PRODIGE 31 – FFCD 1301 - REMINET
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

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PRODIGE 31 - FFCD 1301 – REMINET
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

EUDRACT No.: 2013-004069-14

Core Version 1.2 dated 03/11/2014

This version has been approved by:

The sponsor:

Ms Cécile GIRAULT - Date: 03/11/2014 - Signature:

Coordinating investigator:
Prof. Côme LEPAGE - Date: 03/11/2014 - Signature:

The investigator:

By my above signature, I hereby confirm that I agree:

- To conduct the study described in the protocol, in compliance with the Good Clinical Practices (ICH-GCP), with the standard operating procedures and with all applicable regulations
- To document the delegation of significant study-related duties and to notify the sponsor of changes in site staff involved in the study
- To dispense, track and retain study treatments in accordance with Good Clinical Practice (GCP) and the protocol
- To comply with procedures and all applicable regulations for data recording and reporting including Serious Adverse Events (SAEs)
- To authorise direct access to source data for monitoring, auditing and inspection
- To retain the study-related essential documents 15 years after the end of the study

Furthermore, I hereby confirm that I will have and will use adequate resources in terms of staff and facilities for the conduct of this study.

Name and title: Address and telephone number:

Date: Signature:

SYNOPSIS

Title	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
Study number	PRODIGE 31 – FFCD 1301 - REMINET
Study objectives	**Phase II** Primary objective: • To evaluate the rate of patients alive and progression free at 6 months, assessed by the investigator according to RECIST criteria (version 1.1) Secondary objectives: • 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 (TTP) • Quality of life assessed with the questionnaire QLQ-C30, including module NET 21, and the Spitzer visual analogue scale. **Phase III** Primary objective: • To assess and compare the Progression-Free Survival (PFS) of lanreotide versus placebo according to RECIST criteria (version 1.1) assessed by the investigator Secondary objectives: • Overall Survival (OS) at 3 and 5 years • PFS according to central review • Safety • Response rate at 6 months according to RECIST criteria (version 1.1) • Chemotherapy / biotherapy-free time interval • Quality of life assessed with the questionnaire QLQ-C30, including module NET 21, and the Spitzer visual analogue scale. • Medico-economical assessment: cost-effectiveness analysis at 12 months and cost-utility analysis at 18 months (using EQ-5D questionnaire)

Study phase	Phase II/III
Inclusion criteria for phases II and III	• Metastatic (synchronous or metachronous) or locally advanced, non resectable, well-differentiated duodeno-pancreatic neuroendocrine tumour, of grade 1 or 2 (WHO 2010 classification; Ki-67 ≤ 20%) • Progressive before first-line treatment • Histologically confirmed (either on primary tumour or metastases) • Pathological diagnosis validated by the NET consulting pathologist • Documented stable disease or objective response after first-line treatment, within 4 weeks (28 days) prior to randomisation • The first-line treatment will consist of either a chemotherapy or biotherapy (everolimus or sunitinib) as referred to TNCD or ENETS guidelines. Treatment must have been administered for 3 to 6 months for chemotherapy and for 6 months for biotherapy • Non-functional tumour or gastrinoma controlled by PPIs • Age ≥ 18 years • WHO 0, 1 or 2 • Effective contraception for male or female patients of childbearing age • Signed informed consent prior to initiation of any study-specific procedures or treatment
Non-inclusion criteria for phases II and III	• History of haematological malignancy or other cancer, except those treated for more than 5 years and considered as cured, carcinoma in situ of the cervix and treated skin cancer (excluding melanoma) • Poorly differentiated neuroendocrine carcinoma or NET grade 3 ENETS (Ki-67> 20%) • If primary resected, bone metastases exclusively • Pre-treatment by somatostatin long-acting analogue • Total bilirubin ≥ 60 µmol/L • Uncontrolled diabetes • Contraindication to the product used in the study or its components • Tumour arising in the context of a genetic disease • Pregnancy or lactation • Patients unable to undergo medical follow-up due to geographical, social, psychological or legal reasons • Concomitant participation in another clinical trial investigating a treatment during the treatment phase and within 30 days prior to the start of the study treatment • Employment of the subject or a close relative (i.e. spouse/partner, child, parent or sibling) by the CRO, the study site, • Patients deprived of their liberty by a judicial or administrative decision, patients admitted to a hospital, social institution or who are under a measure of legal protection, patients hospitalized without consent or who are in an emergency situation.

Study design and treatment plan	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. Depending on the phase II results, the study may be continued into phase III. The treatment and follow-up of patients will be the same in phase II and phase III. After the first-line treatment, patients will be randomly assigned with a 1:1 ratio to receive either lanreotide or placebo. The study treatment should be initiated within 6 weeks following the confirmation date of stable disease or objective response. Treatment period: For each patient, the investigational products (lanreotide or placebo) will be provided according to a double-blind procedure until disease progression or toxicity, in accordance with the protocol. The estimated average treatment duration for all patients is 12 months. Follow-up period: To evaluate overall survival, patients in phase II will have a minimum follow-up period of 12 months; if the study continues to phase III, these patients will have a maximum follow-up period of 10 years. Phase III patients will have a minimum follow-up period of 5 years.
Statistical methods	The analysis will be performed according to the intent-to-treat principle, i.e. data from all patients will be analysed according to the treatment assigned at randomisation. The population at baseline will be described using descriptive statistics as percentages (with 95% CI) for categorical and ordinal variables and mean (with standard deviation), median (with interval Inter-quartiles and Min-max) for continuous variables. The results will be presented by treatment and for the overall population. For the efficacy analysis, time-to-event endpoints will be calculated from the date of randomisation and will be estimated using the Kaplan-Meier method. The results will be presented by treatment group. All the toxicities will be described by treatment group according to the "Common Terminology Criteria for Adverse Events v 4.0" scale (NCI-CTCAE, Version 4.0, May 2009). A Statistical Analysis Plan (SAP) will be written before the database lock.
Sample size calculation	**Phase II Study** The following hypotheses were used for sample size calculation: *H0: A rate of patients alive and progression free at 6 months of 45% or less is not sufficient to demonstrate efficacy (p≤p0 with p0=45%).* A rate of patients alive and progression free at 6 months of 45% or less is not sufficient to demonstrate efficacy. The study will not be continued*H1: 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≥p1 with 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 2-sided 95% confidence interval exceeds 45%) leads to the study continuation. With a one-sided alpha risk of 5% and a power of 85%, using a fixed-design

	(binomial-exact method), 56 patients per arm must be randomised. With a rate of 5% of patients not evaluable or lost to follow-up, **59** patients per arm will be included (**118 patients in total**). <u>The following decision rule will apply</u>: If 31 patients or less are alive and progression free at 6 months, the treatment will be considered as not interesting. This rule will apply to the lanreotide arm only. The placebo arm will be kept as a reference arm for phase III. An independent safety committee can also recommend the discontinuation of the study, with respect to the occurrence of SAEs and AEs. Depending on the phase II results, the study may progress to phase III. The patients randomised in phase II of the study will be included in phase III. Because of the uncertainty regarding the phase III hypotheses at the time of the phase II analysis, the phase III hypotheses will be reviewed and the sample size will be re-estimated, if necessary. **<u>Phase III study</u>** The following hypotheses were used for sample size calculation: H_0: No difference between the two treatments in term of progression-free survival H_1: There is a difference in terms of progression-free survival between the two treatments; it is assumed that the median time without progression or death is of 5 months in the placebo group and of 7.5 months in the lanreotide group. HR is equal to 0.67. With an alpha-risk (two-sided) of 5%, and a power of 80%, it is necessary to observe 196 events (progression or death). With the hypotheses of a 24-month follow-up after the last patient is included, an inclusion rate of 50 patients per year and a lost-to-follow-up rate of 10%, it is necessary to randomise 222 patients.
Translational research	1/ Research on biomarkers: The objective will be to test the prognostic and predictive value of the parameters collected during the analysis of tumour tissue slides and blood samples. 2/ Medico-economical evaluation: The objectives will be: At 12 months: • To evaluate the cost-effectiveness ratio associated with treatment with lanreotide versus placebo. It will be expressed in terms of cost per progression-free life year gained (PFLYG) • To compare the average cost and average effectiveness associated with lanreotide versus placebo At 18 months: • To evaluate the cost-effectiveness ratio, expressed in terms of cost per PFLYG • To evaluate the cost-utility ratio associated with treatment with lanreotide versus placebo. It will be expressed in terms of cost per progression-free life year gained adjusted for quality of life (QAPFLYG), using the EQ-5D questionnaire. • To compare the average cost and average utility associated with lanreotide versus placebo

	• To evaluate the share of the different items of expenditure in the total cost of patients' care management at 18 months.
Estimated inclusion and participation period of each patient	**Phase II of study**: Start of inclusions: 2nd quarter 2014 End of inclusions (118 randomised patients): September 2016 End of follow-up period: September 2017 Analysis planned: June 2017 (for the main endpoint) **Phase III of study:** Start of inclusions: January 2018 End of inclusions (104 randomised patients): January 2019 End of follow-up period: January 2024

SCHEDULE OF THE STUDY ASSESSMENTS (TABLE 1)

	Screening / Randomisation	Treatment Phase		Follow-up
Assessments	**D-30 to 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	
WHO score	X	X	X	X
Haematology [4]	X		X	
Blood chemistry [5]	X		X	
Thyroid blood tests	X			
Pregnancy test [6]	(X)			
Treatment administration		X		
Tumour assessments	X [7; 8]		X	
Brain CT/MRI [9]	X		X	
Bone scan [9]	X		X	
CgA [10]	X		X	
Ki-67 (according to the NET referent review)	X			
Survival status				X
Adverse Events [11] / Serious Adverse Events	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	
QoL (QLQ C30 + NET 21)	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: Blood pressure, heart rate, body temperature and weight

4: CBC, platelets

5: electrolytes,total protein, liver function tests (ALT, AST, ALP, GGT, total bilirubin and conjugated), albumin, LDH, HbA1c. Total cholesterol, HDL 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 (see Appendix 7, describing methods for acquisition). 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 NCI CTC 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

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“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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LIST OF ABBREVIATIONS

ALT	ALanine-aminoTransferase
ALP	ALkaline Phosphatase
AST	ASpartate-aminoTransferase
BRC	Biological Research Centre
CA	Competent Authority
CgA	Chromogranin A
CM	Contrast Medium
CRA	Clinical Research Associate
(e)CRF	(electronic) Case Report Form
EC	Ethics Committee
ENETS	European NeuroEndocrine Tumor Society
FFCD	Fédération Francophone de Cancérologie Digestive (French Federation of Digestive Cancerology)
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
HbA1c	Glycated haemoglobin
HDL	High Density Lipoprotein
HR	Hazard Ratio
ICH	International Conference for Harmonisation
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
MRI	Magnetic Resonance Imaging
NCI- CTC	National Cancer Institute - Common Terminology Criteria for Adverse Events
NET	NeuroEndocrine Tumour
OS	Overall Survival
PFLYG	Progression-Free Life-Year Gained
PFS	Progression-Free Survival
PP	Per Protocol
PPI	Proton Pump Inhibitor
PR	Prothrombin Ratio
QAPFLYG	Quality-Adjusted Progression-Free Life-Year Gained
RECIST	Response Evaluation Criteria In Solid Tumours

SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SP	Safety Population
TDM	Tomodensitometry
TNCD	Thésaurus National de Cancérologie Digestive
TSH	Thyroid Stimulating Hormone
WHO	World Health Organisation

I - OBJECTIVES:

I.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 RECIST criteria, version 1.1 (Appendix 3).
The primary objective of phase III is to assess and compare the Progression Free Survival (PFS) of lanreotide versus placebo according to RECIST criteria (version 1.1, Appendix 3), assessed by the investigator.

I.2 - SECONDARY OBJECTIVES

- 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 (TTP)
- Quality of life assessed with the questionnaire QLQ-C30, including module NET 21, and the Spitzer visual analogue scale.

The secondary objectives of phase III are:

- Overall Survival (OS) at 3 and 5 years
- PFS according to central review
- Safety
- Response rate at 6 months according to RECIST criteria (version 1.1)
- Chemotherapy / biotherapy-free time interval
- Quality of life assessed with the questionnaire QLQ-C30, including module NET 21, and the Spitzer visual analogue scale.
- Medico-economical evaluation: cost-effectiveness analysis at 12 months and cost-utility analysis at 18 months (using EQ-5D questionnaire).

I.3 - OBJECTIVES OF TRANSLATIONAL STUDIES

I.3.1 - RESEARCH ON BIOMARKERS

The objective of the biological translational research project associated with this clinical study is to evaluate the prognostic and predictive value of the parameters collected during the analysis of tumour tissues and blood samples. This project will mainly allow the determination of morphological and molecular factors of grade G1 or G2 well-differentiated duodeno-pancreatic neuroendocrine tumours. Further details on the sampling time and types of samples to be collected are provided in chapter V.6 and Appendix 6.

I.3.2 - MEDICO-ECONOMICAL EVALUATION

The objectives will be:
At 12 months:

- To evaluate the cost-effectiveness ratio associated with treatment with lanreotide versus placebo. It will be expressed in terms of cost per progression-free life year gained (PFLYG)
- To compare the average cost and average effectiveness associated with lanreotide versus placebo

At 18 months:

- To evaluate the cost-effectiveness ratio, expressed in terms of cost per PFLYG
- To evaluate the cost-utility ratio associated with treatment by lanreotide versus placebo. It will be expressed in terms of cost per progression-free life year gained adjusted for quality of life (QAPFLYG), using the EQ-5D questionnaire.
- To compare the average cost and average utility associated with lanreotide versus placebo
- To evaluate the share of the different items of expenditure in the total cost of patients' care management at 18 months.

II - OVERVIEW OF THE STUDY DESIGN

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.

Depending on the phase II results, the study may be continued into phase III; the treatment and follow-up of patients will be the same in phase II and phase III.

Patients in phase II will be included in phase III.

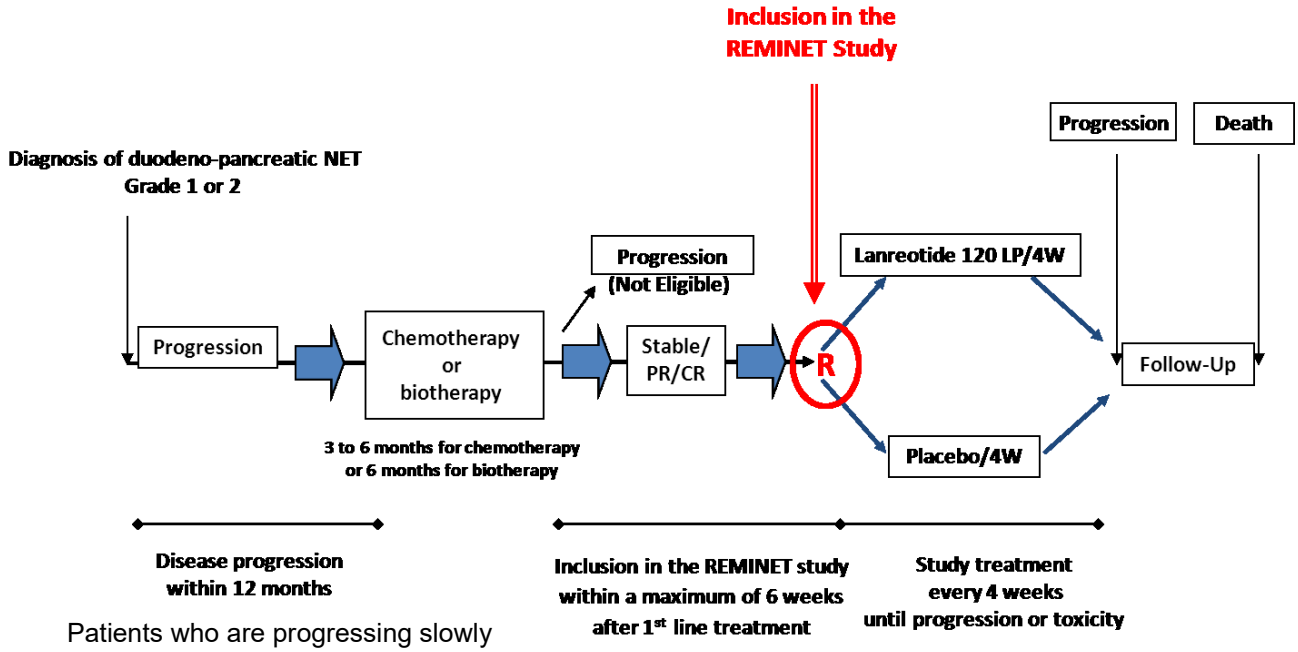
Patients will be randomised with a 1:1 ratio, to receive either lanreotide or the placebo after the first line of treatment.

Randomisation will be conducted using a minimisation technique and stratified according to the following parameters:

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

The randomisation will be conducted via an Interactive Web Response System (see chapter IV.8.1).

Figure 1: Study design



Patients who are progressing slowly should not be included; disease should present a progression within maximum 12 months after diagnosis.

III - STUDY POPULATION

III.1 - ELIGIBILITY CRITERIA

III.1.1 - INCLUSION CRITERIA

- Metastatic (synchronous or metachronous) or locally advanced, non-resectable, well-differentiated duodeno-pancreatic neuroendocrine tumour, of grade 1 or 2 (WHO 2010 classification; Ki-67 ≤ 20%; Appendix 1)
- Progressive before first-line treatment
- Histologically confirmed (either on primary tumour or metastases)
- Pathological diagnosis validated by the NET consulting pathologist
- Documented stable disease or objective response after first-line treatment, within 4 weeks (28 days) prior to randomisation
- The first-line treatment will consist of either a chemotherapy or biotherapy (everolimus or sunitinib) as referred to TNCD or ENETS guidelines. Treatment must have been administered for 3 to 6 months for chemotherapy and for 6 months for biotherapy
- Non-functional tumour or gastrinoma controlled by PPIs
- Age ≥ 18 years
- WHO 0, 1 or 2 (Appendix 2)
- Effective contraception for male or female patients of childbearing age, defined as: oral contraceptives, intra-uterine devices, barrier contraceptive methods along with a spermicide gel, or surgical sterilisation. Female patients should use this contraception throughout the treatment period and for 6 months after the last treatment administration. Male patients should use contraception throughout the treatment period and for 3 months after the last treatment administration.
- Signed informed consent prior to initiation of any study-specific procedures or treatment.

III.1.2 - NON-INCLUSION CRITERIA

- History of haematological malignancy or other cancer, except those treated for more than 5 years and considered as cured, carcinoma in situ of the cervix and treated skin cancer (excluding melanoma)
- Poorly differentiated neuroendocrine carcinoma or NET grade 3 ENETS (Ki-67 > 20%)
- If primary resected, bone metastasis exclusively
- Pre-treatment by somatostatin long-acting analogue
- Total bilirubin ≥ 60 µmol/L
- Uncontrolled diabetes
- Contraindication to product used in the study or its components
- Tumour arising in the context of a genetic disease
- Pregnancy or lactation
- Patients unable to undergo medical follow-up due to geographical, social, psychological or legal reasons
- Concomitant participation in another clinical trial investigating a treatment during the treatment phase and within 30 days prior to the start of the study treatment
- Employment of the subject or a close relative (i.e. spouse/partner, child, parent or sibling) by the CRO, the study site
- Patients deprived of their liberty by a judicial or administrative decision, patients admitted to a hospital, social institution or who are under a measure of legal protection, patients hospitalized without consent or who are in an emergency situation.

III.2 - STUDY DURATION FOR EACH PATIENT

The start of the study is defined when the first patient has provided a signed informed consent. The end of the study is defined as the last follow-up visit of the last patient.

This is a phase II/III study; therefore, the total duration is described for the two parts.

The overall study duration for phase II study will be approximately 3.5 years. The inclusion period is estimated at 30 months, and the last randomised patient will have a minimum follow-up period of 12 months.

For patients in phase II, the minimum follow-up period will be 12 months; however, if the study proceeds to phase III, these patients will participate in phase III and will continue the follow-up during phase III of the study.

The overall duration of phase III will be approximately 6 years. The estimated inclusion period is 12 months, and the last randomised patient will have a minimum follow-up period of 5 years.

For each patient, the study treatment (lanreotide or placebo) will be provided by the sponsor in a double-blind procedure until disease progression or toxicity, according to the protocol.

III.3 - PATIENT IDENTIFICATION

Patients will be identified by their randomisation number. For more security, on important documents such as case report forms (CRF), SAE declaration forms and biological samples, the patients will be identified by this number, their initials and their date of birth.

For phase II, recruitment will be stopped when 59 patients have been randomised in each arm, and for phase III, when 52 additional patients have been randomised in each arm.

III.4 - PREMATURE STUDY DISCONTINUATION

III.4.1 - DEFINITIVE STUDY TREATMENT DISCONTINUATION

Patients may stop the study treatment in the following cases:

- Treatment-limiting toxicity that means any toxicity of grade 3 or more, that cannot be treated with the usual drugs and which prevent the study treatment to be administered
- Disease progression
- Investigator's decision
- Patient's decision
- Pregnancy
- Administration of a cancer therapy other than the study treatment.

As long as the patients have not withdrawn their consent, they will be followed according to the protocol.

Patients should be treated only if the potential risks and inconveniences are medically justifiable, compared with the benefit for the patient.

III.4.2 - DEFINITIVE STUDY DISCONTINUATION FOR A PATIENT

Patients may drop out of the study in case of informed consent withdrawal; in this case, no data relating to these patients will be used.

No medical criteria could induce an individual patient's premature study termination; if a patient stops study treatment, he will continue to be followed up according to the protocol.

III.4.3 - III.4.3 - DEFINITIVE STUDY DISCONTINUATION

The study may be stopped prematurely by the sponsor, based on the independent data monitoring committee's review, if it is considered that the benefit/risk balance is no longer in favor for the patients (in regard with the study data or new data available coming from other studies).

The study could also be stopped upon Health Authorities or Ethic Committees request.

IV - STUDY TREATMENTS

IV.1 - STUDY TREATMENT PRESENTATION

Given that lanreotide and the placebo will have different colour and aspect, and in order to maintain the double-blind status of the study, an independent qualified person designated by the investigator will prepare and carry out the injections.

The provided study treatment will only be used for the purpose defined in this protocol.

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

Lanreotide Autogel 120 mg:

This treatment is similar to the commercialised form available in France under the name SOMATULINE® LP 120 mg, apart from tertiary packaging and labelling.
Treatment will be 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.
The lanreotide is to be stored at the recommended temperature: between +2°C and +8°C.
The instructions regarding the product injection will be provided in a leaflet accompanying each batch.

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.

The placebo is to be stored at the recommended temperature: between +2°C and +8°C.
The instructions regarding the subcutaneous product injection will be provided in a leaflet accompanying each batch.

Both products will be provided by the logistics department of CMC&E, Beaufour IPSEN Industry, 20 rue Ethe Virton, 28100 Dreux (France), and delivered to the study sites.

The study treatment must 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 will receive a single dose every 4 weeks (every 28 days).

IV.2 - PACKAGING AND LABELLING OF STUDY TREATMENTS

The study treatments will be packaged by Beaufour IPSEN Industry (Dreux) and delivered to the study sites.

Two syringes of lanreotide 120 mg and 2 syringes of the placebo will be provided after the initiation of the study site.

Other shipments will be made according to the progress of randomisation and the inventory log provided by the study site.

The laminated bag and the box containing the syringe will both be labelled; the labelling will be in compliance with national requirements and the Good Manufacturing Practices in Appendix 13. For both treatment arms (placebo and lanreotide), the syringe label will indicate “lanreotide 120 mg”.

The study treatments will be packaged by the logistics department of CMC&E (Beaufour IPSEN Industry, 20 rue Ethe Virton, 28100 Dreux, France); a sufficient quantity of the study treatment will be delivered to the study sites. The shipment will contain an acknowledgement of receipt form.

The text of the labels of all packages will be translated or adapted in accordance with the applicable regulatory requirements, the applicable national laws, and according to the local language of the country.
A description of the label text of the study treatment is presented below:

- Study number and EudraCT number
- Pharmaceutical form
- Route of administration
- Quantity of dose units
- Batch number
- Empty space for the patient number
- “For clinical trial use only”
- Name, address and telephone number of sponsor
- Storage instructions
- Expiry date

The study treatment should only be administered to patients included in this study. Dispensation to each patient will be documented in the case report form.

IV.3 - COMPLIANCE

The independent qualified person designated by the investigator must, without being seen, open the laminated bag and fill the empty syringe with the 0.9% NaCl solution (for patients assigned to the placebo arm) or the lanreotide solution (for patients assigned to the lanreotide arm) in order to administer the same volume as for the active treatment. The procedures for administering the placebo and lanreotide are indicated in the product leaflet accompanying each batch.

The compliance will be assessed by recording each study treatment administration in the case report form and on the treatment accountability/dispensing logs.

Any study treatment administration issues should be explained in the case report form.

IV.4 - STUDY TREATMENT STORAGE

The investigator, or the designee (for example a pharmacist), will ensure that study treatments are stored in a safe place, under the controlled storage conditions, at the recommended temperature (between +2°C and +8°C), in compliance with the applicable regulatory requirements, and that they are dispensed by a qualified and independent person.

IV.5 - ACCOUNTABILITY AND DESTRUCTION

The independent qualified person (who is not blind to the process) designated by the investigator will administer the study treatment to the included patients. Each patient will receive the treatment bearing their number only. Distribution to each patient will be documented in the case report form.
All study treatments must be recorded on the study treatment batch accountability forms provided by the sponsor or its representative. It is essential that all unused batches are kept for verification (by the sponsor or its representative). The investigator, or designee, must ensure the input of the correct information on the study treatment batch accountability forms.
All unused packs will be destroyed at the study site, and a copy of the certificate of destruction must be sent to the sponsor.

IV.6 - CONCOMITANT MEDICATION / THERAPY

The following concomitant medications are not allowed during this study:

- Any tumour treatments,

- Somatostatin analogues other than the study treatment.

IV.7 - STUDY TREATMENT OVERDOSE MANAGEMENT

In case of an overdose of the study treatment, all required medical care will be determined by the investigator according to the characteristics of potential events, and recorded in the patient case report form.

All overdoses should be considered as SAEs and should therefore be reported on the SAE declaration form.

IV.8 - STUDY TREATMENT ALLOCATION

All patients included must be identifiable throughout the study. The investigator will keep a list of patient numbers and names so that any information can be retrieved if necessary.
After confirmation of their eligibility in the study, patients will receive a randomisation / treatment allocation number and will be assigned to one of the treatment arms.

IV.8.1 - RANDOMISATION

Patients will be given a randomisation / treatment arm number according to their order of entry into the study by an Interactive Web Response System (IWRS). The IWRS will manage the link between the treatment number and the randomisation number. This system offers a 24/7 service (further details are set out in the IWRS guide, provided to each centre). The IWRS also manages all logistic aspects of the treatments and the management of incidents (replacement of treatment, quarantine, resupply of treatment batches, expiry dates, etc.). For any questions of a medical or technical nature, a 24-hour hotline will be made available - see further information in the investigator's file.

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

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

IV.8.2 - BLINDING AND BREAKING THE BLIND

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 must be administered at the site by a person who is specifically trained and qualified (for example, a nurse), otherwise not involved in the study procedures. This person will have to ensure that this blindness is maintained with respect to the patients.
Lanreotide and the placebo are not identical: lanreotide is a viscous formulation that will be supplied in a pre-filled syringe; the placebo is a solution that will not be provided in a pre-filled syringe. As a result, the person carrying out the injection will fill the syringe with the placebo solution out of the patient's view. In addition, both lanreotide and the placebo will be 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 will be alternated between the left and right side of the body.

The patients, investigators, site staff, persons performing the assessments and the CRAs will remain 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.
To guarantee that blinding is maintained, the following methods will be 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, if the knowledge of the study treatment received may influence the medical care of the patient.

In these medical emergency cases, 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 SAEs that are considered to be related to the study treatment and unexpected, which could therefore require expedited reporting to the regulatory authorities.

IV.9 - TREATMENT DURATION

For each patient, the investigational products (lanreotide or placebo) will be provided according to a double blind procedure until disease progression or toxicity, according to the protocol.

V - SCHEDULE OF ASSESSMENTS

V.1 - STUDY SCHEDULE

The schedule of observations and assessments conducted during the study is set out in the flowchart at the start of the protocol (page 8). It will be the same for phases II and III.

V.2 - INCLUSION/RANDOMISATION

The following assessments will be performed before any administration of the study treatment:

- Verification of eligibility (criteria for inclusion/non-inclusion)
- Medical history, physical examination (blood pressure and heart rate, body temperature and weight)
- WHO performance index
- Serum pregnancy test (for patients of childbearing age)
- 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 the event of a contraindication to the use of a CM, abdominal and pelvic MRI + chest CT scan without injection (see Appendix 7, describing methods for acquisition)
- Haematology (haemoglobin, leukocytes, platelets)

- Biochemistry: electrolytes, PR, liver tests (ALT, AST, ALP, GGT, total and conjugated bilirubin), albumin, LDH, TSH, HbA1c, total and HDL-cholesterols, triglycerides
- Chromogranin A; the method used to measure serum CgA in the study should always be the same as at inclusion
- Ki-67 index
    - Evaluation of quality of life (QLQ-C30 + NET 21)
- Questionnaire EQ-5D including the Spitzer scale, which will be used to estimate the utility scores at inclusion and for the cost-utility evaluation at 18 months
- Randomisation
- Tumour tissue slides from archived samples (sample of primary tumour or metastases) for patient participating in the translational research
- If a patient participates in the translational research, a blood sample must be taken **while fasting** at the same time as the aforementioned blood tests. The plasma must be stored at −80°C at the site: central assessments of biomarkers (see chapter V.6 and Appendix 6).

V.3 - TREATMENT PERIOD

During the treatment period, the following assessments must be performed until disease progression and according to the schedule indicated on page 8 (Table 1):

Every 4 weeks, prior to injection:
- Physical examination
- WHO performance index
- Assessments of adverse events according to classification NCI CTC V4.0 (Appendix 4)

Every 3 months:
- Physical examination
- WHO performance index
- Haematology (haemoglobin, leukocytes, platelets)
- Biochemistry: electrolytes, PR, liver function tests (ALT, AST, ALP, GGT, total and conjugated bilirubin), albumin, LDH, HbA1c
- Chromogranin A; the method used for the measurement of serum CgA under the study should always be the same as the one used at inclusion
- 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 (see Appendix 7, describing methods for acquisition). It is necessary to use the same evaluation method as the one used at inclusion
- Brain or bone CT scan or MRI in case of clinical signs/symptoms of disease
- Evaluation of quality of life: QLQ-C30, specifically module NET 21 and the Spitzer visual analogue scale
    - Questionnaire EQ-5D including the Spitzer visual analogue scale
- If a patient participates in the translational research, a blood sample must be taken **while fasting** at the same time as the aforementioned blood tests. The plasma must be conserved at −80°C at the site: central assessments of biomarkers (see chapter V.6 and Appendix 6).

This quarterly follow-up will be stopped if there is a radiological progression.

In case of progression, the patient may proceed to another treatment. Patient follow-up will then be biannually.

V.4 - END-OF-TREATMENT VISIT

The end-of-treatment visit should take place 30 days after administration of the last dose of the study treatment.
The main objective is to document adverse events associated with the last administration; this visit will include:

- Physical examination
- WHO performance index
- Assessment of adverse events according to classification NCI CTC V4.0.

V.5 - FOLLOW-UP

If treatment is stopped due to disease progression, a visit every 6 months will be scheduled to record the patient's status and further treatment lines.

If treatment is stopped for any other reason, quarterly visits will be maintained until disease progression (same assessments as above). Thereafter, patients will be followed-up every 6 months.

Questionnaire EQ-5D (including the Spitzer visual analogue scale) will be filled out for each patient, every 3 months and until 18 months after randomisation; this will be accompanied by the WHO performance index.

If a patient is unable to return to the site for a follow-up visit, the patient or primary physician will be contacted by telephone in order to collect these data.

For patients in phase II, the minimum follow-up period will be 12 months; however, if the study proceeds to phase III, these patients will continue to be followed-up for a maximum of 10 years (end-of-phase-III study). Patients in phase III will have a minimum follow-up period of 5 years.

V.6 - ASSESSMENTS AND PROCEDURES FOR THE BIOMARKERS TRANSLATIONAL RESEARCH

The objective of the biomarkers translational research associated with this clinical study will be to test the prognostic and predictive value of the parameters collected through the analysis of tumour slides and blood samples.

This project will mainly help to determine morphological, genetic, protein and lipid characteristics of well-differentiated grade G1 or G2 duodeno-pancreatic neuroendocrine tumours.

The sampling for biological translational research in each site is subject to two conditions:

- The approval of the establishment's ethics committee / the ethics committee (CEE/CE) (where applicable) and
- The written informed consent of the patient.

V.6.1 - TUMOUR TISSUE SLIDES

The tumour tissue samples are only to be used for patients consenting to the translational research on biomarkers. Patients may refuse the storage and use of their tissue samples for translational research projects; however, this will not exclude them from the main study.

Tumour tissue samples from the primary tumour or metastases will be collected at baseline and sent to the pathological laboratory of Prof. Jean-Yves Scoazec, at the following address:

Professor Jean-Yves SCOAZEC

Service de Pathologie

Département de Biopathologie

Gustave Roussy

114 Rue Édouard Vaillant,

94805 Villejuif - FRANCE

The tumour samples will be stored under his responsibility for 30 years.

The study requires 10 to 15 tissue slices of 5 µm thick, on slides adapted to immunohistochemistry and hybridisation in situ in fluorescence (FISH) (no less than 5 slides for biopsy samples).

V.6.2 - BLOOD SAMPLES

Blood samples will only be taken from patients consenting to biomarkers translational research. Patients may refuse the collection, storage and use of their blood sample for biomarker projects; however, this does not exclude them from the main study.

Blood samples will be stored at the Biological Resource Centre (Centre de Ressources Biologiques) of Prof. Pierre Laurent-Puig, located in Paris (Laboratoire de Toxicologie moléculaire – 45, rue des Saints-Pères – 75006 Paris - FRANCE), for 30 years.

On these samples, several analyses will be performed, particularly on lipids, proteins, RNA, microRNA, and DNA.

If the patient consents, blood samples will be collected at baseline, at 3 months and after progression (before the start of the next treatment). The sample will be taken **while fasting** at the same time as the blood samples for the main study. The patient should be fasting the day before so that the lipid analyses can be used; if not, please note the time of the last meal on the sampling form.

An EDTA tube of 10 mL of blood will be taken. These blood samples will be managed by the site staff; plasma will be separated from the buffy coat and red blood cells. All the three components obtained will be aliquoted and stored at the site, at −80°C. The shipment of the samples will be organised: one during the study and one at the end of the study. Further details are provided in Appendix 6.

VI - ENDPOINTS

VI.1 - PRIMARY 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 will be done by the investigator according to RECIST criteria (version 1.1, Appendix 3).

The primary endpoint for phase III is progression free survival, considering the first radiological progression of the patient (investigator's opinion) or death (any reason). The time will be calculated between the randomisation date and the date the first event occurred. Patients who are alive and progression free will be censored at the time of the last news or cut-off date (the date the first of these occurs will be considered).

VI.2 - SECONDARY ENDPOINTS

The secondary 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
- Safety: the toxicities will be described using the NCI-CTC AE version 4.0 (Appendix 4)
- Response rate according to RECIST criteria at 6 months (version 1.1), according to the investigator. Response rate will be defined as complete or partial response to the treatment
- Time to progression (median). This endpoint will be calculated from the randomisation date to the date of the first progression (clinical and radiological) according to the investigator
- Quality of life (QLQ-C30 including module NET 21, the Spitzer visual analogue scale) will be described at each time-point.

The secondary endpoints of phase III will consist of the comparison between the placebo and the lanreotide, on:

- Overall survival (OS) at 3 and 5 years. This endpoint will be estimated considering all deaths and the time will be calculated from the randomisation date to the date of death. Patients alive will be censored at the date of the last news or at the cut-off date
- PFS according to central review, evaluated considering the first radiological progression of the patient (central review) or death (any reason). The time will be calculated from the randomisation date to the date the first event occurred. Patients alive and progression free will be censored at the date of the last news or at the cut-off date (the date the first of these occurs will be considered).
- Safety: the toxicities will be described using the NCI-CTC AE version 4.0 (Appendix 4)
- Response rate at 6 months according to RECIST criteria (version 1.1). Response rate will be defined as complete or partial response to the treatment
- Chemotherapy/biotherapy-free time interval: the time will be calculated from the last chemotherapy/biotherapy (first-line treatment) administration, to the date of restart of first-line treatment or to the start of a new line (second-line treatment).
- Quality of life (QLQ-C30 including module NET 21, the Spitzer visual analogue scale) will be described at each time-point
- Average cost at 12 and 18 months
- Effectiveness average at 12 and 18 months and utility index score average at 18 months using EQ-5D questionnaire.
- Efficiency:
  - At 12 months; cost per progression free life year gained (PFLYG)
  - At 18 months: cost per PFLYG and cost per PFLYG adjusted for quality of life (QAPFLYG).

VII - PHARMACOVIGILANCE

VII.1 - ADVERSE EVENT

VII.1.1 - DEFINITIONS

ADVERSE EVENT (AE)

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. In clinical studies, an AE may be an undesirable medical condition occurring at any time, including run-in or wash-out periods, even if no experimental treatment has been administered.

ADVERSE DRUG REACTION

An adverse drug reaction is any untoward and unintended response to an investigational medicinal product related to any dose administered.

UNEXPECTED ADVERSE DRUG REACTION

Any adverse drug reaction the nature, severity or outcome of which is not described in the applicable product information.

In this study, the reference document to be used to evaluate the unexpectedness of the adverse drug reaction will be the Investigator's Brochure (most recent version).

VII.1.2 - DISEASE PROGRESSION

In this study, the signs and symptoms corresponding to the disease progression or worsening of the cancer being studied should not be reported as AEs.

The signs and symptoms of the studied cancer will be reported as AEs if they cannot be defined as exclusively due to the progression or worsening of the disease.

VII.1.3 - LABORATORY TEST ABNORMALITIES

A laboratory test abnormality should only be reported as an AE under the following cases:

- when it is accompanied by clinical symptoms or is considered as medically significant by the investigator,
- when it results in a change in the study treatment schedule of administration (delay in administration, temporary or definitive discontinuation, etc.),
- when it requires an intervention, a change in concomitant treatments, or a diagnostic evaluation in order to determine the risk for the patient.

VII.1.4 - CLASSIFICATION OF INTENSITY OF AES

AEs will be documented and graded according to the NCI-CTCAE version 4.0.

If, for a given AE, the NCI-CTCAE scale is not applicable, the following equivalences will be applied:

NCI-CTCAE grade 1 corresponds to a mild intensity (does not interfere with the patient's normal daily activities),

NCI-CTCAE grade 2 corresponds to a moderate intensity (interferes with the patient's normal daily activities),

NCI-CTCAE grade 3 corresponds to a severe intensity (prevents the patient’s normal daily activities),

NCI-CTCAE grade 4 corresponds to a life-threatening event or a disability (any event exposing the patient to an immediate risk of death at the time of occurrence of the adverse event)

NCI-CTCAE grade 5 corresponds to death (related to the AE).

VII.1.5 - REPORTING AND FOLLOW-UP OF ADVERSE EVENTS

All AEs (related and unrelated, expected and unexpected) occurring in the course of the study, from the signature of the informed consent form and until 30 days after the last dose of the study drug, will be reported by the investigator.

All AEs reported spontaneously by the patient or observed by the investigator, regardless of treatment arm, will be recorded on the AE page(s) of the case report form. AEs already recorded and described as being "ongoing" must be reviewed at each subsequent evaluation.

For all AEs, the investigator must search and obtain the necessary information both to determine the outcome of the AE and to assess whether it meets one of the criteria for classification as a serious adverse event (SAE) requiring an immediate notification to the **PV Department of ICTA PM**.

VII.2 - SERIOUS ADVERSE EVENT

VII.2.1 - DEFINITIONS

SERIOUS ADVERSE EVENT (SAE)

Any harmful clinical manifestation that, at any dose, fulfils at least one of the following criteria:

- is fatal (leads to death ; NOTE : death is an outcome, not an event),
- is life-threatening (NOTE : a "life-threatening event" refers to an event in which the patient was at risk of death at the time of the event),
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity*,
- is defined as a congenital anomaly or a birth defect,
- is a medically significant event.

*The terms "disability" and “incapacity” mean any temporary or permanent physical or mental disability clinically significant which affects the physical activity and/or quality of life of the patient.

Is considered medically significant any clinical event or laboratory results considered as serious by the investigator and not corresponding to the seriousness criteria defined above. These may pose a risk to the patient and may require a medical intervention to prevent an outcome corresponding to one of the previously mentioned seriousness criteria (for example, an overdose, a second cancer, pregnancy or any new event which is susceptible to compromise the safety of the patients may be considered as medically significant).

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

All adverse events, considered as related to the study drug and which are both unexpected and serious (SUSARs) are subject to expedited reporting to the Competent Authorities (CAs) and to the Ethics Committees (EC), in compliance with the local regulatory requirements.

The sponsor will be responsible for reporting the SUSARs, on the basis of the information provided by the investigator.

The local regulatory requirements for expedited reporting to the CAs and EC of each involved country are described in the safety management plan.

VII.2.2 - CAUSALITY OF SAE

The relationship of a SAE to the study drug will be classified according to the following criteria:

Related: an event is considered as related to the study drug when a causal relationship between the event and the administration of the investigational product can reasonably be suspected (plausible time sequence, dose-effect relationship, pharmacology, positive "dechallenge" and/or "rechallenge").

Unrelated: an event is considered as not related to the study drug when a causal relationship between the event and the administration of the investigational product cannot reasonably be

suspected (implausible time sequence and/or event attributable to an intercurrent disease or to other medications).

VII.2.3 - REPORTING OF SERIOUS ADVERSE EVENTS

All SAEs occurring during the study, from the signature of the informed consent form and until 30 days after the last dose of the study drug, regardless of treatment arm or causality to the study drug, must be reported by the investigator **within 24 hours from the date of the first awareness to the PV Department of ICTA PM by fax/email at + 800 53 40 53 40 / pharmacovigilance@icta.fr**.

Furthermore, all SAEs susceptible to be related to the study drug or to a study procedure and occurring during the whole study period, including the post-treatment follow-up period, must be notified according to the reporting procedure described above.

The SAE report form must be signed and dated by the principal investigator or by any other investigator designated by the principal investigator as authorized to notify safety issues.

All available information concerning the SAE (laboratory results, other examinations, hospitalization reports, autopsy report and all other relevant documents) will be transmitted anonymously with the SAE report form.

Further to the notification of a SAE, additional information relative to the SAE may be requested by the sponsor or its representative (by fax, telephone, mail or visit). The investigator must respond to these requests for additional information.

All SAEs must be documented in the patient's medical file, and the SAE report forms (initial report and follow-up reports) must be kept in the investigator's file.

The full requirements of the "ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2" will be adhered to. The study will be conducted in compliance with all local regulatory requirements.

Certain events will not be considered as serious. These are:

- Hospitalizations for elective surgery or treatment / procedure planned before inclusion in the study for a pre-existing condition / disease which has not worsened since the beginning of the study
- Hospitalizations for comfort or social reasons
- Emergency hospital consultations for an outpatient (not staying in hospital overnight) unless they meet one of the seriousness criteria previously described
- As indicated in section VII.1.2, signs and symptoms corresponding to the disease progression or worsening of the cancer being studied must not be reported as AE/SAEs.

VII.2.4 - FOLLOW-UP OF SERIOUS ADVERSE EVENTS

For any new information concerning an SAE that has already been notified, the investigator must complete a new SAE report form (follow-up report) which will be sent by fax/email within 24 hours to the **PV Department of ICTA PM at + 800 53 40 53 40 / pharmacovigilance@icta.fr,** accompanied by anonymised copies of the corresponding laboratory results, other examinations and/or hospitalisation reports.

The reporting of the SAE follow-up information will be done in the same manner as the initial SAE reports.

The SAE must be followed until its resolution or stabilisation (in case of sequelae). This may lead to the follow-up of the patient beyond the study period.

VII.2.5 - SERIOUS ADVERSE EVENTS OCCURRING AFTER ADMINISTRATION OF THE STUDY MEDICINE

All SAEs occurring at any time after the end of study treatment, susceptible to be related to the study drug or to a study procedure, according to the investigator, must be notified according to the reporting procedure described above.

VII.2.6 - REPORTING OF PREGNANCY

If a patient becomes pregnant during the treatment period of the study or within 6 months after the last dose of study drug, the pregnancy must be reported; if the pregnancy occurs during the treatment period, the study drug should be discontinued.

If the partner of a male patient becomes pregnant during the treatment period of the study or within the 3 months following the last dose of study drug, this should be reported to the investigator.

A specific informed consent will be provided to allow the collection of data concerning the follow-up and outcome of the pregnancy of the patient's partner.

Pregnancies must be reported by the investigator, like SAEs, within 24 hours of awareness.

The reporting of pregnancy will be done according to the procedure used for the SAEs reporting.

The sponsor or its representative must follow each pregnancy to term.

The pregnancy outcome must be reported by the investigator, to the sponsor or its representative.

VIII - DATA HANDLING

VIII.1 - CASE REPORT FORM (E-CRF)

The patient data will be recorded on an electronic case report form (e-CRF) provided by the FFCD and developed by LINCOLN. Each user of the e-CRF will be trained and will receive a training certificate.

A clinical research assistant (CRA) working on behalf of FFCD will review study documents in order to verify compliance with the protocol and the accuracy of the data referring to source documents. All information requested in the e-CRF must be completed. If any piece of information is not available, this must be noted.

Any correction or modification made to the e-CRF will be followed up by the e-CRF audit trail.

Each user will have a personal and confidential access code and user name. Each data entry will be attributed to a user. At the end of the study, all the e-CRFs will be signed (procedure consisting of a new registration of user name and password) by the investigator. This procedure will certify that all information entered in the e-CRF concurs with the source data and reflects the patient's state during the corresponding part of the study.

Throughout the centralised process of data review, corrections or changes to the e-CRF may be requested. In this case, requests will be included in the corresponding e-CRF.

VIII.2 - DATA MANAGEMENT

Data management will be performed by a CRO, LINCOLN.

Data will be monitored at the investigator site. Patient questionnaires collected from study sites by the CRA will be sent by courier to the LINCOLN data entry centre.

The sponsor will ensure that the developed e-CRF allows data entry and submission of requests adapted to solve all the problems of missing or contradictory data. All requests for corrections made during the process of cleaning the database will be conducted electronically. It is the responsibility of the investigator to ensure that all requests are resolved by the relevant parties.

The coding of the AE, as well as medical history and concomitant medications will be conducted by LINCOLN, then reviewed and approved by the sponsor. The coding of concomitant medications will be conducted using the dictionary WHODRUG, and that of AEs / medical history with the dictionary MedDRA.

The investigator will receive the patient information in an electronic format (PDF) which will be an exact copy of the e-CRF and which will include the complete audit trail, for the purposes of archiving and future reference.

VIII.3 - STUDY COMMITTEES

VIII.3.1 - STEERING COMMITTEE

A steering committee will be set up, chaired by the coordinating investigator, Professor Côme Lepage. This committee will include Professors Thomas Walter and Michel Ducreux, a representative from each participating country, the president of the FFCD, the operational representative and the statistician of the FFCD, as well as the president of the translational research committee.

VIII.3.2 - DATA SAFETY MONITORING BOARD

An independent data safety monitoring board will be established; it will include two physicians who are experts in neuro-endocrinology, a statistician and a pharmacovigilance expert.

Their functions will be described in the independent committee charter.

VIII.3.3 - CENTRAL IMAGING REVIEW

All tumour imaging assessments performed for each patient until disease progression will be collected for a central review. This central review will be conducted for the final analyses, by a panel of radiologists, via the FFCD's imaging platform.

VIII.3.4 - TRANSLATIONAL RESEARCH COMMITTEE

A biological translational research committee will be created to deal with questions related to tumour and blood samples and their biobanking. This committee, during the study, will also identify the pertinent prognostic and predictive biological factors, as well as the relevant polymorphisms to test. It will organise the analyses with the selected laboratories. This committee will include the members of the study steering committee; its president will be Prof. Jean-Yves Scoazec (Gustave Roussy-Paris, France).

This committee will meet regularly and will report its biological translational research projects to the steering committee and to the sponsor. Each country participating in the steering committee will have a voting member; the weighting of the votes will be proportional to the contribution of the group or country in terms of recruitment.

A working group will also be specifically created for the economical analysis. This group will include, among others, C Lejeune, K Le Malicot, Professors C Lepage, T Walter and M Ducreux.

IX - STATISTICAL ANALYSES

IX.1 - SAMPLE SIZE

Phase II of the study

The hypotheses for the calculation of the sample size as follows:
H0: A rate of patients alive and progression free at 6 months of 45% or less is not sufficient to demonstrate efficacy (p≤p0 with p0=45%) The study will not be continued.
*H1: 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≥p1with 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 2-sided 95% confidence interval exceeds 45%) leads to the study continuation.

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

With a rate of 5% of patients being non-evaluable or lost to follow-up, **59** patients will 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.

Depending on the phase II results, the study may continue into phase III. The randomised patients in phase II will be included in phase III. In case of the study early termination at Phse II, the patients will be followed-up as planned in the protocol.

Given the uncertainty regarding the hypotheses of phase III, at the time of the analysis of phase II, the hypotheses of phase III will be reviewed and if necessary, the sample size will be recalculated.

Phase III of the study

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

$H_{0:}$ No difference between the two treatments in terms of progression-free survival

$H_{1:}$ There is a difference between the two treatments in terms of progression-free survival; it is estimated that the average time without progression or until death will be 5 months in the placebo arm and 7.5 months in the lanreotide arm. The HR is 0.67.

With a (bilateral) alpha risk of 5% and power of 80%, 196 events must be observed (progression or death).

In the hypothesis of a follow-up period of 24 months after the inclusion of the final patient, the rate of inclusion of 50 patients per year and a rate of 10% lost to follow-up, 222 patients must be randomised.

IX.2 - STATISTICAL ANALYSIS PLAN

The data will be analysed using the SAS (Statistical Analysis System) software, version 9.3 or later and the statistical methods are described in a statistical analysis plan. Values of *p* less than or equal to 0,050 (rounded) will be considered as "statistically significant" in the presentation of results. Other modifications made before the breaking of the blinding must be documented. After breaking the blind, any substantial modification made to the statistical analysis plan will be documented in the clinical study report.

IX.2.1 - POPULATION SETS

Three population groups will be considered for the analyses:

The intent-to-treat population (ITT): all randomised patients in the study that meet the eligibility criteria. These patients will be considered in the allocated group by randomisation, even if they receive a different treatment.

The safety population (SP): all patients included in the ITT population having received at least one treatment injection. These patients will be analysed in terms of the treatment received.

The per-protocol population (PP): all patients in the study randomised without major deviation (defined before the meeting for blind review of data). These patients will be analysed in terms of the treatment received.

IX.2.2 - DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The baseline characteristics will be summarised in the ITT population. The statistics will be calculated for each treatment arm and for all patients combined. The description of medical and clinical variables will be done using percentages (95% confidence interval), as well as the mean (standard deviation), the median (min-max) and the inter-quartile range (Q1-Q3).

IX.2.3 - PRIMARY ENDPOINT ANALYSIS

Phase II:

The number and percentage of patients alive and progression free at 6 months will be calculated and described per treatment arm. The unilateral 95% confidence intervals will also be calculated.

For the primary endpoint, if at 6 months the progression is not documented and no progression was noticed before, the patients will be reviewed in its globality to classify him as Progressive or not progressive at 6 months.

Phase III:

The primary endpoint for phase III is progression free survival, considering the first radiological progression of the patient (investigator's opinion) or death (any reason). The time will be calculated between the randomisation date and the date the first event occurred. Patients who are alive and progression free will be censored at the time of the last news or cut-off date (the date the first of these occurs will be considered).

No missing data is expected for this parameter.

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.

IX.2.4 - SECONDARY ENDPOINT ANALYSES

Efficacy endpoints

The quantitative variables will be described per treatment arm. The usual statistics (mean, standard deviation, median, inter-quartile intervals and range) will be used. The quantitative variables may also be categorised using the known clinical threshold.

The qualitative variables will be classed in frequencies and percentages. The confidence intervals at 95% may also be calculated.

In the phase III study, the comparison of qualitative variables may be conducted using an X^2 test or a Fischer test. A Wilcoxon's or Student test may be used for quantitative variables.

The Kaplan Meier method and the Cox method (only in phase III) will be used for the analysis of censored data.

Efficiency endpoints

For medico-economical evaluation, incremental cost-effectiveness and cost-utility ratio will be calculated. A sensitivity analysis will be performed on the economic parameters. It will allow the consideration of possible differences in costs between France and other European centres taking part in the study. A non-parametric bootstrap analysis of the incremental costs and effectiveness / utility observed between the two strategies will help to consider the uncertainty and to estimate the interval at 95% of the differential ratio of the base analysis.
The costs and utility / effectiveness will not be updated in consideration of the short follow-up period (12 and 18 months).

Safety endpoints

The analyses and the summary tables will be analysed in the safety population and described per treatment arm.

AEs will be coded according to the MedDRA (Medical Dictionary for Regulatory Activities) classification version 17.0, and classed per MedDRA term and by organ system. We will use the most recent version of MedDRA at the time of analysis.

The summary tables will be presented by type of event and by grade.

Usual statistics (mean, median, standard deviation and range) per treatment arm will be presented for vital signs.

The injections and injection reports will be described.

IX.3 - HANDLING OF MISSING OR INVALID DATA

No replacement of missing data is envisaged, for any variable.

For all the endpoints concerning time to event variable, no missing data is expected. In case the event is not presented (Progression or Death) then patients will be censored at the time of the last news (consultation, imagery...) or cut-off date (the date the first of these occurs will be considered).

X - QUALITY CONTROL / MONITORING

Monitoring is conducted by ICTA PM or its representative, on behalf of the sponsor; it allows the progression of the study to be supervised and ensures the scientific integrity of the study.

In order to guarantee compliance with the Good Clinical Practices and the applicable regulations, the Clinical Research Associate (CRA) is responsible for verifying that the study is conducted in compliance with the protocol and all other written instructions. The main responsibilities of the CRA are to verify investigators' adherence to the protocol, accurate and complete data recording and reporting in the CRF, and that informed consent is obtained and recorded for all patients by the investigator before their participation in the study.

The CRA will contact and visit the investigator at regular intervals during the study. He/she will, compare the CRFs with medical records and other relevant documentation through direct access, during the on-site monitoring visits. He/she ensures the completeness, consistency, and accuracy of the data being recorded in the CRF by the investigator.

The CRA will explain the protocol and study-related procedures to all study staff, including the investigator. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the CRA.

The investigator and the study investigator collaborators commit to cooperating with the CRA to resolve any problems, corrections, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

As part of the supervision of the study progress, other sponsor staff or ICTA PM or its representative may, upon request, accompany the CRA on visits to the study site.

XI - CONFIDENTIALITY

XI.1 - RESPONSIBILITIES

XI.1.1 - SPONSOR'S RESPONSIBILITIES

ICTA PM or its representative, on behalf of the sponsor, will submit an application to Ethics Committees and Competent Authorities for approval of the clinical study. A copy of the approval of the Ethics Committee and the Competent Authorities must be received by the sponsor before the study starts.

In accordance with the provisions of the law and the GCP, the sponsor will have an insurance policy intended to indemnify for possible damages resulting from the research.

The studies and/or experiments performed on behalf of the sponsor will be specifically and expressly guaranteed. It is advisable to underline that noncompliance with the Research Legal Conditions is a cause for guarantee exclusion.

XI.1.2 - RESPONSIBILITIES OF THE INVESTIGATOR

The investigator will be responsible for performing the study according to this protocol, the procedures, the ICH GCP guidelines and the legislation in force. He/she will have to collect, record, and report the data accurately and properly.

Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented by the signed protocol acceptance form (duplicate on page 2).

The investigator will be responsible for giving information and training about the study to all staff members involved in its conduct or in the patients' care, (e.g., when new staff become involved).

The investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). The investigator is responsible for ensuring the privacy, health, and welfare of the patients.

The investigator must be familiar with the background and requirements of the study and with the properties of the study treatment as described in the IB.

XI.2 - PERSONAL DATA PROTECTION AND CONFIDENTIALITY

The investigator must ensure that the personal data of patients, including their identity and all other personal medical information, will be kept confidential at all times.

A patient number and initials will identify the patients in the CRF. On other documents or photographic materials (including the results of imaging) submitted to the sponsor, patients will not be identified by their names but by an identification code (e.g. initials and patient number).

By signing this protocol, the investigator undertakes to ensure that the protocol and all attached information are and will remain confidential. The investigator agrees that after providing the protocol and all information necessary for the staff involved, he/she remains responsible for their complete confidentiality. This obligation is detailed in the confidentiality agreement signed by the investigator before the initiation of the study.

The investigator agrees that, subject to local regulations and ethical considerations, a sponsor representative or any regulatory agency may consult directly and/or copy study documents in order to verify a case report, provided that the subject's identity remains anonymous.

The investigator undertakes to treat all subject data used or disclosed in connection with the conduct of study in compliance with European and local applicable laws relating to data protection.

The investigator will be responsible for keeping a list of all enrolled patients including patient numbers, full names and dates of birth.

XI.3 - STUDY DOCUMENTATION ARCHIVING

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The study documents, including patient CRFs, should be filed in the investigator's file.

The investigator's file will contain the protocol/amendments, the correspondence with the ethics committee and the health authorities, a sample of informed consent form, study treatment data, staff curriculum vitae and authorisation forms, correspondence, etc.

The investigator must keep the Study File until the sponsor destruction authorisation, and by default for at least 15 years after completion or discontinuation of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

XII - REGULATORY AND ETHICAL ASPECTS

XII.1 - PATIENT INFORMATION AND CONSENT FORMS

The patient information sheet must be given to patients before they decide whether to participate in the clinical study, in compliance with local regulations and good clinical practices.

The investigator must give patients the written information sheet and the consent form, and explain the study verbally. The consent form must be validated and signed by the patient before beginning any procedure related to the study.

There is also a specific patient information sheet for the biological translational research.

The consent form is issued in duplicate: the original is kept by the investigator and a copy is provided to the patient.

In the event new information is acquired during the study that may affect the patient's wish to continue their participation, this information must be given to the patient so that they can confirm their agreement to continue to participate.

XII.2 - ACCESS TO SOURCE DATA

The investigator must authorise the CRA to have direct access to all source documents related to the patient, required for the verification of the data recorded in the case report form.

In case of requests from the health authorities, it is also essential to have access to all information related to the study.

XII.3 - STUDY CONDUCT

The study must be conducted in compliance with the ICH standards of good clinical practice, the Declaration of Helsinki (Appendix 5), as well as all applicable European and/or local laws and regulations relating to the conduct of the studies.

XII.4 - ETHICS COMMITTEES AND COMPETENT AUTHORITIES

The present protocol and other documents (investigator's brochure, patient information, questionnaires, etc.) will be submitted by ICTA PM or its representative, on behalf of the sponsor, to an Ethics Committee (EC). Before beginning the study, the investigator must have received permission in writing for the protocol and patient information sheet from the EC. The approval of the EC must indicate the version of study protocol, as well as the documents reviewed.

Throughout the study, the sponsor must inform the EC of any change to the protocol, all SUSARs, and any new information likely to affect the safety of the patients or the conduct of the study.

Complying with local regulations, ICTA PM or its representative, on behalf of the sponsor, and the investigators must verify that all legal aspects have been complied with and that the approval of the competent regulatory authorities, if necessary, has been obtained prior to the beginning of the study.

The competent local authorities must be informed of the conduct of the clinical study and its status by ICTA PM or its representative on behalf of the sponsor.

XII.5 - AMENDMENTS

All substantial amendments are submitted for the approval / authorisation of the EC and the competent authorities before their implementation.

All substantial amendments concerning safety measures are submitted for the approval / authorisation of the ethics committee and competent authorities, but may be immediately implemented in circumstances specifically defined by the sponsor.

XII.6 - AUDIT AND INSPECTION

The investigator must make the source documents of this study available for staff deemed qualified by the sponsor or its representatives or health authority inspectors, upon prior notice. The

monitoring of data in the e-CRF must be conducted with a verification / inspection of the source documents.

The investigator must be ready to respond to all questions asked by auditors / inspectors and prepare for the smooth performance of the audit / inspection.

XIII - PUBLICATION OF DATA

The final clinical study report must be written in compliance with the ICH E3 guidelines (Structure and content of clinical study reports).

XIV - RULES OF PUBLICATION

All publications resulting from data generated by this Intergroup will quote PRODIGE/GTE/FFCD in their title.

1) The Coordinating Investigator will be responsible for drafting any publication (abstract and/or manuscript).

2) The Coordinating Investigator will chair a writing committee, comprising representatives of the participating countries that fulfil the Intergroup guidelines for authorship.

3) The Steering Committee must approve the manuscript prior to submission for publication.

4) The Coordinating Investigator will inform the Steering Committee of any publication and/or presentation (2 weeks' notice).

5) The Coordinating Investigator will be the primary (first) author of the publication of the final results. Co-authors are defined according to the guidelines for authorship (see below). A list of all the participating countries and Investigators will be published as an appendix at the end of major publications. Acknowledgement for any financial support or grant will be reported in each publication.

6) Presentations: the Coordinating Investigator and the FFCD board (represented by its chairman) must agree with the contents and authorship of any presentation.

7) Guidelines for Authorship: the following persons will be considered for authorship by the Steering Committee:

- Coordinating Investigator (first author)

- Main recruiters, biologists, …

- Statistician taking responsibility for the analysis of the study

- A member of the UMR866 (INSERM Unit), to which the FFCD clinical data centre is attached, as equally contributing last author.

XV - RATIONALE OF THE STUDY

XV.1 - BACKGROUND

XV.1.1 - CONTEXT

Neuroendocrine tumours (NETs) are rare tumours with various pathological presentations. However, their incidence is increasing and because of a less unfavourable prognosis than most digestive cancers[1], their prevalence is high[2]. Well-differentiated duodeno-pancreatic NETs represent

the second most frequent location of digestive tract NET and their 5-year survival is about 30%[1, 2]. More than half of the cases of these tumours are diagnosed at a metastatic stage, and 75% of them have liver metastasis.

Patients with metastatic or locally advanced, non-resectable, well-differentiated duodeno-pancreatic neuroendocrine tumour, grade 1 or 2 are treated following ENETS[3] and TNCD[4] recommendations. For patients with a small tumour volume, asymptomatic, non-progressive, current recommendations are simply to undertake monitoring until progression[3, 5]. However, the majority of these patients will progress within one year after diagnosis: 82% of patients in a median time of 10 months after diagnosis (PFS median: 14 months)[6]. Patients with progressive and / or symptomatic metastases and / or with significant hepatic invasion (> 30-50%), and / or bone metastases, anti-tumour therapy should be started. The reference treatment is systemic combination chemotherapy adriamycin and streptozotocin[5, 7]. However, given its toxicity, some experts recommend as first-line chemotherapy either dacarbazine[8] with or without 5FU (LV5FU2-dacarbazine)[9], or its analogues, temozolomide[10], with or without oral 5FU[11] or oxaliplatin combined with 5-FU[12] (FOLFOX or XELOX). These different strategies generally induce a response or stabilisation in 60-97% of cases after 4-6 months of treatment, for a period of 9-20 months[13]. These patients have a long life expectancy. Therefore, the recommendations are to stop chemotherapy once a response (partial or complete) or disease control is obtained, and before complications or progression under treatment occur. Unlike many other tumour models, it is usual to observe long periods of non-progression after a first induction anti-tumour treatment. Resuming treatment is advocated only in the event of progression[5], which can be done either with the same treatment as during induction, or with a second-line therapy. For this second-line therapy, everolimus and sunitinib may be prescribed based on the new recommendations[5, 14, 15]. Some patients receive these medicines as first-line therapy.

The concept of maintenance therapy has been tested in the treatment of metastatic colorectal cancer. It makes it possible in case of response or stabilisation, when metastases are unresectable, to stop chemotherapy until progression, with reassessment every 3-months. This concept has been validated with either the association LV5FU2[16], or FOLFIRI[17], or FOLFOX[18, 19], particularly when the general state of health is good (WHO 0-1), when there is one metastatic site only, and when CEA level is normal[18, 20]. This approach allows resting periods for patients, who will benefit from several lines of treatment and thereby improve the tolerance and quality of life of these patients. The OPTIMOX2 clinical trial in colorectal cancer[18, 21] with a maintenance therapy and reintroduction of a more aggressive therapy (oxaliplatin) in case of progression reinforced this concept; it is possible to increase the interval of time between cycles of more aggressive treatment. The quality of life of patients is excellent because of a well-tolerated treatment, which at best does not require intravenous administration.

Chemotherapy discontinuation with a maintenance treatment with a targeted therapy has been tested in colorectal cancer with cetuximab, which was continued during the chemotherapy-break periods (COIN study) allowing lengthening of the chemotherapy-free period[22] . The same approach is tested in a different protocol, with bevacizumab, pursued or not after chemotherapy discontinuation[23].

XV.1.2 - STUDY TREATMENT

The somatostatin analogues are very well tolerated and could be the ideal candidates in well differentiated NET to play this role of maintenance therapy after an aggressive chemotherapy. The antiproliferative indication is, for the time being, reserved to sandostatin LAR based on PROMID[24] results in well-differentiated mid-gut tumours but this trial did not include patients with NET in the duodeno-pancreatic region. However, several open studies or Phase II studies have shown that it was possible to stabilise in 35 to 80% of cases, duodeno-pancreatic NET with both somatostatin analogues (octreotide and lanreotide), and especially when the disease was slowly progressing[25]. The progression-free survival data in these studies are disparate, ranging from 5 to 25 months[25]. The CLARINET study is a large phase III trial assessing the anti-proliferative effect of lanreotide scheduled for a total of 24 monthly injections in neuroendocrine tumours (NETs). Compared to placebo, there was a highly significant advantage in progression-free survival (PFS) with the use of

lanreotide (p=0.0002 HR=0.47 [95% CI: 0.30, 0.73]). In the subgroup of patients with duodeno-pancreatic tumours, this advantage remained interesting (p=0.0637 HR=0.58 [95% CI: 0.32, 1.04])[4]. Unlike somatostatin analogues, oral cytotoxic chemotherapy (temozolomide or capecitabine) and the new 'targeted therapies' (everolimus and sunitinib) do not have a very favourable safety profile for this potential long-term maintenance treatment role [11, 14, 15]. Lanreotide is currently used to relieve the symptoms of NETs. Most NETs have receptors on the surface of the cells which respond to somatostatin. Lanreotide inhibits the signal-transmission pathways mediated by somatostatin receptors, causing a reduction in hormone and amine secretion, which may improve tumour-related symptoms and stabilise tumour growth. It is therefore a potential candidate for maintenance therapy in NET patients who require chemotherapy.

Further details are available in the Investigators' brochure (provided in the Investigators' folder).

XV.2 - RATIONALE OF THE STUDY

In consideration of the information described in chapter I.1.2, somatostatin analogues may be good candidates for maintenance treatment in well-differentiated NETs.

The objective of this clinical phase II/III study is to assess if lanreotide administered at 120 mg every 4 weeks, can maintain the objective response / stabilisation induced by a first-line treatment of patients with non-resectable duodeno-pancreatic neuroendocrine tumours.

The study is currently proposed as a double-blind, placebo-controlled study in 222 patients (for phase II and phase III) who have received first-line chemotherapy for a duodeno-pancreatic neuroendocrine tumour, and who were stable or in objective response after this treatment. Patients may receive lanreotide in a dose of 120 mg every 4 weeks until progression of the disease.

XV.3 - RATIONALE FOR DOSE SELECTION

Lanreotide 120 mg will be administered by deep subcutaneous injection every 28 days. It has been previously reported that this dose of somatostatin analogue allows anti-tumour activity[26]. This anti-proliferative effect has recently been confirmed in the CLARINET study, with a significantly high achievement in progression-free survival (PSF) under lanreotide compared to placebo (p=0.0002 HR=0.47 [IC 95%: 0.30, 0.73]) for a total of 24 monthly injections of 120 mg in cases of digestive neuroendocrine tumours (DNET)[4]. Consequently, this dose of lanreotide will be used in the study.

XV.4 - REFERENCES

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XVI - APPENDICES

XVI.1 - Classification of NETs - WHO 2010

XVI.2 - WHO Index

XVI.3 - RECIST criteria version 1.1

XVI.4 - NCI-CTC AE criteria version 4.0

XVI.5 - Helsinki declaration

XVI.6 - Management of samples for translational biological studies

XVI.7 - Radiological recommendations

XVI.8 - Recommendations on the drafting of anatomic pathology reports - Minimum information that must appear in the report

APPENDIX 1: Classification of digestive NETs - WHO 2010 [RINDI 2010].

The WHO 2010 classification uses grades G1 to G3 initially proposed by the ENETS in 2006. There are 3 main categories: (a) neuroendocrine G1 tumours; (b) neuroendocrine G2 tumours, which are well-differentiated by definition and (c) neuroendocrine G3 small or large-cell carcinomas which are poorly differentiated by definition. It introduces mixed exocrine-endocrine carcinoma (called adeno-neuroendocrine) and tumour-like lesions.

- Neuroendocrine G1 tumours
- Neuroendocrine G2 tumours
- Neuroendocrine G3 carcinoma (as of small or large-cell)
- Mixed adeno-neuroendocrine carcinoma
- Tumour-like lesions.

However, this classification does not take into account morphologically well-differentiated NETs with proliferation of > 20% and therefore grade 3, whose exact frequency is not known [Vélayoudom-Céphise 2013].

Definition of grade of tumour according to WHO 2010
The tumour grade has been replicated from the grading defined by the ENETS in 2006 (adapted from [Rindi 2006] and [Rindi 2010]

Grade	Mitotic count (for 10 HPF)*	Ki-67 index (%¤)**
G1	< 2	≤ 2
G2	2 -20	3 -20
G3	< 20	< 20

*10HPF (High Power Field) = 2 mm^2, at least 40 fields (at 40x magnification) evaluated in areas of highest mitotic density
** MIB1 antibody; % of 2000 tumor cells in areas of highest nuclear labelling

APPENDIX 2: WHO Performance status

0 = Capable of an identical lifestyle to that prior to illness, with no restrictions.

1 = Physical activity diminished but ambulatory and able to work

2 = Ambulatory and capable of taking care of themselves, unable to work. Bedridden 50% of the time.

3 = Capable of only some personal care. Bedridden or seated at least 50% of the time.

4 = Unable to take care of themselves, bedridden or seated all of the time.

APPENDIX 3: RECIST criteria version 1.1

"New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)" E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij;

Eur J Cancer, 4 5 (2 0 0 9) 2 2 8 –2 4 7.

1. Measurability of tumour at baseline

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable:
Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non measurable disease

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥ 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target and non-target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).
Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

2. Response criteria:

Evaluation of target lesions:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stabilisation (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of the lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Evaluation of non-target lesions

Complete response: Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR / Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease: Unequivocal increase in the size of non-target lesions or appearance of a new lesion (note: the appearance of one or more new lesions is also considered progression).

3. Overall response:

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	**CR**
CR	Non CR/Non PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non PD or not all evaluated	No	**PR**
SD	Non PD or not all evaluated	No	**SD**
Not all evaluated	Non PD	No	**NE**
PD	Any	Yes or no	**PD**
Any	PD	Yes or no	**PD**
Any	Any	Yes	**PD**

CR: Complete Response; PR: Partial Response; PD : Progressive Disease; SD: Stable Disease; NE: Inevaluable.

APPENDIX 4: NCI-CTC AE criteria version 4.0

Refer to the CTCAE scale of assessment of toxicity version 4.0.

The original English version can be downloaded from the NCI website.

Cancer Therapy Evaluation Program

http://ctep.cancer.gov/

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

(Publication Date May 28, 2009)

APPENDIX 5: Helsinki declaration

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 6: Blood sample collection and handling for biological translational studies

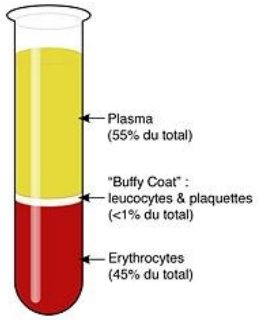
To retrieve buffy coat and plasma from blood sample: The whole blood is collected in an EDTA tube (avoids blood coagulation and neutralises PCR inhibitors).

- Centrifuge the blood samples at 3000 rpm for 15 minutes at 4°C
- Prepare the cryotubes in the rack:
  5 to 6 for plasma
  2 for buffy coat
  2 for red blood cells
- Label tubes with the patient's inclusion number (followed by PL for plasma, BC for buffy coat and RBC for red blood cells), the name of the study and the sample date.
- After centrifugation, there are 3 phases:

  Higher phase: plasma

  Intermediate phase: buffy-coat (white suspension)

  Lower phase: red blood cells



The quantity of blood drawn and aliquoted may depend on the patient.

- First recover the plasma (higher phase) bringing it gently to the surface until the intermediate phase, distribute into cryotubes
- Retrieve the intermediate phase bringing all of the white suspension to the surface and place it in the cryotubes
- Retrieve the end of the red blood cells
- Store the cryotubes at -80°C
- Create a table indicating the patient number, the initials, the dates of sample collection, and reception, and placing it into the freezing boxes.

APPENDIX 7: Radiological recommendations

CT scan

A **tri-phasic Helical computed axial tomography scan (**without injection, arterial phase, portal phase) of the liver must be carried out.

It has therefore 3 helical rotation from the hepatic dome to the tip of segment VI.

The patient must have a **sufficient gauge venous line** (>=18G) ideally in the elbow. Injection into a central venous line is perfect.

The injection must use an iodised **contrast medium with a concentration ≥ 350 mg I/mL**

The **injection rate must be ≥ 4 cc/s.**

For the arterial phase, it is recommended to use a **bolus detection system** in the aorta and to release the helical rotation, **15 seconds** after a detection threshold ≥ 150 UH in the aorta.

For the portal phase, the helical rotation should start **50 seconds** after the same detection threshold.

Magnetic resonance imaging (MRI)

MRI should include:

- **2 T2-weighted sequences**:
  - a single-shot technique for liver imaging: either half-Fourier acquisition single-shot turbo spin echo (HASTE).
  - the other with signal saturation of the fat in fast spin echo (sequence type TSE or FSE)

- **A diffusion sequence** with at least 2 values of b: b=100s/mm2 and b=600s/mm2. Other values of b are optional.

- **An echo sequence of gradient T1 without injection**

- **All sequences should be repeated in arterial, portal, late phase** (3min and 5min).

- The use of a standard gadolinium chelate is recommended.

APPENDIX 8: Recommendations for the anatomopathological reports - Minimum information that must appear in the report

• Anatomical location

• Specimen type

• Macroscopic characteristics (if available)

– number of visible tumours, size of each one

• Diagnostic arguments

– histological: tumour well or poorly differentiated

– based on immunohistochemistry: chromogranin A, synaptophysine

• Histological grade

– mitotic index: absolute value (to be evaluated in 2 mm^2)

– Ki-67 index: absolute value (indicate the immunodetection technique and reading method, to evaluate in 500 to 2000 cells according to WHO recommendations)

– Grade G1, G2, or G3

• WHO classification of 2010

– Neuroendocrine G1 tumour

– Neuroendocrine G2 tumour

– Small-cell neuroendocrine carcinoma

– Large-cell neuroendocrine carcinoma

– Adeno-neuroendocrine carcinoma

• Extension of the tumour

– Local invasion (invasion in depth in the digestive wall, peri-pancreatic adipose tissue invasion, invasion of adjacent organs)

– Limits status, measurement margins

• TNM stage

– pT/pN: clearly indicated the classification used (minimum: TNM/UICC)

– Number of metastatic lymph nodes/ examined

• Other information

– Other histoprognostic factors (vascular emboli, peri-nerve sheathing; if appendix: extension to the mesoappendix, depth of invasion, distance from base)

– Lesions associated with peritumoural tissue