screening) <12 months / >=12 months) and symptoms (diarrhoea or flushing at baseline: Yes / No)

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using Windows 7.

4.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.4. All outputs will be in Microsoft Word Format, and delivered by the CRO as one single file per tables, listing, figure, and a compilation per ICH section.

4.3 Validation programs

SAS® programs are developed to produce clinical study output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Chiltern International CCI [redacted] "CCI [redacted] s.

Chiltern CCI [redacted] CCI [redacted] describes the quality control procedures that must be performed for all SAS® programs and outputs. Quality control (QC) is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the proper clinical study output by checking for their logic, efficiency and commenting, and by inspection of the produced outputs.

A Program Output Release form (CCI [redacted] will be prepared to document the methods of validation.

Copies of the QC documentation produced as confirmation that the validation process has been followed will be provided by Chiltern and will be retained by the sponsor.

4.4 Restitution of the programs

All programs (including Macros and analysis datasets) producing the tables, listings and statistical output along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

5 CHANGES FROM PROTOCOL

2.4 Primary population

A change from the protocol has been made in this SAP, concerning section 10.1.1 Populations Analysed of the protocol, were it is stated that a PP population analysis will be performed on the primary and secondary endpoints of PFS (i.e. median PFS and PFS rate), median time to progression, ORR, DCR, best overall response and median duration of SD. In the section 2.4 Primary population of this SAP, it has been added that these analyses will be performed only if the difference in number of subjects between FAS and PP population is > 10%, based on subjects in FAS.

Table 6 Censoring Rules for PFS of the protocol section 10.4.5 Efficacy Evaluation has been updated in this SAP, from:

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

to:

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
Initiation of medications or therapy not permitted during the study	Date of initiation of non permitted medication or Therapy

* An assessment is considered NE when no imaging/measurement is done at all at a particular time point, or only a subset of lesion measurements are made at the time point. The subject is considered NE at that time point.

(see Table 5, section 3.2.1.1 Primary analysis of this SAP)

3.1.2 Secondary efficacy endpoint(s)

A change from the protocol has been made in this SAP, concerning section CCI [redacted]). CCI [redacted]

6 APPENDICES TO THE SAP TEMPLATE

6.1 List of TFLs

List of TFLs to be produced for the analysis are provided in this section. Tables and listings to be performed for the baseline interim analysis are flagged with an asterisk (*)

6.1.1 Listings index

CCI

CCI

CCI

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted])

CCI

CCI [redacted]

CCI

CCI

CCI [redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]

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[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted] (FAS)
CCI [redacted]	[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

7 REFERENCES

1 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205 216.

2 International Conference on Harmonisation (ICH) E9 Guidance on statistical principles for clinical trials. Federal register Vol 63, No. 179 (September 1998).

3 Ferté C, Fernandez M, Hollebecque A et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. Clin Cancer Res. 2014;20:246 252

4 US Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer and Drugs and Biologics. Rockville, MD: US Food and Drug Administration, US Dept of Health and Human Services; 2007