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STATISTICAL ANALYSIS PLAN

PRODIGE 31 – FFCD 1301 – REMINET

EudraCT number 2013-004069-14

A EUROPEAN, MULTICENTRE, PHASE II/III RANDOMISED DOUBLE-BLIND, PLACEBO CONTROLLED STUDY EVALUATING LANREOTIDE AS MAINTENANCE THERAPY IN PATIENTS WITH NON-RESECTABLE DUODENO-PANCREATIC NEUROENDOCRINE TUMOURS AFTER FIRST-LINE TREATMENT

Final Version – 03 December 2019

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DOCUMENT HISTORY

Version	Date	Description of change	Performed by
Draft 1	19JUN2018	Document creation	Isabelle Josse
Version 2.0	18 SEP2019	Finalisation	Karine Le Malicot
Version 2.1	08 OCT2019	Correction suite à Programmation des Mock Tables	Karine Le Malicot
Version 2.2	03 DEC 2019	Final Version	Karine Le Malicot

APPROVALS

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ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CgA	Chromogranin A
CM	Contrast Medium
CR	Complete Response
CRO	Clinical Research Organization
CI	Confidence Interval
CT	Computed Tomography
ENETS	European NeuroEndocrine Tumor Society
FFCD	Fédération Francophone de Cancérologie Digestive (French Federation of Digestive Cancerology)
ICH	International Conference for Harmonisation
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
NE	Not Evaluable
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
NCI- CTC	National Cancer Institute - Common Terminology Criteria
NET	Neuro Endocrine Tumour
PP	Per-Protocol
PPI	Proton Pump Inhibitor
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious AEs
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
Std	Standard Deviation
SOC	System Organ Class
TNCD	Thésaurus National de Cancérologie Digestive
WHO	World Health Organisation

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses to be performed on the phase II of the study, contains the definition of analysis sets and protocol deviations, defines derived data, and specifies the methodology for analysing primary and secondary endpoints.

This SAP is based on:

- Study Protocol version 3.0 dated on 16-June-2016,
- Case Report Form final version 3.0 dated on 28-October-2014.

The analyses closely follow the International Conference for Harmonisation (ICH) guidelines for industry on topic E3 - Structure and Content of Clinical Study Reports and E9 - Statistical Principles for Clinical Trials.

2 DESCRIPTION OF THE STUDY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of phase II is to evaluate the rate of patients alive and progression free at 6 months, assessed by the investigator according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria, version 1.1.

2.1.2 Secondary objective(s)

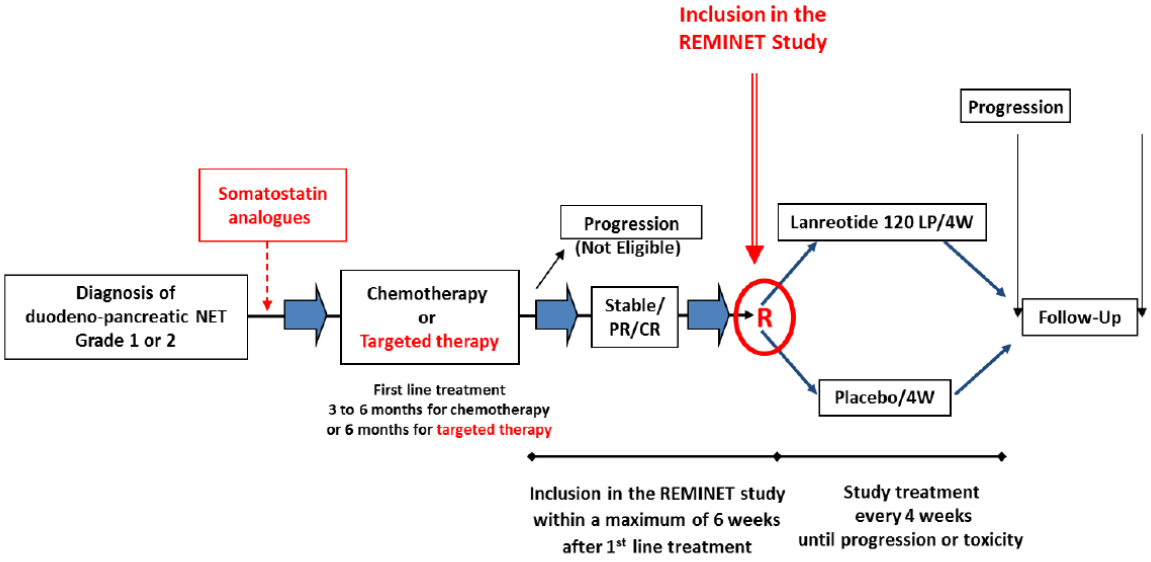
The secondary objectives of phase II are:

- Rate of patients alive and progression free at 12 months, assessed by the investigator according to RECIST criteria (version 1.1),
- Rate of patients alive and progression free at 6 months, according to central review,
- Safety,
- Response rate at 6 months according to RECIST criteria (version 1.1),
- Time To Progression,
- Quality of life assessed with the questionnaire QLQ-C30, including module NET21, and the Spitzer visual analogue scale.

2.2 Study design

2.2.1 Description

This is a European, prospective, multicentre, double-blind randomised study evaluating lanreotide (120 mg every 28 days until disease progression) versus placebo in patients with metastatic/locally advanced, non-resectable, duodeno-pancreatic neuroendocrine tumours, stabilised or in objective response after the first line of treatment.



2.2.2 Schedule of assessments and study procedures

The schedule of observations and assessments conducted during the study is set out in the following flowchart:

Flow Chart - Schedule of the study Assessments

	Screening / Randomisation	**Treatment Phase**		**Follow-up**
Assessments	**D-30 à D1**	**Day 1 = C1 Every 28 days**	**Every 3 months until progression**	**Every 6 months**
Informed Consent	X			
Demographic data [1]	X			
Relevant medical history [2]	X			
Eligibility criteria	X			
Randomisation	X			
Physical examination [3]	X	X	X	
World Health Organisation (WHO) score	X	X	X	X
Haematology [4]	X		X	
Blood chemistry [5]	X		X	
Thyroid blood tests	X			
Pregnancy test [6]	(X)			
Electrocardiogram	X			
Treatment administration		X		
Tumour assessments	X [7; 8]		X	
Brain Computing Tomography (CT) / Magnetic Resonance Imaging (MRI) [9]	X		X	
Bone scan [9]	X		X	
Chromogranin A (CgA) [10]	X		X	
Ki-67 (according to the Neuro Endocrine Tumour [NET] referent review)	X			
Survival status				X
Adverse Events (AEs) [11] / Serious AEs (SAEs)	X	X	X	SAEs [12]
Further treatment lines				X
Tumour slide [13]	X			
Informed consent for biomarker research	X			
Blood sample collection (biomarker research) [14]	X		X	
Quality of Life (QLQ-C30 + NET21)	X		X	
Medico-economical evaluation (EQ-5D including the Spitzer visual analogue scale)	X		X	X [15]

1: Sex, age
2: Including ongoing medical history
3: Weight
4: Complete blood count, platelets
5: Electrolytes, total protein, liver function tests (alanine-aminoTransferase, aspartate-aminoTransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin and conjugated), albumin, lactate dehydrogenase, glycated haemoglobin, glycaemia. Total cholesterol, high density lipoprotein cholesterol and triglycerids done only at the inclusion.
6: Serum pregnancy test within 7 days prior to randomisation
7: Scans showing response or stabilisation after fist line therapy should be done at least 2 weeks after the end of the first-line treatment and within 4 weeks before randomisation
8: Chest, abdomen and pelvis CT scan with early arterial timing or abdominal and pelvic MRI + chest CT scan with injection of iodised contrast medium (CM). In case of contraindication to use of a CM, abdominal and pelvic MRI + chest CT scan without injection. It is necessary to use the same evaluation method as the one used at inclusion
9: As clinically indicated
10: CgA assessment must always be performed with the same method in the same laboratory
11: According to National Cancer Institute – Common Terminology Criteria for AE V4.0
12: All SAE occurring at any time after the end of the study treatment phase, and likely to be related to the study treatment or to a study procedure (in investigator's opinion), must be reported according to the reporting process described in the protocol
13: For all patients consenting to the biomarker translational research, tumour slides will be collected at the central pathological laboratory; biomarker translational research program will be done on these slides
14: Sample to be taken while fasting, at the inclusion, at the 1st of the 3-month evaluation only, and after progression
15: EQ-5D questionnaire will be completed until 18 months after randomisation or until the end-of-treatment visit, in case of study drug discontinuation prior to 18-months post-randomization

2.3 Study endpoints

2.3.1 Primary efficacy endpoints

The primary endpoint for phase II is the rate of patients alive and progression free at 6 months, evaluated according to the results of imaging assessment done 6 months after the randomisation. This evaluation is done by the investigator according to RECIST criteria (version 1.1).

2.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints of phase II are the following:

- Rate of patients alive and progression free at 12 months (according to RECIST criteria version 1.1), assessed by the investigator,
- Rate of patients alive and progression free at 6 months, according to central review,
- Response rate according to RECIST criteria at 6 months (version 1.1), according to the Investigator,
- Time to progression (median),
- Progression-Free Survival,
- Overall Survival,
- Quality of life (QLQ-C30 including module NET21, the Spitzer visual analogue scale).

2.3.3 Safety endpoints

The secondary safety endpoints of phase II are the following:

- Adverse Events (AEs): the toxicities will be described using the National Cancer Institute – Common Terminology Criteria for AE (NCI-CTC AE) version 4.0,
- Vital Signs (Weight) and WHO performance index.

2.4 Study treatments

2.4.1 Treatment groups

The Investigational Medicinal Products used in this study (lanreotide, placebo) were provided by Beaufour IPSEN Industry in the following presentations:

Lanreotide Autogel 120 mg:

Treatment was provided in a pre-filled syringe of 0.5 mL with a 20 mm needle of 1.2 mm external diameter, sealed in a laminated bag and in a cardboard box. Each pre-filled syringe has an automatic security system. Each 0.5 mL syringe contains a supersaturated acetate solution of lanreotide corresponding to 0.246 mg of lanreotide base/mg of solution, for subcutaneous injection of a 120 mg dose of lanreotide.

Placebo:

The placebo injection will consist of a 0.9% saline solution provided as follows:

- A 2 mL ampoule containing 1 mL of NaCl at 0.9%,
- An empty syringe of 0.5 ml with an automatic security system and a 20 mm needle of 1.2 mm external diameter and 1.0 mm internal diameter sealed in a laminate bag.

2.4.2 Treatment duration

The study treatment should be initiated after randomisation, within the 6 weeks following the confirmation date of stable disease or objective response.

Once the randomisation has been performed, the patients received a single dose of the investigational products (lanreotide or placebo) every 4 weeks (every 28 days) according to a double blind procedure until disease progression or toxicity.

2.4.3 Randomization

2.4.3.1 Randomization procedure

After confirmation of their eligibility in the study, patients received a randomisation / treatment allocation number according to their order of entry into the study by an Interactive Web Response System (IWRS). The IWRS was manage the link between the treatment number and the randomisation number.

The randomisation was conducted according to the technique of minimisation; treatments were randomised in a 1:1 ratio, stratified according to the following criteria:

- Centre,
- Grade 1 versus grade 2,
- First-line treatment: chemotherapy vs. targeted therapy (everolimus or sunitinib).

2.4.3.2 Blinding

In order to guarantee blinding of the investigator and all the staff participating in the evaluation or the recording of the results of the treatment, all injections carried out during the double-blind phase should be administered at the site by a person who was specifically trained and qualified (for example, a nurse), otherwise not involved in the study procedures. This person had to ensure that this blindness was maintained with respect to the patients.

Lanreotide and the placebo are not identical: lanreotide is a viscous formulation that was supplied in a pre-filled syringe; the placebo is a solution that was not provided in a pre-filled syringe. As a result, the person carrying out the injection filled the syringe with the placebo solution out of the patient's view. In addition, both lanreotide and the placebo were administered in the currently-approved injection site, in the superior external quadrant of the buttock, in order to limit the patient's view of the injection. At each cycle, the injection site was alternated between the left and right side of the body.

The patients, investigators, site staff, persons performing the assessments and the Clinical Research Associate remained blind to the process and will not have access to the identity of the treatment allocated to the patients (lanreotide or placebo), from the date of randomisation until the final database lock of phase III of the study.

The blinding will be broken for the staff responsible for the statistical analysis at the end of phase II of the study, when the database will be locked for the data analysis of this phase. Individual patient data (with decoded treatment) will not be communicated to investigators or any other persons involved in the conduct of the study, in order to guarantee the absence of any bias during the long-term survival follow-up, until the end of phase III of the study, except in case of confirmed disease progression.

To guarantee that blinding is maintained, the following methods are applied:

- The randomisation code will be kept in the strictest confidentiality until the unblinding and will not be accessible to any person involved in the conduct of the study,
- The identity of the treatment (lanreotide or placebo) will be hidden on the packaging and the label.

The study randomisation code should not be broken, except in the case of a medical emergency and in case of confirmed disease progression, if the knowledge of the study treatment received may influence the medical care of the patient.

In these medical emergency cases and in case of confirmed disease progression, the investigator may break the blind using the IWRS system.

The date and reason for unblinding must be detailed on the IWRS and on the case report form.

The sponsor reserves the right to break the blind for Serious AEs (SAEs) that are considered to be related to the study treatment and unexpected, which could therefore require expedited reporting to the regulatory authorities.

2.5 Sample size considerations

The hypotheses for the calculation of the sample size as follows:

H_0: A rate of patients alive and progression free at 6 months of 45% or less is not sufficient to demonstrate efficacy ($p \leq p0$ with $p0=45\%$). The study will not be continued.

H_1: A rate of patients alive and progression free at 6 months of more than 45% is sufficient to demonstrate efficacy. A rate of 63% is expected ($p \geq p0$ with $p0=45\%$ and $p=p1 = 63\%$). A rate of patients alive and progression free at 6 months of more than 45% (i.e. if the lower bound of the exact binomial two-sided 90% confidence interval (CI) exceeds 45%) leads to the study continuation.

With a one-sided alpha risk of 5% and power of 85% (binomial-exact method), 56 patients should be randomised in each arm.

With a rate of 5% of patients being non-evaluable or lost to follow-up, 59 patients should be included in each arm (118 patients in total).

The following decision rule will be applied:

If 31 patients or less are alive and progression free at 6 months or before, the treatment will be considered as not interesting.

This rule will apply only to the lanreotide arm. The placebo arm will be maintained for reference for phase III. A data safety monitoring board may also stop the study with regard to the occurrence of SAEs and AEs.

If the phase II results are positive, the study will continue into phase III. The randomised patients in phase II will be included in phase III. In case of study termination for futility at phase II, the patients will stop the study treatments and their care.

3 ANALYSIS POPULATIONS

Three populations will be considered for the analyses:

3.1 Intent-to-treat (ITT) population

All randomised patients in the study. These patients will be considered in the allocated group by randomisation, even if they receive a different treatment.

3.2 Modified Intent-to-treat (mITT) population

All randomised patients in the study who did not withdrew their consent before the randomisation. These patients will be considered in the allocated group by randomisation, even if they receive a different treatment.

mITT population will be considered as the primary population for efficacy analysis.

3.3 Safety population

All patients included in the mITT population having received at least one treatment injection. These patients will be analysed in terms of the treatment received.

The safety population will be considered as the primary population for safety analysis.

4 GENERAL CONSIDERATIONS FOR DATA ANALYSES

Statistical analyses will be performed by the Biostatistics department of Aixial. Analyses will be conducted with SAS® software, version 9.4 or higher (SAS Institute, North Caroline, USA).

All statistical tests will be two-sided and type I error (alpha) set to 10% for the primary endpoint and set to 5% for the other parameters.

Continuous data will be described in summary tables presenting, for each treatment group and for the overall population, the number of non-missing observations (n), mean, standard deviation (StD), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum, and 95% CI of the mean.

Categorical data will be described in summary tables presenting, for each treatment group and for the overall population, the number of non-missing observations (n), count and percentage of each modality, and CI.

90% CI of a proportion will be calculated using the Clopper-Pearson method for the primary endpoint and 95% CI of a proportion will be calculated using the score method of Wilson without continuity correction for the other parameters.

Except minimum and maximum, descriptive statistics are presented with one more decimal than the recorded value.

For all variables, the number of missing values will also be reported in the tables, but they will not be counted for the percentage calculation (categorical data).

4.1 Statistical hypotheses

The hypotheses as follows:

H_0: A rate of patients alive and progression free at 6 months of 45% or less is not sufficient to demonstrate efficacy ($p \leq p0$ with p0=45%). The study will not be continued.

H_1: A rate of patients alive and progression free at 6 months of more than 45% is sufficient to demonstrate efficacy. A rate of 63% is expected ($p \geq p0$ with p0=45% and p=p1 = 63%). A rate of patients alive and progression free at 6 months of more than 45% (i.e. if the lower bound of the exact binomial two-sided 90% CI exceeds 45%) leads to the study continuation.

4.2 Display of analysis results

Labels used for treatment groups will be Lanreotide and Placebo.

4.3 Interim analyses

No interim analysis will be performed.

4.4 Centre effect management

Centre effect will not be tested.

4.5 Subgroup analyses

No subgroup analysis is planned.

4.6 Other strata and covariates

No other strata or covariates will be tested.

4.7 Multiple comparisons and multiplicity

Not Applicable.

5 DATA HANDLING CONVENTIONS

5.1 Missing data

If a patient discontinues prematurely the study, the investigator should perform all the investigations planned at the final visit.

Missing data will not be replaced.

For the primary endpoint of the phase II, if at 6 months the progression is not documented and no progression was noticed before, the patients will be reviewed by the independent committee to classify him as progressive or not progressive at 6 months according to the medical data collected.

5.2 Visit windows

Not Applicable

5.3 Derived and transformed data

Following derived data used for analyses will be calculated.

5.3.1 Time to initial diagnosis from randomisation (months)

Time to initial diagnosis from randomisation (months) will be calculated as:
(Date of randomisation – Date of initial diagnosis+1) / 30.4375.

If the day is missing and month is present the 15 of the month will be used. Else time to initial diagnosis from randomisation will be missing.

5.3.2 Time to initial progression from start of 1st line therapy (months)

Time to initial progression from start of 1st line therapy (months) will be calculated as:
(Star date of 1st line therapy – Date of initial progression+1) / 30.4375.

If the day is missing and month is present the 15 of the month will be used. Else time to initial progression from start of 1st line therapy will be missing.

5.3.3 Time to initial progression from randomisation (months)

Time to initial progression from randomisation (months) will be calculated as:
(Date of randomisation – Date of initial progression + 1) / 30.4375.

If the day is missing and month is present the 15 of the month will be used. Else time to initial progression from randomisation will be missing.

5.3.4 Duration of 1st line therapy (months)

Duration of 1st line therapy (months) will be calculated as:
(End date of treatment – Start date of treatment + x days) / 30.4375.

If the day is missing and month is present the 15 of the month will be used. Else duration of 1st line therapy will be missing.

Number of days depends of the treatment taken for 1st line:

- 5FU/Xeloda/Oxaliplatine/Irinotecan = 14 days
- Adriamycine = 28 days
- Streptosocyne = 42 days
- Temozolomide (Daily Oral Treatment)
- Dacarbazine= 21 jours

- Gemcitabine / Gemzar : 21 days
- Carboplatin : 28 days
- Doxorubicine : 28 days
- Cisplatin : 21 days
- Bevacizumab : 14 days
- Sunitinib : 42 days

5.3.5 Number of cycle performed

A cycle will be considered as performed if administration of study treatment is performed

5.3.6 Number of cycle delays

A cycle will be considered as delays if:
(Date of study treatment administration of Cycle x – Date of study treatment administration of Cycle x-1) > 28

5.3.7 Duration of study treatment (years)

Duration of study treatment (months) will be calculated as:
(Last intake of study treatment– 1st intake of study of treatment +28) / 365.25.

5.3.8 Response

Response is defined as complete response (CR) or partial response (PR) to the treatment according to RECIST.

5.3.9 Time to Progression

This time to progression is calculated from the randomisation date to the date of the first progression (clinical or radiological) according to the investigator for progressive patients.

5.3.10 Progression-free survival

This time is calculated from the randomization date to the date of the first progression (clinical or radiological) according to the investigator. Patients alive without progression will be censored to the date of last news.

5.3.11 Overall Survival

This time is calculated from the randomization date to the date of death (whatever the cause is). Patients alive will be censored to the date of last news.

5.3.12 Quality of life

<u>EORTC QLQ-C30 score and subscores</u>

The scale is made of 30 items that can be divided in nine multi-item scales (including five functional scales (15 items), one global health status / quality of life scale (2 items) and three general symptom scales (7 items)) and six single items. The Table below presents the conceptual structure of QLQ-C30.

Possible answers to the first 28 items (all items except the two concerning global quality of life) go from 1 (“Not at all”) to 4 (“Very much”). No inversion is necessary to calculate the different

corresponding scores. The answers for the two last questions (29, 30) go from 1 (“Very poor”) to 7 (“Excellent”).

Dimension	Sub-scales	Number of items	Item numbers
FUNCTION	Physical functioning	5	1 to 5
	Role functioning	2	6, 7
	Emotional functioning	4	21, 22, 23, 24
	Cognitive functioning	2	20, 25
	Social functioning	2	26, 27
GLOBAL HEALTH STATUS	Global quality of life	2	29, 30
GENERAL SYMPTOMS	Fatigue	3	10, 12, 18
	Nausea and vomiting	2	14, 15
	Pain	2	9, 19
SPECIFIC SYMPTOMS	Dyspnoea	1	8
	Insomnia	1	11
	Appetite loss	1	13
	Constipation	1	16
	Diarrhea	1	17
	Financial difficulties	1	28

Scores will be calculated in agreement with the scoring manual [5]. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / quality of life represents a high quality of life, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

For multi-item scales, the raw score will be calculated by the addition of item responses divided by the number of items. Then a linear transformation will be used to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher (“better”) level of functioning, or a higher (“worse”) level of symptoms.

Raw score (RS):

RS = sum of item responses / number of items.

Standardised score (S):

Functional scales: $S = 100 – [(RS – 1) / 3] \times 100$.
Global health status: $S = (RS – 1) / 6 \times 100$.
Symptom scales / items: $S = (RS – 1) / 3 \times 100$.

Missing data: For multi-item scales, if at least 50% of the items from the scale have been answered then raw score will be calculated by the addition of available responses divided by the number of not missing items. If less than 50% of the items from the scale have been answered then the raw score will be set to missing.

EORTC QLQ-G.I.NET 21 score and subscores

The scale is made of 21 items that can be divided in five multi-item scales and four single items. The following table presents the conceptual structure of G.I.NET 21.

		Number of items	Item numbers
Multi-item scales	Endocrine	3	31, 32, 33
	Gastro Intestinal	5	34, 35, 36, 37, 38
	Treatment	3	39, 40, 46
	Social function	3	42, 44, 49
	Disease related worries	3	41, 43, 47
Single items	Muscle/Bone pain	1	48
	Sexual function	1	51
	Information/communication function	1	50
	Body image	1	45

Possible answers go from 1 (“Not at all”) to 4 (“Very much”). A high score is equivalent to worse or more problems. The patient can also answer “N.A” to items 39, 40, 47 and 51. No inversion is necessary to calculate the different scores.

For each scale, the raw score will be calculated by the addition of item responses divided by the number of items. Then a linear transformation will be used to standardise the raw score, so that scores range from 0 to 100.

Raw score = sum of item responses / number of items.
Standardised score = (raw score – 1) / 3 x 100.

Single items will be treated individually. They will be linearly transformed to a 0-100 scale.

Standardised score = (raw score – 1) / 3 x 100.

Missing data: For multi-item scales, if at least 50% of the items from the scale have been answered then raw score will be calculated by the addition of available responses divided by the number of not missing items.

Not applicable box: for calculations N/A data should be managed as for missing data.

6 DESCRIPTION OF THE STUDY POPULATION

6.1 Disposition of patients

Patients’ disposition will be described for each treatment group and for the overall population.

The number and percentage of screened and randomised patients will be presented, as well as the number of patients in all analysis populations.

Following data will be described on mITT population:

- The number of patients per visit/cycle,
- The number of patients per centre,
- The number of patients who stopped the treatment and the reason of treatment withdrawal,
- The number of patients who stopped the follow-up visit and the last status reported.

The number of patients with at least one major protocol deviation will be described for each treatment group and for the mITT population. Major deviations will be also presented in an individual data listing.

6.2 Demographics and baseline characteristics

The demographics and baseline characteristics of the patients will be described by treatment group and overall on mITT population.

6.2.1 Demographic characteristics

The following characteristics will be summarised by treatment group and overall:

- Age (years),
- Gender.

6.2.2 Medical or surgical history

Medical or surgical history will be coded using the Medicinal Dictionary for Regulatory Activities (MedDRA) version 22.0.

Number (%) of patients will be presented by System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall.

6.2.3 Previous and concomitant medications

Previous and concomitant medications will be coded using the World Health Organisation-Drug Dictionary (WHO-Drug) version Q1-2018.

Treatments will be summarized according to the Anatomical Therapeutic Chemical (ATC) class (level 2 and level 4) of the WHO-Drug by treatment group and overall.

A previous treatment will be defined as a treatment stopped prior to (or the same day as) the first intake of the study treatment.

A concomitant treatment will be defined as a treatment i) started after (or the same day as) the first intake of the study treatment, ii) started prior to and continued after the first intake of the study treatment. If the classification is not possible due to partial start/end date(s) of treatment, the treatment will be considered as concomitant.

6.2.4 Other baseline characteristics

Cancer history will be summarised by treatment group and overall:

- Time to initial diagnosis from randomisation (months),
- Resectable cancer (Yes/No),
- Type de cancer and details:
  - Type of cancer (Locally advanced / Metastatic),
  - If metastatic, localisation (Hepatic / Pulmonary / Bone / Other; *Note: A same patient can have several localisations*),
- Histological grade (Grade 1 / Grade 2 / Grade 3),
- Ki67 (%),
- Ki67 assessed by the referent NET pathologist (Yes/No).

First line of therapy will be summarised by treatment group and overall:

- Time to initial progression from start of 1st line therapy (months),
- Time to initial progression from randomisation (months),
- Treatment:
  - Type of treatment (Conventional / Targeted),
  - If conventional therapy, details of treatment (5FU / Oxaliplatine / Irinotecan / Adriamycine / Streptosotocyne / Xeloda / Temozolomide / Dacarbazine / Other). In case where a patient received several treatments, should we count the patient in only for the combination
  - If targeted therapy, details of treatment (Sunitinib / Evorolimus / Other),
  - Duration of therapy (months).
- Response of first line treatment (CR / PR / Stable Disease [SD] / Progression [PD] / Not Evaluable [NE]).

Values before first study treatment intake of the efficacy and safety endpoints will be provided in statistical tables with assessments post-baseline (see Section 6).

6.3 Treatment exposure and compliance

The following data on the use of study treatment will be summarized by treatment group and overall on the Safety population.

- Number of cycles performed,
- Number of cycles delays,
- Duration of study treatments (years).

7 EFFICACY ANALYSIS

Primary efficacy endpoint will be primarily analysed on the mITT population. Secondary efficacy endpoints will be analysed on the mITT population.

7.1 Primary efficacy endpoint

The primary endpoint for phase II is the rate of patients alive and progression free at 6 months, evaluated according to the results of imaging assessment done 6 months after the randomisation. This evaluation is done by the investigator according to RECIST criteria (version 1.1).

The number and percentage of patients alive and progression free at 6 months will be calculated and described by treatment group and overall on the mITT population. The two-sided 90% CIs will also be calculated.

7.2 Secondary efficacy endpoints

7.2.1 Rate of patients alive and progression free at 12 months, assessed by the investigator

The number and percentage of patients alive and progression free at 12 months will be calculated and described by treatment group and overall on the mITT population based on Kaplan-Meier method with the estimation of this number at 12 months. Rate of patients alive and progression free at 6 months, according to central review

The number and percentage of patients alive and progression free at 6 months will be calculated and described by treatment group and overall on the mITT population. Data taken into account will be overall response at Cycle 4 and Cycle 7 + death if before injection of cycle 7. Patients alive and progression free before or at cycle 7 will be reviewed separately.

7.2.2 Response rate at 6 months

Overall Response (CR, PR, SD, PD, NE) and Clinical Progression (Yes/No) will be presented every 3 months (at Cycles 4, 7, 10, 13, 16, …).

Response rate according to RECIST criteria at 6 months (version 1.1), according to the investigator will be calculated and described.

Patients alive and progression free before or at cycle 7 will be reviewed separately.

7.2.3 Time to progression

Among the patient with a progression during the phase II, the time to progression will be calculated and described by treatment group and overall.

7.2.4 Progression-Free Survival

Progression-free survival will be analysed using the Kaplan Meier method. The description will be made using the median, and the rates will be estimated at different stages of evaluation (95% confidence intervals will also be provided). The comparison between the two treatment arms will be made using a log-rank test.
The hazard ratio will be estimated using a Cox model. An unadjusted model (only with treatment effect) and a model adjusted to the stratification factors will be used. All hypotheses associated with the use of this model (proportionality and linearity) will be verified.

7.2.5 Overall Survival

Overall survival will be analysed using the Kaplan Meier method. The description will be made using the median, and the rates will be estimated at different stages of evaluation (95% confidence intervals

will also be provided). The comparison between the two treatment arms will be made using a log-rank test.
The hazard ratio will be estimated using a Cox model. An unadjusted model (only with treatment effect) and a model adjusted to the stratification factors will be used. All hypotheses associated with the use of this model (proportionality and linearity) will be verified.

7.2.6 Quality of life

The scores and subscores of EORTC QLQ-G.I.NET 21 and EORTC QLQ-C30 as well as the Spitzer visual analogue scale will be described every 3 months (at Cycles 4, 7, 10, 13, 16, …).

8 SAFETY ANALYSIS

Safety endpoints will be analysed on the Safety population.

8.1 Adverse events

Adverse events will be coded using MedDRA version 22.0. Pre-defined AEs and other AEs should be analysed together.

An overall summary table presenting the number and the percentage of patients with at least one AE and one with at least SAE will be presented by treatment group and overall.

Following descriptions will be performed by treatment group and overall:

- Number of patients with AEs by SOC and PT,
- Number of patients with AEs by SOC, PT and maximal grade,

In addition, the same description will be performed for SAEs.

A patient with more than one AE within a particular SOC and PT are counted only once for that SOC and PT. Percentages are based on the number of patients actually receiving a given treatment (based on the safety population) within each treatment group.

A listing of all AEs will be provided.

No formal statistical tests will be performed.

8.2 Vital signs

Vital Signs (Weight) and WHO performance index will be described by treatment group and overall, at each cycle and at end of treatment visit. For Weight, change from baseline will be also described by treatment group and overall.

9 CHANGES FROM STUDY PROTOCOL

Not Applicable.

10 VALIDATION OF STATISTICAL PROGRAMMING

Validation of statistical programming will be performed in agreement with Aixial's Standard Operating Procedure on Statistical Analysis.

Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings.

A third party will review all statistical outputs (tables, figures) and results from statistical tests/models, as well as SAS code of all statistical programs. This includes programs used to derive data and macros developed for the study.

Any undocumented updating of study data in statistical programs instead of change in clinical database (or source data) is not allowed. Specifically, this refers to the cases where patients or the data are added/changed using a statistical program rather than updating the database. This kind of hard coding is usually proposed to correct deficiencies (missing values, wrong values, and wrong measurement units) in the database when these errors are detected after database lock.

No hard coding is done in any programs used for the creation of analysis data sets, tables, listings, or analyses that are intended for external reporting after database lock (i.e. clinical study reports, publications, abstracts, etc.).

This policy ensures integrity of clinical data, since no changes are made to the study data without appropriate documentation from the investigator sites and appropriate audit trails within the clinical trial database.

11 REFERENCES

[1] ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] SAS 9.4; © 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

[4] NewCombe R.G. (1998) Two sided confidence intervals for the single proportion: comparison of seven methods in Medicine; 17,857-872.

[5] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

APPENDIX 1. TEMPLATES FOR STATISTICAL ANALYSIS AND SUMMARY TABLES

Study: XXXXX
Population: XXXXX

Table X – Summary of patients disposition

	Lanreotide	Placebo	Total
Screened patients			xx
Randomised patients	xx	xx	xx (xx.x%)
Safety population	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ITT population	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
mITT population	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Per-Protocol population	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Name of SAS program: P:\XXXXX\XXXX\Analysis\Pgm*program_name*.sas
Date and time program was run: JJMMMYYYY HH:MM

Study: XXXXX
Population: XXXXX

Table X – Summary of visits/cycles

	Lanreotide (N=XX	Placebo (N=xx)	Total (N=xx)
Screening/Randomisation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cycle 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cycle 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Follow-up 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Follow-up 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Name of SAS program: P:\XXXXX\XXXX\Analysis\Pgm*program_name*.sas
Date and time program was run: JJMMMYYYY HH:MM

Study: XXXXX
Population: XXXXX

Table X – Summary / Analysis of qualitative and quantitative variables

	Lanreotide (N=XX)	Placebo (N=XX)	Total (N=XX)
Quantitative variable			
n	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
95%CI mean	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
Median	xx.x	xx.x	xx.x
Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
Min. ; Max.	xx ; xx	xx ; xx	xx ; xx
Missing data	xx	xx	xx
Qualitative variable			
n	xx	xx	xx
Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
95%CI (Modality 1)*	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
95%CI (Modality 2)*	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
…	…	…	…
Modality n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
95%CI (Modality n)*	[xx.x ; xx.x]	[xx.x ; xx.x]	[xx.x ; xx.x]
Missing data	xx	xx	xx

** Will be replaced by 90%CI for primary endpoint*

Name of SAS program: P:\XXXXX\XXXX\Analysis\Pgm*program_name*.sas
Date and time program was run: JJMMMYYYY HH:MM

Study: XXXXX
Population: XXXXX

Table X – Summary of events per System Organ Class and Preferred term

	Lanreotide (N=XX)	Placebo (N=XX)	Total (N=XX)
	Nb (%) of patients	Nb (%) of patients	Nb (%) of patients
At least one AE	x (xx.x%)	x (xx.x%)	x (xx.x%)
Body system 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Preferred term n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Body system 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Preferred term n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….			
Body system n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Preferred term n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nb (%) of patients : Number (%) of patients with at least one AE *Each patient is counted once per Preferred Term then per System Organ Class*			

Name of SAS program: P:\XXXXX\XXXX\Analysis\Pgm*program_name*.sas
Date and time program was run: JJMMMYYYY HH:MM

Study: XXXXX
Population: XXXXX

Table X – Summary of events per SOC, PT and grade

	Lanreotide (N=XX)	Placebo (N=XX)	Total (N=XX)
	Nb (%) of patients	Nb (%) of patients	Nb (%) of patients
At least one AE	x (xx.x%)	x (xx.x%)	x (xx.x%)
Body system 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Preferred term n	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Grade 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….			

Nb (%) of patients : Number (%) of patients with at least one AE
Each patient is counted once per Grade, Preferred Term then per System Organ Class

Name of SAS program: P:\XXXXX\XXXX\Analysis\Pgm*program_name*.sas
Date and time program was run: JJMMMYYYY HH:MM