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Study protocol

"An observational real-world study of the systemic treatment of well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours (pNET): a study of morbidity and mortality at 2 years"

OPALINE

Sponsors	Novartis pharma S.A.S and Pfizer S.A.S
Document type	Observational study protocol
Version 13	17th July 2018

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Rationale for the amendment

- Revision to section 7 "Pharmacovigilance" in respect of new Novartis internal rules (Procedures). The investigator's obligations remain unchanged, only the internal Novartis rules concerning the management of cases have been changed.
- Two sections have been added concerning the management of data further to compliance with the GDPR: General Data Protection Regulation. (Sections 8.2.1 and 8.2.2).
- Three sections have been added concerning provision of patient information further to compliance with the GDPR: General Data Protection Regulation. (Sections 11.4.1 to 11.4.3).
- Two sections have been added concerning the French law known as Jardé's law and the MR-003: Regulatory considerations (Section 11 and 11.3).
- Changes have been made to the register (version 15 dated 17/07/2018) to ensure that all of the patients identified have been included in the study and that the non-inclusion register does not have to be completed.
- The information line has been updated in the non-inclusion register (version 15 dated 17/07/2018): phone number to call for any information: **0800 940 170.**
- Changes have been made to the CRF (version 15 dated 17/07/2018) to remove grade 0, to allow a visit without tumour assessment to be entered, to add the statement NK (not known) for certain data and to add clarifications to the "anticipated end of study form" page in the event of death. The list of abbreviations has been updated: The abbreviation "NK" (not known) has been added.
- In section 9, Limitations of the study, one type of bias has been added, and in section 8.3, Statistical Analysis, the version of SAS used has been clarified.

Summary of the protocol

Nature of the study:
This is an observational, descriptive, prospective (partially retrospective), multicentre study carried out in France in adult patients treated for a well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumour. The study will be carried out in sites involved in the management of neuroendocrine tumours of the pancreas. The inclusion phase is 28 months with prospective monitoring of 24 months.

Title:
"An observational real-world study of the systemic treatment of well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours (pNET): a study of morbidity and mortality at 2 years"- OPALINE.

Study medication:
Treatment for well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours (pNET). Two treatment groups will be set up: the "targeted therapies" group with two sub-groups for Everolimus (AFINITOR®) and Sunitinib (SUTENT®); and the "other treatments" group with four sub-groups: chemotherapy, somatostatin analogues, interferon alpha and radionuclide therapy.

Objectives:

- Primary objectives: to describe the real-world outcome of adult patients treated (targeted therapies and other treatments) for a well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumour in terms of morbidity and mortality at 2 years (by describing progression-free survival, overall survival and safety).
- Secondary objectives:
    - To describe the characteristics of the population of adult patients treated for a well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumour
    - To describe the management of patients treated for pNET

Population concerned:

- Number of patients: 150 patients in total
- Inclusion criteria: Adult patients treated for well-differentiated, unresectable or metastatic, progressive pNET before initiation of the treatment chosen by the investigator
- Exclusion criteria: Patients with a diagnosis of poorly differentiated neuroendocrine carcinoma or adeno-neuroendocrine carcinoma, patients who have already received a targeted therapy (everolimus or sunitinib) in a previous line of therapy (patient in

rechallenge), patients on their fifth or higher line of systemic treatment, patients who refuse to give their consent

Method and duration of observation

The study will be carried out in sites involved in the management of neuroendocrine tumours of the pancreas. These sites will be identified from a database of doctors specialised in oncology, gastroenterology and endocrinology built up as part of this study by the two sponsors. Patients who meet the eligibility criteria will be invited to enrol in the study until the required number is met, and each patient may only be enrolled once in the study. The patient's therapeutic management will not be altered by taking part in the study and it will follow the recommendations made in a Multidisciplinary Team Meeting (MDTM) in accordance with good practice guidelines.

The inclusion phase is 28 months.

All patients may be included who are seen for a consultation or hospitalisation and start (incident cases) or have already started at the time of inclusion (as long as the treatment has been initiated by the recruiting site; these are prevalent cases) a systemic treatment that is either targeted therapy with sunitinib or everolimus or another treatment of either chemotherapy, somatostatin analogues, radionuclide therapy or interferon alpha as a first, second, third or fourth line therapy. The patients will be prospectively monitored for the whole duration of the study (24 months of follow-up) starting from inclusion in the study.

Data will only be collected retrospectively for the 'prevalent case' patients (those who started treatment before the enrolment visit), so that data from treatment initiation onward is recorded. Safety data will be collected for 'prevalent case' patients as described in the following paragraph and in paragraph 7: pharmacovigilance. The monitoring data will be collected at the tumour assessment visits that are carried out in practice around every 2-3 months, and are separate from any treatment interruptions, changes or discontinuation that may be needed.

Origin and nature of the data collected:

The patients who start treatment at enrolment ('incident' cases) will have indirectly nominative medical data collected prospectively on enrolment and throughout their follow-up. The following information will be collected:

- Social and demographic characteristics
- Characteristics of patients at the start of their treatment: comorbidities and medical history, ECOG performance status
- A description of the disease: initial diagnosis, localisation of metastases at the start of treatment, symptoms of functioning disease at the start of treatment, most recently performed radiology examinations
- Description of the treatment line started at the time of enrolment: targeted therapies or other treatments, date of initiation, dose and treatment regimen, monotherapy/combined treatment
- Description of previous treatments
- Description of changes to the dose/treatment regimen or discontinued treatment

- Tumour assessments
- Safety (see paragraph 7: pharmacovigilance)

The patients who started treatment before enrolment ('prevalent' cases) will have indirectly nominative medical data collected retrospectively on enrolment, then prospective data collected throughout their follow-up. The following information will be collected:

Retrospectively:

- Social and demographic characteristics
- Characteristics of patients at the start of their treatment: comorbidities and medical history, ECOG performance status
- A description of the disease: initial diagnosis, localisation of metastases at the start of treatment, symptoms of functional disease at the start of treatment, most recently performed radiology examinations
- Description of the treatment line ongoing at the time of enrolment: targeted therapies or other treatments, date of initiation, dose and treatment regimen, monotherapy/combined treatment
- Description of previous treatments
- Description of any dose changes or treatment interruptions since initiation of treatment
- Safety (see paragraph 7: pharmacovigilance):
  - If the treatment ongoing at enrolment is Everolimus:
    - Adverse events clearly related to Everolimus that occurred between starting treatment and enrolment
    - Adverse events clearly related to a Pfizer product that occurred between starting the first line of treatment for the illness and enrolment
  - For all other treatments ongoing at enrolment (Sunitinib, chemotherapy, somatostatin analogues, interferon alpha or radionuclide therapy):
    - Adverse events clearly related to a Pfizer product that occurred between starting the first line of treatment for the illness and enrolment.

Prospectively:

- Description of any dose changes or treatment interruptions
- Tumour assessments
- Safety (see paragraph 7: pharmacovigilance)

Data analysis:

All tests will be carried out using a type I error risk of α =5%.

The descriptive analysis of the qualitative and ordinal variables will consist of the number and frequency of each category with a confidence interval of 95%, and the number of missing data. The quantitative variables will be presented in table form showing the overall population and that of each sub-group of patients analysed: total numbers, mean and median, standard deviation, confidence interval, and the number of missing data. The estimate of progression-free survival and overall survival will be made using the Kaplan-Meier method. The survival S(t) function will be the

probability that the event of interest (progression or death respectively) does not occur before the date t.

The survival rates will be estimated and presented for each of the groups of interest:

- Targeted therapy group (with an estimate for the everolimus and sunitinib sub-groups)
- Other treatments group (with estimates for the sub-groups if there are sufficient total numbers)

It is important to note that statistical comparisons in the strictest sense between the different treatment groups in this observational study are not appropriate due to the expected bias and because the groups are not comparable at enrolment (treatments not assigned randomly). If, however, comparisons are envisaged, a Cox multivariate model will be used in order to adjust for patient characteristics that may potentially be associated with the type of treatment received and with survival that could be liable to skew the estimates (confounding factors, effect modification).

Calculation of the number of patients needed:

The calculation of the number of patients needed is based on the primary objective of describing morbidity and mortality evaluated specifically in terms of progression-free survival and overall survival. The calculation is based on the expected precision of the estimate of median survival (confidence interval).

In view of:

- The target population, estimated at 150-170 cases per year,
- The prevalence of the treatment groups of interest and the need to stratify enrolments across the treatment sub-groups,
- The criteria for inclusion in the study (exclusion of patients on their 5th or higher treatment line),

A total of 150 patients enrolled over a period of around 2 years seems to be a realistic target. The inclusion of 150 patients in total would allow the median survival (progression-free or overall) to be estimated with a precision of around 8%.

It should be noted that in the analyses of the sub-groups (targeted therapies, other treatments) the median will be estimated with less precision since the total numbers in each stratum will be lower. For example, if we assume a balanced distribution of patients between the targeted therapies and other treatments groups, or 75 patients per group, precision will be 11%.

1. Abbreviations

(S)AE	(Serious) Adverse Event
AEM	Adverse Event Monitoring
MA	Marketing Authorisation
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé [French national agency for the safety of medicines and health products]
CRA	Clinical Research Associate
COPD	Chronic Obstructive Pulmonary Disease
CCTIRS	Comité Consultatif sur le Traitement de l'Information dans le domaine de la recherche en Santé [consultative committee on data processing in healthcare research]
CNIL	Commission Nationale de l'Informatique et des Libertés [French data protection commission]
CNOM	Conseil National de l'Ordre des Médecins [French doctors' professional association]
EC	Ethics Committee
(e)CRF	(electronic) Case Report Form
CRO:	Contract Research Organization
SC	Scientific Committee
CSP	Code de la Santé Publique [French public health code]
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
ENETS	European Neuroendocrine Tumour Society
EORTC	European Organisation for Research and Treatment of Cancer
GTE	Groupe d'étude des Tumeurs Endocrines [Endocrine tumour study group]
HAS	Haute Autorité de Santé [French health authority]
CI	Confidence Interval
MRI	Magnetic Resonance Imaging
NK	Not Known
NIS	Non-Interventional Study
SAP	Statistical Analysis Plan
PASS	Post Authorization Safety Study
PET scan	Positron Emission Tomography
PFS	Progression Free Survival
RMP	Risk Management Plan
PV	Pharmacovigilance
QLQ-C30	Quality of Life Questionnaire-Core 30
MDTM	Multidisciplinary Team Meeting
RECIST	Response Evaluation Criteria In Solid Tumours
CT	Computed Tomography
CRT	Clinical Research Technician
TNCD	Thésaurus National de Cancérologie Digestive [French thesaurus of gastrointestinal oncology]
NET	Neuroendocrine tumour grading system
pNET	Pancreatic neuroendocrine tumour
WHO	World Health Organization

2. Introduction

Epidemiology

The standardised incidence ratios over the world population of well-differentiated pancreatic neuroendocrine tumours (pNET) are 0.19 in men and 0.12 in women (sex ratio 1.6) per 100,000 people per year(1), meaning they account for only a small proportion (2.8 %) of all pancreatic cancers (2-6). Since pNET patients have higher survival rates than those with pancreatic adenocarcinoma, the prevalence of pNET is greater, estimated at 10% of pancreatic cancers.

In France, the incidence of pancreatic cancer is estimated at around 10,000 new cases per year (7). One type of presentation is known as functioning pNET, in which digestive hormones are produced and symptoms connected with this secretion occur, while the other more common type is non-functioning pNET without hormone secretion and corresponding symptoms. It is estimated that 60 - 90% of pNET are non-functioning (8, 9) and that 85% of pancreatic neuroendocrine tumours are well-differentiated. The degree of differentiation of the tumour is based on the 2010 WHO NET grading system (10): well-differentiated tumours (grade 1 and 2) as against poorly differentiated tumours (grade 3). The management of these patients varies according to the degree of differentiation.

Prognosis

In the Yao et al study (3), the overall median survival of patients with pNET was 38 months and the 5-year survival rate was 43%. In a French study (1) the survival rate was 61.3% at 1 year and 44.2% at 5 years. The same trends could be seen in an English study (11) with a survival rate at 1 year estimated at 64.7% and 38.6% at 5 years.

The factors for a poorest prognosis are in particular the type and localisation of metastases, the tumour grade, the degree of differentiation and age over 40 years (3, 12). The criteria for assessing the prognosis for pNET are set out in the table below (drawn from the publication of the ENETS consensus (9)):

Biological behavior	WHO classification (2000)	WHO classification (2010)	Metastases	Invasion	Tumor size, cm	Angioinvasion	Ki67, %
Benign	Well-differentiated endocrine tumor	NET G1 or NET G2	–	–	≤2	–	usually around 2
Benign or low-grade malignant	Well-differentiated endocrine tumor	NET G1 or NET G2	–	–	>2	±	usually around 2
Low-grade malignant	Well-differentiated endocrine carcinoma	NET G1 or G2	+	+	any	+	usually >2
High-grade malignant	Poorly-differentiated endocrine carcinoma	NEC or G3	+	+	any	+	>20

NET = Neuroendocrine tumor; NEC = neuroendocrine carcinoma.

Table 1 – Criteria for assessing the prognosis of endocrine pancreatic neoplasms

Therapeutic management

The criteria for choice of management are extension of the tumour locally, how much disease progression is seen and symptoms.

There are "anti-secretory" treatments for functioning disease consisting in particular of somatostatin analogues for VIPoma, glucagonoma and insulinoma (which can also be effective against the tumour).

In localised forms, surgery is the gold standard curative treatment. In well-differentiated, localised, small tumours <2cm, treatment abstention may be justified with simple monitoring only, especially if the surgery proposed is a Whipple's procedure (pancreaticduodenectomy) and if the tumour is well-defined, rather than recourse to surgery which does remain the gold standard curative treatment.

In locally advanced or metastatic forms the following "anti-cancer" treatments are used (13-15):

- Hepatic (chemo)embolization, which is a good palliative option for patients who are not candidates for surgery (16)
- Chemotherapy: proven efficacy in well-differentiated pancreatic tumours (e.g. a combination of streptozotocin and 5-FU and/or doxorubicin with an objective response rate of around 35-40% (17-19))
- Somatostatin analogues
- Interferon alpha: 42% show symptomatic response (secretions) and 11% show tumour reduction
- Radionuclide therapy with radiolabelled somatostatin analogues

The following figure shows a treatment algorithm used in patients with pancreatic neuroendocrine tumours and based on the degree of differentiation (figure from publication (20)).

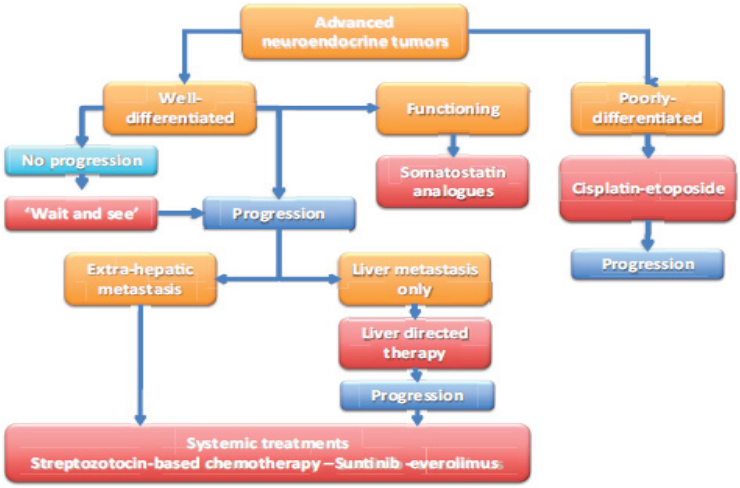

Figure 1 - Therapeutic algorithm for patients with well-differentiated and poorly differentiated pancreatic neuroendocrine tumours

Targeted therapies are systemic treatments that offer a new therapeutic option. There are two treatments that have shown efficacy in the therapeutic management of patients with unresectable pNET in placebo-controlled clinical trials (21, 22), particularly on a primary outcome measure of progression-free survival (PFS): sunitinib and everolimus. PFS was defined as the time between randomisation and the date of first documented disease progression or death, irrespective of the cause. The absolute gain in PFS was 5.9 months for sunitinib and 6.4 months for everolimus. The secondary outcome measures for both drugs were overall survival (defined as the time between randomisation and death irrespective of cause), the objective response percentage according to the RECIST criteria, the duration of response, safety and quality of life based on the EORTC QLQ-C30 scale (for sunitinib). Adverse effects were observed with a higher frequency in the everolimus and sunitinib groups than in the placebo groups.

On the basis of these trials, applications to extend the indications have been granted by the health authorities for both products.

Justification for the study

In an opinion of 21st September 2011 (23) concerning an extended indication for sunitinib to the treatment of well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours in adults, the transparency commission asked for data that would allow them to look at the impact of sunitinib based on a register of well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours in adults, in comparison with other treatments. Based on these data, the outcomes of treated patients in terms of morbidity and mortality at two years would be able to be described.

In an opinion of 28th March 2012 (24) concerning an extended indication for everolimus to the treatment of well or moderately differentiated, unresectable or metastatic, progressive neuroendocrine tumours of pancreatic origin in adults, the transparency commission asked for data that would allow them to look at the impact of everolimus from a register of well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours in adults, in comparison with other treatments. Based on these data, the course of treated patients in terms of morbidity and mortality at two years would be able to be described.

In order to respond to the requests from the authorities, the two pharmaceutical companies (Novartis and Pfizer) firstly approached the Groupe d'étude des Tumeurs Endocrines (GTE, Endocrine Tumours Study Group)[1] to explore whether it would be feasible to use their data and to look at the possibility of grafting a study on to the existing GTE endocrine tumours register. However, due to major problems with using the data from this register to respond specifically to the request from HAS (the type of data collected being basically epidemiological, the timeframe and the difficulties with collecting data), this option was rejected.

[1] http://www.fichiergte.com/

Furthermore, it would not be possible to compare the two treatments (everolimus, sunitinib) to each other and to other treatments from a statistical perspective. This is because the population size needed for a statistically significant comparison based on, for example, the criterion of mortality, would take over 6 years of recruitment to reach (if 4 treatment groups were compared, with the hypothesis of a 20% relative reduction in mortality, and 250 patients needed per group, so 1000 patients[2]) given that the target population is estimated at 150 patients per year. Furthermore, it was important to consider that at the same time there are a number studies in France recruiting from the same limited population (at least four studies known of) which would have an even greater effect on the feasibility and potential for inclusion.

These issues and the similarity of the two study requests made by HAS led the two pharmaceutical companies to consider a single observational study, estimating the impact on morbidity and mortality at 2 years of well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours (pNET) in adults.

In order to answer the questions from HAS, two broad groups of treatments were decided upon:

- The "targeted therapies" group, made up of two sub-groups:
    - Everolimus (AFINITOR®)
    - Sunitinib (SUTENT®)
- The "other treatments" group, made up of four sub-groups of the most commonly prescribed treatments:
    - Chemotherapy
    - Somatostatin analogues
    - Interferon alpha
    - Radionuclide therapy

  Local treatments (chemoembolization, radiofrequency ablation etc.) and surgery were excluded in order to ensure sufficient population numbers to meet the objectives.

[2] Case set out in detail as sent by Novartis to HAS in a letter of 7th March 2012

3. Objectives of the study

3.1. Primary objective

The primary objective of this observational study is to describe the real-world outcomes in adult patients treated (targeted therapies and other treatments) for a well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumour in terms of morbidity and mortality at 2 years. The following parameters will be assessed in order to meet this objective:

- Rate of progression-free survival at 2 years. Progression-free survival is defined as the time between the start of treatment (of the treatment line ongoing at the time the patient was enrolled in the study) and the date of the first disease progression or death, irrespective of the cause.
- Overall survival at 2 years. Overall survival is defined as the time between the start of treatment (of the treatment line ongoing at the time the patient was enrolled in the study) and death, irrespective of the cause.
- Safety of the treatments (targeted therapies and other treatments) defined by instances of treatment discontinuation and the reasons, adverse events (graded according to the 'Common Terminology Criteria for Adverse Events' (CTCAE) version 4.0 of May 2009), and any complications of adverse events.

3.2. Secondary objectives

This study will also enable us to meet the following secondary objectives:

- To describe the characteristics of the population of adult patients treated for a well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumour
- To describe the management of patients with well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours and treated with targeted therapies and other treatments (types of treatment, treatment regimens and prescription modalities)

4. Nature of the study

This is a national observational, descriptive, prospective (partially retrospective), multicentre study carried out in France in adult patients treated for a well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumour.

The study will be carried out in sites involved in the management of neuroendocrine tumours of the pancreas.
These sites will be identified from a database of doctors specialised in oncology, gastroenterology and endocrinology built up as part of this study by the two sponsors. Patients who meet the eligibility criteria will be invited to enrol in the study until the required number is met, and each patient may only be enrolled once in the study. The patient's therapeutic management will not be altered by taking part in the study and it will follow the recommendations made in a Multidisciplinary Team Meeting (MDTM) in accordance with good practice guidelines.

The inclusion phase is 28 months and will enable us to prospectively include patients seen for a consultation or hospital admission during the inclusion phase and treated by targeted therapies (Everolimus or Sunitinib) or by another treatment (one of those defined as part of this study: chemotherapy somatostatin analogues, radionuclide therapy or interferon alpha), for which the following apply:

- Treatment is started as first, second, third or fourth line treatment at the time of enrolment in the study with a change of treatment line being defined as a change of drug or combination thereof (incident cases)
- The treatment ongoing at inclusion was started as a first, second, third or fourth line therapy prior to enrolment in the study as long as treatment was started at the same site that is enrolling the patient in the study (prevalent cases)

The patients will be prospectively monitored for the whole duration of the study (24 months of follow-up) starting from inclusion in the study. The monitoring visits will take place during the patient's usual consultations for tumour assessment carried out at the site (around every 2-3 months), separately from any treatment interruptions, changes or discontinuation that may be needed.

The study will also consist of a retrospective and/or prospective data collection phase, depending on whether patients are prevalent or incident cases, concerning their cancer treatment at the time of their enrolment in the study (Table 2, § 5.2.2 "*Data collection*").

The study data will be collected *via* an electronic case report form (eCRF) by either the doctors or the Clinical Research Associates (CRA)/Clinical Research Technicians (CRT) at the enrolment and monitoring visits.

5. Study plan

5.1. Patient selection

Each doctor participating in the study will have to include all consecutive patients seen at the site who meet all the inclusion and exclusion criteria until the numbers required for each sub-group have been reached (targeted therapies group, other treatments group) and the total number for the study has been met at a national level.

In order to ensure that inclusion adheres to this consecutive pattern, a non-inclusion register (appendix 2) will be set up. Eligible patients who are not enrolled in the study must be recorded in this register throughout the inclusion phase and/or until the expected number of patients has been reached. Only minimal characteristics will be recorded: sex, age of patient, ECOG performance status and reason for non-inclusion.

Within the inclusion phase a maximum of 75 patients treated with "other treatments" irrespective of treatment line will be observed, and a minimum of 75 patients treated with "targeted therapies" irrespective of treatment line, of which 35 patients minimum treated with sunitinib and 35 patients treated with everolimus. It should be noted that on 15th September 2017, recruitment will end even if sufficient numbers of patients for the "other treatments" and "targeted therapies" cohort have not been recruited.

5.1.1. Inclusion criteria

Patients who meet all of the following criteria can be enrolled:

1. Patients over the age of 18 years
2. Patients treated with a targeted therapy (sunitinib, everolimus), or by other treatments (interferon, or radionuclide therapy, or chemotherapy or a somatostatin analogue)* for:

   **patients who are started on a 1st, 2nd ,3rd or 4th line of treatment (targeted therapy or other treatment) at the time they are enrolled (incident cases) or patients whose 1st, 2nd, 3rd or 4th line of treatment is ongoing as long as this treatment was started at the site that is enrolling the patient in the study (prevalent cases); a change of treatment line is defined as a change of drug or combination thereof.*

   - a neuroendocrine tumour of the pancreas, that is unresectable or metastatic and confirmed by histology,
   - well-differentiated,
   - with disease progression prior to initiation of treatment in the investigator's opinion (clinical or radiological progression),
3. Patients who have been informed about the study design and have signed the informed consent form.

Patients who are participating in another observational study can still be enrolled. Moreover, it will be important to enrol patients from clinical trials since the follow-up bias this could entail (connected to the schedule and terms of follow-up imposed by the trial) will have less impact than selection bias, which could lead to this study only including patients who are not eligible for clinical trials. However, in order to identify and categorise patients into the different groups of interest, patients participating in a clinical trial will be able to be included if they are in a treatment arm in the trial with a treatment that has been validated with an MA (Marketing Authorisation) and by the TNCD

(Thésaurus National de Cancérologie Digestive; French thesaurus of gastrointestinal oncology) based on the versions of December 2013, if the clinical trial is not double blinded and if patients are not included in the placebo arm in a placebo-controlled trial.

5.1.2. Exclusion criteria:

The following patients may not be included in the study:

1. Patients with a diagnosis of poorly differentiated neuroendocrine carcinoma or adeno-neuroendocrine carcinoma.
2. Patients receiving a targeted therapy (everolimus or sunitinib) that they have already received in an earlier treatment line (patient in rechallenge).
3. Patients who refuse to give consent.
4. Patients on their fifth or higher line of systemic treatment.
5. Patients participating in a clinical trial with a treatment that is not validated by an MA and by the TNCD in the versions of December 2013.
6. Patients who have been randomised to the placebo arm in a placebo-controlled trial or who are in a double-blind clinical trial.

It is important to limit the number of lines of systemic treatment to four because some pNET patients on their 5th line may have up to a 12-year history of treatment. Data collection would be neither feasible nor reliable (information bias). Moreover, it will also be important to standardise the sample of patients as far as possible, and targeted therapies are rarely prescribed beyond the first four treatment lines.

5.1.3. Recruitment of doctors and patients

The study will be offered to sites involved in the management of pNET (from a database of doctors specialised in oncology, gastroenterology and endocrinology) built up as part of this study by the two sponsors. Doctors will be recruited by a specialist Service Provider under contract to Novartis Pharma and Pfizer. The study will be open to the greatest number of sites in order to have a representative group of doctors participating and to have the greatest potential for enrolments in the study (in view of the limited numbers of potential patients).

The doctors who agree to participate will form the population of participating doctors.

After completing training for the study, each doctor participating must include patients seen consecutively for consultations or hospital admissions who meet all of the eligibility criteria. In order to reduce selection bias, doctors must enrol patients consecutively and exhaustively, until the overall required numbers for the study nationally are achieved, by sub-group and by treatment line in the targeted therapies group.

5.2. Study design

5.2.1. Schedule and duration of the study

Doctors who are specialists in oncology, gastroenterology or endocrinology working at sites involved in the management of patients with pNET will be invited to recruit patients for the study. After

agreeing to the study protocol, the participating doctor has 28 months to recruit the planned number of patients.

In order to answer the questions from HAS, two broad groups of treatments will be formed:

- The "targeted therapies" group, made up of two sub-groups:
    - Everolimus
    - Sunitinib
- The "other treatments" group, made up of four sub-groups of the most commonly prescribed treatments:
    - Chemotherapy
    - Somatostatin analogues
    - Interferon alpha
    - Radionuclide therapy
- Either a first, second, third or fourth line of treatment will be started at the time of enrolment, or the patient will already be on a first, second, third or fourth line of treatment before enrolment in the study (as long as the treatment was started at the site that is enrolling the patient in the study), with a change of line defined as a change of drug *or combination thereof.*

Within the inclusion phase a maximum of 75 patients treated with "other treatments" irrespective of treatment line will be observed and a minimum of 75 patients treated with "targeted therapies" irrespective of treatment line, of which a minimum of 35 patients will be treated with sunitinib and 35 with everolimus. It should be noted that on 15th September 2017, recruitment will end even if sufficient numbers of patients for the "other treatments" and "targeted therapies" cohort have not been recruited.

The participating doctors will consecutively and exhaustively enrol (until the number of patients expected by the site is reached) all patients treated either with a targeted therapy or "other treatment" who meet the study inclusion criteria, and each patient may only be enrolled once in the study. Once all sites have been opened and trained, the inclusion phase is estimated at 28 months.

These patients will be prospectively monitored throughout the whole duration of study follow-up (which is 24 months from the time of enrolment in the study) at their usual consultations for tumour assessment at the sites (or approximately every 2/3 months), which are separate from any treatment interruptions, changes or discontinuation that may be needed. There will be no consultations scheduled by the protocol of this observational study, with the methods of treatment and follow-up remaining those that are judged appropriate by the doctor.

Figure 2 Overall study design

5.2.2. Data collection

The data will be collected in an electronic case report form (eCRF). Patients will be indirectly identified by a number that is for the study only (a combination of the site number and patient number).

Questionnaires will be collected at different measuring points:

- When the site is opened: doctor's questionnaire
- On enrolment of patients: at enrolment visit completed by the doctor (collection of retrospective and/or prospective data depending on whether the patient is a prevalent or incident case)
- During patient follow-up: at follow-up visits completed by the doctor (collection of prospective data)
- If the study is stopped: at the anticipated end of study visit, completed by the doctor

Doctors' data

Each participating doctor will complete the following information:

- Characteristics of the site (type of site, active patient list).

Patient data

Patients who are enrolled will have their indirectly nominative medical data collected (patient questionnaires completed by the doctor) at enrolment and at each follow-up visit, around every 2 - 3 months in line with the usual schedule of consultations for tumour assessment at the site.

The study will include a phase of retrospective and/or prospective data collection (Table 2) depending on whether patient is a prevalent case (systemic treatment started before the enrolment visit) or incident case (systemic treatment for the study started at the enrolment visit).

All patients will have prospective data collected irrespective of the treatment line ongoing and this applies until the end of their follow-up within the study (2 years), or until the patient leaves the study, or, for safety data, until 28 days after the patient has stopped the treatment.

All prevalent case patients will have safety data collected retrospectively.

The methods of declaring safety data are set out in paragraph 7. Pharmacovigilance

	Prevalent cases	**Incident cases**
Recorded retrospectively	- Initial diagnosis of the tumour - Previous cancer treatments - Characteristics of the patient and description of the disease at the time of starting the study treatment - Initiation of the study treatment and reference data at initiation - Safety (see 7. Pharmacovigilance): - **If the treatment ongoing at enrolment is Everolimus,** adverse events will be recorded retrospectively: - If they are clearly related to Everolimus and occurred after it was started and before enrolment. - If they are clearly related to a Pfizer product and occurred after the first treatment line was started and before	- Initial diagnosis of the tumour - Previous cancer treatments

	enrolment. - **For all other treatments ongoing at enrolment** (Sunitinib, chemotherapy, somatostatin analogues, radionuclide therapy or interferon alpha), adverse events will be recorded retrospectively: - If they are clearly related to a Pfizer product and occurred after the first treatment line was started and before enrolment.	
Recorded prospectively	- Follow-up data after enrolment in the study: description of the treatments and tumour assessments (2 years) - Safety (see 7. Pharmacovigilance)	- Characteristics of the patient and description of the disease at the time of starting the study treatment - Initiation of the study treatment and reference data at initiation - Follow-up data after enrolment in the study: description of the treatments and tumour assessments (2 years) - Safety (see 7. Pharmacovigilance)

Table 2 – Data recorded retrospectively and/or prospectively

An end of study questionnaire will be completed by the investigating doctor for every patient who leaves the study before 24 months of follow-up is complete (patients lost to follow-up):

The following data will be recorded for each patient:

Table 3 - Patient variables collected

	Prior to initiation of the current treatment line	On initiation of the current treatment line	At the enrolment visit	At the follow-up visits	Anticipated end of study
Patient reference data					
Compliance with inclusion and exclusion criteria			X		
Social and demographic characteristics (sex, age)			X		
Medical and treatment history					
Initial diagnosis: date of diagnosis, type of tumour (localised, metastatic)	X				
Description of previous treatments: chemotherapy (type, number of cycles, name of treatments), somatostatin analogue, radionuclide therapy, interferon alpha	X				
Characteristics of the tumour at treatment initiation (metastases and localisation, symptoms)		X			
Clinical parameters					
Comorbidities and history: renal function, diabetes, heart failure, coronary heart disease, history of cerebrovascular accident, hypertension, hypercholesterolaemia, lung disease (asthma, COPD etc.)		X			
ECOG performance status (score, examination date)			X	X	
Status of patient (living, lost to follow-up, deceased and cause of death)					X
Study treatments					
Description of the initiation of treatment: which treatment (targeted therapy or other treatment), date of initiation, dose and treatment regimen, monotherapy/combined treatment		X			
Changes to current treatment: dose changes, temporary interruption, discontinuation and reason for discontinuation			X*	X	X
New treatment line(s) since last visit: which treatment (targeted therapy or other treatment), date of initiation, dose and treatment regimen, monotherapy/combined treatment, dose changes, temporary interruptions, discontinuation and reasons for discontinuation				X	X
Tumour assessment					
Examinations performed to assess the tumour (imaging and/or histology)			X	X	
Radiological and clinical responses as judged by the investigator				X	X
Safety					
Retrospective safety (adverse events that occurred prior to inclusion in the study) as described above (Table 2).			X*		
Prospective safety (all adverse events observed during the study)				X	X

**Recorded for ALL prevalent case patients.*

6. Study monitoring and quality control

6.1. Set up and monitoring

The study will be set up by a specialist Service Provider (CRO) under contract to Novartis Pharma and Pfizer. All of the documents required to participate will be sent to each doctor.

The monitoring and logistics of the study will be the remit of a specialist Service Provider under contract to Novartis Pharma and Pfizer. This provider will deliver centralised management of the various documents for the participating doctors (verification, entry). A database specifically to manage the monitoring of the study will be developed through which regular editing of the study progress reports will be possible.

6.2. Quality control

Data will be monitored, quality controlled, entered and analysed by the service provider specialised in data management and processing who are under contract to Novartis Pharma and Pfizer.

- Data will be monitored, quality controlled, entered and analysed by the service provider specialised in data monitoring, management and processing in observational studies in line with current best practice, under contract to Novartis Pharma SAS and Pfizer SAS.
- Requests for additional information and/or corrections may be addressed (by sending an electronic form) to the participating doctors if any information is missing or unclear for the purposes of the data validation plan.

This study will be subject to enhanced monitoring with two components:

- Throughout the study, the doctors will be contacted by specially trained staff from the Service Provider under contract to Novartis Pharma and Pfizer in order to make sure that they have understood the protocol and the electronic case report form, and that they are following the protocol. Each one of these contacts will be documented.
- On-site quality control of data will be carried out based on a sample of 10% of active sites. The active sites for quality control will be chosen at random at the end of the inclusion phase. Before this is set up, a quality control plan will be drafted by the Service Provider and discussed with the study Scientific Committee.

Clinical Research Associates at the specialised Service Provider under contract to Novartis Pharma and Pfizer will be required to check on site that the enrolled patients exist, the quality of the data collected and that the data transferred into the data collection form are identical to the source data (a small amount of clinically relevant and important data will be checked as defined in advance in agreement with the Scientific Committee). This information will be checked by the clinical research associates directly accessing the patient's file. The patient will have been informed in advance of this and agreed to it (Appendix 1: information letter for the patient and consent form).

A report on the quality control visits will be drafted by the Service Provider and presented to the Scientific Committee for analysis and advice on any corrective action that needs to be taken. The Scientific Committee may decide that a further quality control campaign should be carried out.

6.3. Scientific Committee

A scientific committee has been set up to monitor this study. Its role is to define and validate the methodology of the study and the ways in which the study is to be carried out, and to review and validate the statistical analysis report. If there are anomalies in the process of checking data, the committee will look at all measures judged to be necessary to improve data quality. The committee will play a part in communicating the results of the study.

It is made up as follows:

Clinical experts

- Doctor PPD , PPD PPD
- Doctor PPD , PPD PPD

Epidemiology expert

- Professor PPD , epidemiologist - PPD in gastroenterology and gastrointestinal oncology, PPD

Statistics expert

- Professor PPD , PPD PPD

7. Pharmacovigilance

PHARMACOVIGILANCE REQUIREMENTS

Collection and declaration of adverse events to Pharmacovigilance departments – Prospective data

The table below (Table 4) summarises the requirements the investigators are subject to concerning the recording of serious and non-serious adverse events on the electronic case report form and declaring them to the pharmacovigilance departments of Pfizer and Novartis using the Non-interventional study adverse event monitoring (NIS AEM) report form.

These requirements are set out for three types of events:

(1) Serious adverse events (SAE)

(2) Non-serious adverse events (AE) (if applicable)

And (3) Specific scenarios: meaning situations involving

- Exposure to a medication, including exposure during pregnancy via the mother or father whether or not the outcome is known
- Exposure to a medication during breastfeeding
- Medication errors
- Dispensing errors
- Medication administration errors or accidental exposure to a medication
- Overdose
- Misuse
- Abuse
- Interaction with another medication or a food
- Lack of efficacy
- Off-label use
- Withdrawal or rebound symptoms
- Extravasation
- Occupational exposure

These events are defined in the section "Definition of an adverse event".

Table 4 – How adverse events are collected and declared

Adverse event	Recorded in the study eCRF by the investigator	Declared to Pharmacovigilance using the NIS AEM Report Form (declared via the eCRF)	
		Pfizer	Novartis

Adverse event	Recorded in the study eCRF by the investigator	Declared to Pharmacovigilance using the NIS AEM Report Form (declared via the eCRF)	
Serious Adverse Event (SAE)	All Entered in the eCRF within 24 hours of becoming aware of the event	All Within 24 hours of becoming aware of the event	All Within 24 hours of being entered in the eCRF or of the CRO staff becoming aware of the event
Non-Serious Adverse Event (AE)	All Entered in the eCRF within 24 hours of becoming aware of the event	All Within 24 hours of becoming aware of the event	All Within 24 hours of being entered in the eCRF (or of the CRO or Novartis staff becoming aware of the event)
Situation involving exposure to a study medication during pregnancy via the mother or father whether or not the outcome is known	All (Irrespective of whether there is an associated AE) Entered in the eCRF within 24 hours of becoming aware of the event	All (Irrespective of whether there is an associated AE) Within 24 hours of becoming aware of the event	All (Irrespective of whether there is an associated AE) Within 24 hours of being entered in the eCRF (or of the CRO or Novartis staff becoming aware of the event)
Situations involving exposure to a study medication, including exposure during breastfeeding, medication errors, dispensing errors, medication administration errors or accidental exposure to a medication, overdose, misuse, abuse, interaction with another medication or a food, off-label use, withdrawal or rebound symptoms, extravasation, lack of efficacy or occupational exposure	All (irrespective of whether there is an associated AE), **except for occupational exposure** Entered in the eCRF within 24 hours of becoming aware of the event	All (Irrespective of whether there is an associated AE) Within 24 hours of becoming aware of the event	All (Irrespective of whether there is an associated AE) Within 24 hours of being entered in the eCRF (or of the CRO staff becoming aware of the event)

For each AE, the investigator must seek and obtain sufficient information at the time to be able to determine the course of the adverse event and to assess whether it meets the criteria to be categorised as an SAE (see section "serious adverse events" below).

The investigator must enter all adverse events, serious adverse events and specific scenarios in the electronic CRF within 24 hours of becoming aware of this event and this applies whether or not the investigator considers the event to be related to a study medication, and the CRO in charge of the study must send it to the Pharmacovigilance Departments following the process specific to each pharmaceutical company as set out in table 4 above.

Furthermore, if the serious adverse event is fatal or life-threatening, the Pfizer/Novartis Pharmacovigilance Departments must be notified immediately, including whatever information is available about the adverse event. This time frame also apples to any new (follow-up) information concerning adverse event or serious adverse event notifications that have already been submitted. In the rare situations in which the investigator is not immediately informed that an adverse event has occurred, the investigator must enter the adverse event or serious adverse event in the electronic CRF within 24 hours of becoming aware of it, and the time when he/she first became aware of this adverse event must be recorded.

In the case of adverse events considered to be serious or that fit into the right column of the table above entitled "Declared to pharmacovigilance" which need to be declared to the Pfizer/Novartis pharmacovigilance departments within 24 hours of becoming aware of them, the investigator must seek and provide all additional information to Pfizer/Novartis within this 24-hour time frame. Furthermore, Pfizer/Novartis can ask an investigator to urgently obtain specific additional follow-up information. This information may be more detailed than what has been logged in the study case report form. In general, this information will include a sufficiently detailed description of the adverse event for a complete medical assessment of the case, and an independent judgement on whether there is a causal link. All relevant information pertaining to the event, such as concomitant treatments or illnesses, must be provided. If the patient dies, a summary of the available autopsy results must be sent to Pfizer/Novartis or to the approved representative as soon as possible.

Note: For any death entered in the electronic CRF without an associated SAE being declared, the Pfizer/Novartis Pharmacovigilance Departments will be notified immediately and the investigator will be asked for additional information.

Notification period

For each patient, the period for notification of adverse events begins from the time when the patient receives the first dose of the study medication or from the date when the patient gives his/her informed consent if he/she has already been exposed to the study medication, and it ends at the end of the observation phase of the study, which is a minimum of 28 calendar days after the last administration of the study medication; the process for declaring the different types of adverse events to the Pfizer/Novartis Pharmacovigilance departments or approved representative during this period are listed in table 4 above. If the patient receives the study medication on the last day of the observation phase, the notification period will be extended by 28 calendar days after the end of the observation phase. Usually, the date when the consent form is signed will correspond to the date that the patient is enrolled in the study.

In some cases, they may be a delay between the date that the consent form is signed and the date of enrolment in the study.

In cases in which the patient gives his/her consent but is never enrolled in the study (for example: the patient changes his/her mind about participating; does not meet the screening criteria), the notification period ends on the date when the decision is made not to include the patient.

If the investigator becomes aware of a serious adverse event occurring at any time after the end of the observation phase that he/she considers to be related to a study medication, this serious adverse event must also be declared to the Pharmacovigilance department at Pfizer.
If an SAE, non-serious AE or specific scenario occurs after the end of the observation phase, it only needs to be declared to the pharmacovigilance department at Novartis, by fax or by e-mail, if the investigator suspects a causal link with the study medication(s).

Assessing causality

The investigator must assess causality and report on it. The investigator must obtain sufficient information to determine the causality of every adverse event. For AE considered to be related to a study medication, the investigator must monitor these events until resolution or stabilisation of the event and/or of any sequelae to the extent deemed to be acceptable by the investigator, and with the approval of Pfizer/Novartis of this assessment.

The investigator's assessment of causality is the determination of whether there is a reasonable possibility that a study medication could have caused or contributed to an adverse event. If the final determination of causality is unknown and the investigator is unable to determine whether a study medication has caused the event, then the adverse event (Pfizer) or serious adverse event (Novartis) must be reported within 24 hours.

If the investigator is unable to determine the aetiology of the event but he/she has determined that no study medication was the cause of the event, this must be clearly stated on the case report form and the non-interventional study adverse event monitoring form (Pfizer) or non-interventional study serious adverse event monitoring form (Novartis).

DEFINITION OF AN ADVERSE EVENT

Adverse events

An adverse event is an unwanted medical effect occurring in a patient who has been administered a medication. The event does not necessarily have to be causally linked to the treatment or usage. The same definition applies to medical devices and to nutritional products (including formulations for babies or young children [henceforth designated by “paediatric formulation”]). Examples of adverse events include the following from this non-exhaustive list:

- Abnormal test results (see below for the circumstances in which an abnormal test result constitutes an AE)
- Clinically significant signs and symptoms
- Change to results on a clinical examination
- Hypersensitivity
- Lack of efficacy
- Abusive use

- Dependence

In addition, for medications, this can include signs or symptoms resulting from:

- Overdose
- Withdrawal
- Misuse
- Use outside the indications of the MA (marketing authorisation)
- Interactions with other medications
- Extravasation
- Exposure during pregnancy
- Exposure during breastfeeding
- Medication errors
- Occupational exposure

Abnormal test results

The following criteria are used to determine whether an abnormal result on an objective test should be reported as an adverse event:

- The test result is associated with symptoms, and/or
- The test result leads to additional diagnostic investigations or a medical/surgical intervention, and/or
- The test result leads to a change of dosage, withdrawal from the study, administration of an additional and significant concomitant treatment, or another treatment, and/or
- The test result is considered to be an adverse event by the investigator or the sponsor

Simply needing to repeat an abnormal test, in the absence of the above conditions, does not constitute an adverse event. Any abnormal test result that turns out to be due to an error does not need to be reported as an adverse event.

Serious adverse events

A serious adverse event is defined an unwanted medical effect occurring in a patient receiving a medication or nutritional product, regardless of the dose, that:

- Leads to death
- Is life-threatening
- Requires hospitalisation of the patient or prolongs a hospitalisation (see below for the circumstances in which this does not constitute an adverse event)
- Leads to a persistent or significant incapacity (substantial disruption to the ability to conduct acts of daily living)
- Leads to a congenital anomaly or birth defect

Progression of the malignancy over the course of the study (including signs and symptoms of progression) must not be reported as a serious adverse event, unless this results in death during the study or during the adverse events notification period. Hospitalisation due to the signs and

symptoms of disease progression must not be reported as a serious adverse event. If the malignancy results in death during the study or adverse events notification period, then the event leading to death must be recorded as an adverse event, and as a grade 5 serious adverse event.

An event will be defined as a medically important event on the basis of medical and scientific judgement. A medically important event is not immediately life-threatening and/or does not lead to death or hospitalisation. However, if it is established that the event may jeopardise the patient and/or require an intervention in order to avoid the outcomes outlined above, the medically important event must be reported as serious.

For example, this category of medically important events would include allergic bronchospasm requiring intensive care in the emergency department or at home, blood dyscrasias, convulsions that do not lead to hospitalisation, or even the development of dependence on a medication or abuse of a medication.

Moreover, any suspected transmission of an infectious agent, whether pathogenic or not, by a Pfizer/Novartis product is considered to be a serious adverse event. This kind of event may be suspected based on clinical symptoms or examination results indicating an infection in a patient exposed to a Pfizer/Novartis product. The terms “suspected transmission” and “transmission” are considered to be synonyms.

These cases are considered to be unexpected and must be managed as serious cases by the Pfizer/Novartis Pharmacovigilance departments. These cases may also be reported as a product defect, if applicable.

Hospitalisation

Hospitalisation is defined as any initial admission (even one lasting under 24 hours) in a healthcare establishment or any prolongation to an admission.

An admission also includes a transfer within the hospital to an intensive care unit (for example, from the psychiatric ward to a medical ward, from a medical ward to a coronary intensive care unit, from the neurology ward to a tuberculosis care unit).

Attending the emergency department does not necessarily constitute a hospitalisation; however, an event that leads to an attendance at the emergency department must be considered to be medically important.

A hospitalisation in the absence of an adverse event does not constitute an adverse event in itself and does not need to be declared. For example, the following reasons for hospitalisation without AE do not need to be declared:

- Social admission (for example, the patient has no accommodation)
- Administrative admission (for example, for an annual examination)
- Elective admission with no causative AE (for example, for a scheduled cosmetic surgery intervention)
- Hospitalisation for observation in the absence of an AE

- Admission for treatment of a pre-existing condition that is not associated with either the development of a new AE or with the pre-existing condition worsening (for example, for assessment further to persistent abnormal results on laboratory tests that pre-date the treatment)
- Admission scheduled in the protocol during the clinical study (for example, for an act that is required by the study protocol)

Situations that must be declared to the Pfizer and Novartis Pharmacovigilance Departments within 24 hours during pregnancy and following the same guidelines as for an adverse event in the other situations (except when the criteria for a serious adverse event are met, in which case it must be declared within 24 hours).

These are situations involving exposure to a medication, including exposure during pregnancy via the mother or father with or without the outcome being known, exposure during breastfeeding, medication errors, dispensing errors, medication administration errors or accidental exposure to a medication, overdose, misuse, abuse, interaction with another medication or a food, lack of efficacy, off-label use, withdrawal or rebound symptoms, extravasation and occupational exposure. Some of these situations are described below.

Exposure during pregnancy (or prenatal exposure)

Exposure during pregnancy occurs if:

1. A woman becomes pregnant or discovers she is pregnant while she is receiving or has been exposed to a study medication (for example, environmental exposure), or a woman becomes pregnant or discovers that she is pregnant after stopping and/or having been exposed to a study medication (maternal exposure);
   An example of environmental exposure would be a case in which a pregnant woman had direct contact with a study medication (for example, a nurse reporting that she is pregnant and has been exposed to chemotherapy products).

2. A man has been exposed to a study medication, either as part of treatment or by environmental exposure, before or around the time of conception and/or he has been exposed during his partner's pregnancy (paternal exposure).

As a general rule, cases of prospective and retrospective exposure during pregnancy, irrespective of the source, need to be declared whether there is an associated adverse event or not, following the reporting procedure for serious adverse events.

If a female patient in the study or the female partner of a male patient in the study becomes pregnant or discovers she is pregnant during treatment with the study medication, the investigator must declare this information to the Pfizer/Novartis Pharmacovigilance Departments, whether or not this has resulted in an adverse event, and complete the non-interventional studies adverse event monitoring form and also the "Exposure during pregnancy" form.

Furthermore, information relating to the environmental exposure to a study medication of a pregnant woman (for example, a patient reports that she is pregnant and she has been exposed to a cytotoxic product by inhalation or after accidentally spilling it) must be declared to the Pfizer/Novartis Pharmacovigilance Departments, whether or not this has resulted in an adverse event, by completing the non-interventional studies adverse event monitoring form and also the "Exposure during pregnancy" form.

The information sent must include the predicted date at which the pregnancy will reach full-term (see below for information concerning the term of pregnancy).

Follow-up must be set up in order to obtain general information about the pregnancy.

Furthermore, follow-up must be set up to obtain information about the outcome of the pregnancy in all cases that are subject to a notification of exposure during pregnancy for which the outcome is unknown.

A pregnancy must be monitored until it reaches full term or until termination of the pregnancy (for example, elective termination of the pregnancy), and Pfizer/Novartis must be informed of the outcome.

This information will be provided as a follow-up to the initial report of exposure during pregnancy. If the outcome is a birth, the newborn can be assessed at that point for anomalies or defects.

If the pregnancy ends in termination, the reason must be specified and, if clinically possible, the foetus must be assessed for anomalies or defects by means of a visual inspection (unless the results

of tests carried out before the procedure have led to the conclusion of a congenital anomaly and the results have been declared).

If the outcome of the pregnancy meets the criteria for an SAE (for example, an extra-uterine pregnancy, spontaneous abortion, intrauterine foetal death, neonatal death or congenital anomaly [in a live birth, aborted foetus, intrauterine foetal death or neonatal death]), the procedures for declaring an SAE must be followed.

Additional information on pregnancy outcomes that must be reported as SAE:

- Spontaneous abortion includes miscarriage and missed miscarriage;
- Neonatal deaths that occur in the months following the birth must be declared, regardless of the cause, as SAE. Furthermore, the death of a young infant aged over 1 month must be declared as an SAE when the investigator deems that the death of the young infant is linked or possibly linked to exposure to the study medication.

Additional information on the exposure during pregnancy may be requested. Monitoring of cases in which the outcome is birth will be treated on a case by case basis (for example, monitoring of infants born pre-term in order to identify any developmental delays).

In cases of paternal exposure, an information form for pregnant partners will be given to the patient participating in the study for his partner. It must be documented that this form has been given to the patient participating in the study to be passed on to his partner.

Exposure during breastfeeding

Cases of exposure during breastfeeding must be reported, regardless of whether there is an associated AE.
A notification of exposure during breastfeeding must not be submitted when a Pfizer/Novartis product is specifically indicated for use in breastfeeding women (e.g. vitamins) and it has been administered in line with the MA.
However, if the baby presents with an associated AE on administration of such a product, the AE must be declared as exposure during breastfeeding.

Medication error

A medication error is understood to be any unintended error in prescription, dispensing or administration of a medication that may lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient or consumer. Such events may be related to professional practice, healthcare products, or procedures and systems, including: prescribing, order communication, product labelling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.

Medication errors include:

- Near-misses, whether or not these involve a patient directly (for example, inadvertent or mistaken administration, which is the accidental use of the product outside of its indication or prescription by a healthcare professional or a patient/consumer)
- Confusion concerning the name of a product (for example, trade name, brand name).

The investigator must declare the following medication errors to the Pfizer/Novartis Pharmacovigilance Departments, regardless of whether there is an associated AE/SAE:

- Medication errors involving patient exposure to the product, regardless of whether the medication error is accompanied by an adverse event or not.
- Medication errors that do not directly involve a patient (for example, potential medication errors or near-misses). When a medication error does not involve patient exposure to the product, the following are the minimum criteria for a case of medication error:
  - Identifiable notifier
  - Suspected product
  - Medication error

Overdose, Misuse, Extravasation

Cases of overdose, misuse and extravasation associated with the use of a Pfizer/Novartis product must be declared to the Pfizer/Novartis Pharmacovigilance Departments by the investigator, regardless of whether there is an associated AE/SAE or not.

Lack of efficacy

Cases of lack of efficacy of a Pfizer/Novartis product must be declared to the Pfizer/Novartis Pharmacovigilance Departments by the investigator, regardless of whether there is an associated AE/SAE or not; or indication for a Pfizer/Novartis product.

Occupational exposure

Cases of occupational exposure to a Pfizer/Novartis product must be declared to the Pfizer/Novartis Pharmacovigilance departments by the investigator, regardless of whether there is an associated AE/SAE or not.

The serious or non-serious adverse event monitoring form must be sent by fax within 24 hours to the Novartis Pharmacovigilance Department on the following number: 01 55 47 68 00 or to the Pfizer Pharmacovigilance Department on the following number: 01 70 74 57 33.

As part of the enhanced monitoring of specific risks as defined in the Risk Management Plans for AFINITOR (Afinitor RMP, V 9/8) and for SUTENT (SUTENT RMP V14.0) respectively, the Novartis/Pfizer Pharmacovigilance Departments may need to send to the doctor or to any other involved healthcare professional a targeted questionnaire about these events and this will need to be returned to the Novartis/Pfizer Pharmacovigilance Department once it has been completed.

Collection and declaration of adverse events to Pharmacovigilance departments – Retrospective data

This protocol also requires the investigator (or an individual under the investigator's responsibility) to carry out a review of so-called "unstructured" patient data: unstructured data is medical data, including written or visual descriptions of medical information such as medical files, doctors' notes, neurological tests, radiography, or "comments" fields in a database.

The person in charge of this review must enter on the electronic CRF all serious and non-serious adverse events (AE) that are clearly related to a Pfizer medication or to Everolimus that may appear in the data that are reviewed (defined by patient population and by the specific study phase of the protocol), if they meet the conditions for retrospective declaration of (S)AE as defined in § 5.2.2 of the protocol, i.e.:

- If the treatment ongoing at enrolment is Everolimus, enter the following in the electronic CRF so that the CRO in charge of the study can submit a declaration to the Pharmacovigilance departments:
  - (S)AE(s) clearly related to Everolimus that occurred between starting Everolimus and enrolment.
  - (S)AE(s) clearly related to a Pfizer product that occurred between starting the first line treatment for the illness and enrolment
- For all other treatments ongoing at enrolment (Sunitinib, chemotherapy, somatostatin analogues, radionuclide therapy or interferon alpha), retrospective declaration in the electronic CRF is required, so that the CRO in charge of the study can submit a declaration to the Pfizer Pharmacovigilance Department, in the following cases:

  - (S)AE(s) clearly related to a Pfizer product that occurred between starting the first treatment line for the illness and enrolment.

The temporal relationship between administration of the medication and the adverse event cannot be used as the basis for a judgement of whether the event can be attributed to the medication, and instead this must be founded on a health professional making an unquestionable determination of causality that will establish a link between the medication and the AE.

All serious and non-serious adverse events as well as specific situations that need to be declared to the pharmacovigilance departments that are identified based on the data examined must, if they meet the conditions for retrospective declaration of (S)AE, be recorded in the electronic CRF.

These events will be declared to the Pharmacovigilance Departments of Pfizer and Novartis directly via the eCRF (there is no need for any additional submission) using the NIS AEM Report Form and following the requirements applicable to the reporting of adverse events to the pharmacovigilance departments concerned:

- All serious and non-serious adverse events must be declared to the Pharmacovigilance Departments concerned as follows:
  - Serious and non-serious adverse events clearly related to a Pfizer medication will be reported to the Pfizer Pharmacovigilance Department by the CRO within 24 hours of the event coming to light (entered on the electronic CRF by the investigating site)
  - Serious and non-serious adverse events clearly related to everolimus will be reported to the Novartis Pharmacovigilance Department by the CRO within 24 hours of the event coming to light (entered on the electronic CRF by the investigating site)

- Situations involving exposure during pregnancy via the mother or father in which the outcome is unknown must be declared to the Pharmacovigilance Departments within 24 hours of the event coming to light:

- For exposure to a Pfizer product: report to Pfizer Pharmacovigilance Department
- For exposure to everolimus: report to Novartis Pharmacovigilance Department

- Situations concerning exposure during breastfeeding, medication errors, dispensing errors, medication administration errors or accidental exposure to a medication, overdose, misuse, abuse, interaction with another medication or food, lack of efficacy, off-label use, withdrawal or rebound symptoms, extravasation or occupational exposure associated with the use of a Pfizer product or everolimus must be declared to the Pharmacovigilance Departments concerned as follows:
  - All situations associated with use of a Pfizer medication will be reported to the Pfizer Pharmacovigilance Department within 24 hours of the situation coming to light
  - All situations associated with use of everolimus will be reported to the Novartis Pharmacovigilance Department within 24 hours of the situation coming to light

For adverse events clearly related to or associated with the use of a Pfizer product/everolimus, the data entered in the medical file will constitute all of the known clinical information concerning these adverse events. There will be no follow-up concerning these adverse events.

All members of staff at the CRO in charge of monitoring the study must meet the requirements of Pfizer and Novartis in terms of training in: *"Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* (Pfizer) and 5 P training, which is validated through a specific test in "Management of local interventional studies - DVL.OC.P.0002 (Novartis)" as well as any other additional training deemed to be useful. This training will be provided to all CRO staff before the study begins. All training will include a "certificate of training" (signed by the person trained) as confirmation, and this must be kept in an accessible format. Copies of all signed training certificates must be provided to Pfizer and to Novartis.

8. Data Processing

8.1. Determining the sample size

Calculating how many patients to include

The calculation of the number of patients needed is based on the primary objective of describing morbidity and mortality evaluated specifically in terms of progression-free survival and overall survival.

The calculation is based on the expected precision of the estimate of median survival (confidence interval).

An estimate of the variance of S(t) (Kaplan Meier estimator) is given using Greenwood's formula:

$$\hat{Var}[\hat{S}(t)] = [\hat{S}(t)]^2 \sum_{j:t_j \leq t} \frac{d_j}{n_j(n_j - d_j)}$$

Where t_j is the event time, d_j is the number of events in this time and n_j is the population at risk

With the hypothesis that there is no right-censoring before the median and only a single event by the event time, it is possible to simplify Greenwood's formula for median survival as follows:

$$\hat{Var}[\hat{S}(t)] = \frac{0,5^2}{n}.$$

We may then calculate different variances and CI of S(t) depending on n and also the precision.

$s(t)^2$	n	variance $(s(t)^2/n)$	Lowest CI	Highest CI	precision
0.25	75	0.0033	0.38	0.61	0.113
	100	0.0025	0.40	0.59	0.098
	125	0.0020	0.41	0.58	0.088
	150	**0.0016**	**0.42**	**0.58**	**0.080**
	200	0.0012	0.43	0.56	0.069
	225	0.0011	0.43	0.56	0.065
	250	0.0010	0.43	0.56	0.062
	360	**0.0010**	**0.44**	**0.55**	**0.052**

For precision of 5%, 360 patients must be included.

Furthermore, in view of:

- The target population, estimated at 150 - 170 cases per year,
- The prevalence of the treatment groups of interest and the need to stratify enrolments across the treatment sub-groups,
- The inclusion criteria,

The calculation of how many patients to include in the study must find a balance between the statistical calculations and the feasibility of the study. Therefore, according to the data available, a total of 150 patients enrolled over a period of around 2 years seems to be a realistic target. The inclusion of 150 patients in total would allow the median survival (progression-free or overall) to be estimated with a precision of around 8%.

It should be noted that in the analyses of the sub-groups (targeted therapy, other treatments) the median will be estimated with less precision since the totals in each stratum will be lower. For example, if we assume a balanced distribution of patients between the targeted therapies and other treatments groups, or 75 patients per group, precision will be 11%.

Where the other descriptive objectives of the study are concerned, the estimated number of patients rests on the precision of the relative frequency based on the following formula:

$$n = \frac{\varepsilon^2}{i^2} p(1-p)$$

In the absence of a hypothetical value of expected relative frequencies, with the hypothetical maximum value of a relative frequency of 50%, an α risk = 5% and a power (1-β) = 80%, 384 patients will need to be included.

According to the relative frequencies observed and the patient numbers (overall or by treatment stratum) the following precision can be expected:

Relative frequencies observed	Expected precision		
	n=75	n=150	n=200
10 – 90	6.8	5.3	4.2
20 – 80	9.1	7.0	5.5
30 – 70	10.4	8.0	6.4
40 - 60	11.1	8.6	6.8
50	11.3	8.8	6.9

8.2. Data management

A study-specific database will be created, tested and validated before data entry begins. A data validation plan will be set out and it will describe in detail the checks that will need to be performed for each variable as well as the list of authorised self-evident corrections.

A data processing manual will describe the procedures for data management (coding, entry, verification) as well as the questionnaires for the doctor and patient components.

Data will be entered by the participating doctors directly on the secure website. This will feed automatically into the study database. The database will be backed up on a daily basis. The key data will be set as compulsory fields in the electronic CRF in order to manage the proportion of missing data concerning the key parameters of the study.

The consistency of data will be checked exhaustively for all questionnaires in line with the rules that will be defined in the data validation plan. A significant part of the consistency checks will be carried out as the data is entered on the eCRF. The consistency checks set out by the data validation plan will separate out in particular cases concerning a request for clarification of data sent to a participating doctor; self-evident corrections and/or other cases of inconsistency or missing data will be handled in line with the decision-making rules agreed on with the scientific committee, which will be described in the data validation plan.

The database will be locked after a final quality assurance check.

While the study is ongoing, the original documents will be stored at the premises of the specialised service provider under contract to Novartis Pharma and Pfizer, and will only be accessible to authorised persons. They will then be sorted into archiving boxes and sent directly to the company in charge of archiving for Novartis Pharma and Pfizer.

8.2.1. Case report form and data collection

Where the term is used in this protocol, CRF (Case Report Form) must be understood as referring to a hard copy or electronic copy of data, or both, depending on the method of data collected used in the study.

In this study, the data of interest will be recorded in a case report form in electronic format (e-CRF).

A CRF is required and must be completed for each enrolled patient. The original and duly completed CRF are the sole property of the Sponsors and must not be disclosed to any third parties, irrespective of their nature, with the exception of representatives authorised by the Sponsors or competent regulatory authorities, without the written authorisation of the Sponsors. The participating doctor must ensure that the CRF are stored securely on the study site in an encrypted electronic form and/or hard copy and will be password protected or kept safely in a locked room in order to ensure they are not accessed by unauthorised third parties.

The participating doctor has ultimate responsibility for the collection and notification of all clinical, safety and laboratory test data entered on the e-CRF and any other data collection resource (source documents), and for ensuring the data is correct, authentic, original, unquestionable, complete, consistent, legible and available (if necessary).

The CRF must be signed by the participating doctor or by an authorised staff member in order to guarantee the authenticity of the data entered on the CRF. All corrections made to the data entered on the CRF or source documents must be dated, initialled and explained (if necessary) and must not mask the original entry.

In the majority of cases, the source documents are the hospital or doctor's records. In these cases, the data collected in the CRF must correspond to the data in these records.

In some cases, the CRF may also be the source document. In these cases, a document available on-site and from the Sponsors must clearly identify the data that have been recorded in the CRF, and for which data the CRF is the source document.

8.2.2. Data retention

In order to allow the regulatory authorities or Sponsors to perform evaluations and/or inspections/audits, the investigator agrees to retain the records, including the identities of all participating patients (sufficient information to make the link with the records, for example the CRF and hospital records), all original signed informed consent forms, copies of all CRF, pharmacovigilance notification forms, source documents, detailed records of treatment distribution and sufficient documentation of relevant correspondence (for example, letters, minutes of meetings and records of telephone calls). These records must be kept by the participating doctor in line with local regulations or in accordance with the specifications in the study contract, whichever is the longer.

The participating doctor must ensure that the records continue to be stored securely for as long as he/she is required to be retain them.

If the participating doctor is no longer able to retain the study records for the required period for any reason whatsoever (for example: retirement, relocation), the participating doctor must inform the Sponsors. The study records must be transferred to a designated person with the prior approval of the Sponsors, such as another participating doctor, another institution or an independent third party designated by the Sponsors.

The participating doctor's records must be retained for a minimum of 15 years after the end of the study (last visit of last patient) or interruption to it or for longer if required by local regulations. The participating doctor must obtain prior written authorisation from the Sponsors to disclose any records, even if the retention requirements have been met.

8.3. Statistical analysis

The statistical analysis plan will be set out by the service provider instructed by Novartis Pharma and Pfizer and it will be validated with the members of the scientific committee before analysis begins.

8.3.1. Population and variables analysed

8.3.1.1. Analysis methods

The software SAS® (version 9.1 or later, SAS Institute, North Carolina USA) will be used for the analysis.

The descriptive analysis of the qualitative and ordinal variables will consist of the number and frequency of each category with a confidence interval of 95%, and the number of missing data. The quantitative variables will be described in terms of totals, mean and median, standard deviation, confidence interval and the number of missing data.

The overall survival and progression-free survival data will be described using Kaplan Meier curves. Median survival will be estimated and presented with a CI 95%.

As far as possible, graphic representations will be presented with the results of the analyses.

The association measures between two variables (univariate analyses other than comparisons of the sub-groups of interest) will use the usual methods. The association between two qualitative variables will be measured using Pearson’s chi-squared test. If a condition for validity is not met, the correction for continuity will be used (Yates chi-squared test) as long as there is a logical possibility of regrouping the categories. The mean values of the quantitative variables will be compared using Student’s t-test with and without the hypothesis of equal variance. The equality of variance will be estimated using Levène's test and a diagnosis of normality will be assessed based on the appearance of histograms and Shapiro-Wilk test results.

The total number of missing values for each variable analysed will be given in the results table. The key data will be set as compulsory fields in the electronic CRF in order to manage the proportion of missing data, and if necessary imputation techniques will be used.

8.3.1.2. Representativeness of doctor and patient samples

The participating doctors will be described. Comparisons will be made between doctors who have participated actively in the study (included at least one patient) and doctors who were not active or who refused to participate. Patients who are lost to follow-up during the study (who leave the study with no information on whether or not treatment was continued or on death) will be compared to the patients who are monitored until the event date (progression, death or end of treatment) or the end date of 2 years.

8.3.2. Analysis of the objectives

8.3.2.1. Analysis of the primary objective

The primary objective of this observational study is to describe the real-world outcomes of adult patients treated (with targeted therapies and other treatments) for a well-differentiated unresectable or metastatic progressive pancreatic neuroendocrine tumour in terms of morbidity and mortality at 2 years.

The following parameters will be assessed in order to meet this objective:

- Rate of progression-free survival at 2 years. Progression-free survival is defined as the time between the start of treatment (of the treatment line ongoing at the time the patient was enrolled in the study) and the date of the first documented disease progression or death, irrespective of the cause.
- Rate of overall survival at 2 years. Overall survival is defined as the time between the start of treatment (of the treatment line ongoing at the time the patient was enrolled in the study) and death, irrespective of the cause.

Progression-free survival and overall survival will be estimated using the Kaplan-Meier method. The survival S(t) function will be the probability that the event of interest (progression or death respectively) does not occur before the date t. This function will be represented in a graph using a survival curve that will include 95% confidence intervals, estimated using Rothman's formula.

Survival until progression will be estimated taking into account the date of initiation (of the treatment line ongoing at enrolment of the patient) of the targeted therapy or other treatment (as defined in this study) and the event date, i.e. the date of progression or of death. Patients with no event or who are lost to follow-up will be censored at the last date they are known to be alive.

Overall survival will be estimated considering the date of origin to be the date of initiation (of the treatment line ongoing at enrolment of the patient) of the targeted therapy or other treatment, and the event date to be the date of death. Patients with no event or who are lost to follow-up or alive at the end of the study will be censored at the last date they are known to be alive.

These survival rates will be estimated and presented for each of the groups of interest:

- Targeted therapy group (with an estimate for the everolimus and sunitinib sub-groups)

- Other treatments group (with estimates for the sub-groups if there are sufficient total numbers)

It is important to note that statistical comparisons in the strictest sense between the different treatment groups in this observational study are not appropriate due to the expected bias and because the groups are not comparable at enrolment (treatments not assigned randomly). If, however, comparisons are envisaged, a multivariate Cox model will be used in order to adjust for patient characteristics that may potentially be associated with the type of treatment received and survival and that could be liable to skew the estimates (confounding factors, effect modification).

- Safety of the treatments (targeted therapies and other treatments) during the prospective phase of the study, defined by instances of treatment discontinuation and the reasons for this, adverse events (graded according to the 'Common Terminology Criteria for Adverse Events' (CTCAE) version 4.0 of May 2009), and any complications of adverse events.

The proportion of patients for whom adverse events are reported (total proportion and proportion reporting grades 3 or 4 adverse events) will be estimated as well as the proportion who stop treatment due to an inability to tolerate it.

8.3.2.2. Analysis of secondary objectives

The analysis of secondary objectives will be purely descriptive and will use the usual methods as set out in 7.3.1.1. It will be presented in detail in the final statistical analysis plan.

9. Limitations of the study

This protocol has been set out in a way that best meets the objectives set for this observational study and to respond to the request from HAS. However, it does have some limitations that must be discussed and that will need to be taken into account when the study is implemented and the results are being used.

9.1. Selection bias

It is fundamental that the study sample should be as representative as possible of the target population in order for the study results to be able to be extrapolated to the target population. The representativeness of the sample depends on internal validity (precision of estimates and selection criteria for the study population – the patients) and on external validity (plan and sampling fluctuation).

9.1.1. Representativeness of enrolled patients

Once again there is a potential selection bias in observational studies. It is inevitable that patients will be consciously selected for or excluded from enrolment by doctors. Participating doctors will be asked to include the first patients that meet the eligibility criteria in a sequential and exhaustive manner until the numbers for each sub-group have been reached (targeted therapies group, other treatments group) and the total number for the study at a national level, in order to reduce this bias.

In order to ensure that inclusion adheres to this consecutive pattern, a non-inclusion register (appendix 2) will be set up. Eligible patients who are not included in the study must be recorded in this register throughout the inclusion phase and/or until the expected number of patients has been reached. Only minimal characteristics will be recorded: sex, year of birth, ECOG performance status and reason for non-inclusion.

Moreover, it will be important to enrol in this study patients participating in clinical trials (under certain conditions set out in section 4.1.1) since the follow-up bias this could entail (connected to the schedule and terms of follow-up imposed by the trial) will have less impact than selection bias, which could lead to this study only including patients who are not eligible for clinical trials.

A decision has also been made to restrict the inclusion of patients by excluding all patients who have received 5 or more lines of treatment. The reason for this is that, although this criterion restricts and filters the study population, it will allow the sample of patients treated for pNET that we wish to assess in this study to be standardised as far as possible. In fact, pNET patients have often received very different sequences/lines of treatment because there is no validated sequence. By standardising the sample, we will therefore ensure that the descriptions for the treatment sub-groups are valid and if appropriate, based on these previous treatment lines.

9.1.2. Patients lost to follow up during the study

There will be a particular focus on patients who leave the study, or who the investigator does not see again for a visit due to the observational nature of the study (the frequency of visits for patient follow-up can vary from one doctor to another). For patients who are lost to follow-up, a last visit/anticipated end of study questionnaire will be completed by the investigator. The statistical analyses will compare the characteristics of the enrolled patients who participate in the whole duration of the study with the enrolled patients who were later lost to follow-up and/or left the study.

9.1.3. Left truncation and left censoring

For prevalent case patients who have started their current treatment before enrolment in the study, there is left truncation bias due to the fact that it is impossible to include deceased patients in the study. Prevalent case patients all lead to left censoring bias due to the absence of retrospectively recorded tumour assessments.

These types of bias will be taken into account in the analysis of overall survival and progression-free survival through use of a statistical method that will be detailed in the statistical analysis plan.

9.2. Measurement bias

On the face of it, there should be minimal measurement bias, especially since the objectives are basically descriptive and the patients will be included and data collected prospectively. However, there may be measurement bias for the patients who have started treatment (targeted therapy or other treatment) before inclusion in the study. The reason for this is that for these patients' data will be collected retrospectively up to the date that the current treatment line was started where the primary objectives of estimating progression-free survival and overall survival rates are concerned. Nonetheless, the information collected (progression/response, current treatment) are key data in the monitoring of the patient and must be logged in the patients' records. Furthermore, the specific

retrospective data collected concerning response and treatment will only include the treatment line ongoing at enrolment. This is because the only information required about any previous treatment lines is the number of lines and the corresponding treatment regimens (not detailed).

The estimate of progression-free survival will be less accurate than if it were from a clinical trial because of the intervals between assessment visits, which follow real-world practices and are scheduled less frequently than in clinical trials. Equally, the assessment of progression/response will be based on the investigator's judgement (which will be based on the RECIST criteria).

9.3. Missing data

Data will be recorded on the electronic CRF. Use of this tool will mean that missing data is minimised in the first place because it consists of drop-down lists and compulsory fields, validated by the Scientific Committee.

Furthermore, the approach to managing missing data, which is especially important in the context of longitudinal studies, will be discussed and methodology will be validated in the analysis plan.

9.4. Confounding factors

Confounding by indication is expected in this observational study in which a treatment is chosen from a number of possible options and not at random; instead it is selected by the investigator based on the characteristics of the patient, their illness and their previous treatments. A statistical comparison in the strictest sense of the impact of treatments for pNET in terms of morbidity and mortality is not appropriate in this study since there is a high exposure to confounding factors. It is for this reason that the study has been designed to describe the impact on morbidity and mortality in each treatment group (targeted therapies, other treatments) independently.

If, however, comparisons are envisaged, a multivariate Cox model will be used in order to adjust for patient characteristics that may potentially be associated with the type of treatment received and survival and that could be liable to skew the estimates (confounding factors, effect modification).

9.5. Study size

Pancreatic neuroendocrine tumours are an orphan disease. The target population is estimated at 150 patients per year. In this study, the calculation of study size must find a balance between the statistical calculations and the feasibility of the study. Therefore, according to the data available, a total of 150 patients enrolled over a period of around 2 years seems to be a realistic target. The inclusion of 150 patients in total would allow the median survival (progression-free or overall) to be estimated with a precision of around 8%. It should be noted that in the analyses of the sub-groups (targeted therapies, other treatments) the median will be estimated with less precision since the total numbers in each stratum will be lower.

It is also important to emphasise that these simulated calculations (beyond taking into account the practical and real feasibility of recruiting patients) are based on the primary objective of describing morbidity and mortality evaluated specifically through progression-free survival and overall survival. The calculations have not been carried out with the objective of drawing a comparison. This is because the population size needed for a statistically significant comparison based on, for example,

the criterion of mortality, would take over 6 years of recruitment to reach (if 4 treatment groups were compared, with the hypothesis of a 20% relative reduction in mortality, and 250 patients needed per group, so 1000 patients) given that the target population is estimated at 150 patients per year.

10. Schedule of the study

The study is scheduled to be set up once the necessary regulatory approvals have been obtained, which will be September 2014 at the earliest.

All of the patients recruited by sub-group (targeted therapies and other treatments) and by type of treatment for the targeted therapies group (everolimus and sunitinib) will be monitored by the specialised service provider under contract to Novartis Pharma and Pfizer.

As stipulated in paragraph 10 “Schedule of the study” of version 11 of the protocol dating from 1st July 2016, if at the end of the two years of the inclusion phase the total population has not been reached or if the recruitment target of one of the sub-groups has not been reached, the Scientific Committee will be asked to decide whether recruitment for the study should continue or not, and how it should be carried out.

On 20th April 2017 (3 weeks before the end of the 2-year inclusion phase), neither the total target population nor the sub-group target had been reached and they would not be reached by 12th May 2017 (end date of the 2-year inclusion phase).

As a result, on 24th April 2017, there was a meeting between the Scientific Committee and the pharmaceutical companies Pfizer and Novartis. After a reminder of the context, the timelines and the progress report of the study, the scientific committee agreed that the target of including a total of 150 patients was feasible and realistic. A decision was therefore made firstly to extend the recruitment phase until 15th September 2017 and secondly that there would be no further extension after that date.

If the total recruitment target (150 patients) and the cohort recruitment targets for the “other treatments” (at least 75 patients) and “targeted therapies” groups (at least 35 patients on everolimus and 35 patients on sunitinib) were reached before 15th September 2017, inclusions would be stopped.

11. Regulatory considerations

This study does not fall under the scope of French law n° 2006-450 of 18th April 2006 concerning research or law n° 2004-806 of 9th August 2004 article 88 chapter II article L1121-1 so there is no requirement to submit the plan to the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM, French national agency for the safety of medicines and healthcare products), or to an Ethics Committee (EC).

Ruling n° 2016-800 of 16th June 2016 concerning research involving human subjects states in article 8 that studies properly declared or authorised by the date at which the implementation decree (of the French legislation known as the Jardé law, law n° 2016-1537 of 16th November 2016) came into

force could continue for five years in accordance with the legislation that was initially applicable to them.

At the end of this 5-year period, they would need to be assessed again by an Ethics Committee and, if necessary, by ANSM under conditions set out in the French public health code.

The OPALINE study received an opinion before 16th November 2016 and will end within the 5-year period set out above, meaning that substantial amendments to this study are not within the jurisdiction of an Ethics Committee and these will be managed in accordance with the applicable texts.

11.1. Declaration to the CNOM (French doctors' professional association)

Since doctors participating in this study are remunerated, the study protocol and the participating doctors' financial contract will be submitted for an opinion to the Conseil National de l'Ordre des Médecins (CNOM; article L.4113-6 of the French public health code) by Novartis Pharma and Pfizer.

Novartis Pharma and Pfizer will also submit the financial contracts for the members of the Scientific Committee to CNOM for an opinion.

Each participating doctor will receive a copy of the contract along with a letter from Novartis Pharma and Pfizer stipulating that the financial contract has been submitted to CNOM and since the timeframe of 2 months has expired, the opinion from CNOM is deemed to be favourable. A copy of this letter will need to be sent to each doctor's regional branch of CNOM along with a copy of the financial contract (articles L.4113-9, L.4113-10, L.4163-10 of the French public health code).

11.2. Financial agreement

The doctors participating in the study commit to following the protocol as it is written.

This is a contractual agreement and a financial agreement is submitted by Novartis Pharma and Pfizer before a doctor agrees to participate. This agreement sets out the planned remuneration for participating doctors.

11.3. Declarations to the CCTIRS (French consultative committee on data processing in healthcare research) and the CNIL (French data protection commission)

Since this study requires personal data to be collected for the purposes of research in the field of healthcare, it comes under the scope of chapter IX of the French data protection law of 6th January 1978, amended. It has been submitted to the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS, consultative committee on data processing in healthcare research) for an opinion and to the Commission Nationale Informatique et Libertés (CNIL, French data protection commission) to request authorisation.

Since this study is no longer the jurisdiction of CCTIRS as of 5th May 2017, the date when the ruling was made concerning the creation of the Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé (CEREES, French Committee for expertise in research, studies and assessments in the field of healthcare) in line with French law n° 2016-41 concerning modernisation of the healthcare system of 26th January 2016 and the implementation decree of

Jardé's law n° 2016-1537 of 16th November 2016, the departments of the ministry for research no longer have jurisdiction over analysing corrections made to research studies.

However, in accordance with French data protection law 78-17 of 6th January 1978, amended by law 2004-801 of 6th August 2004 concerning the protection of private persons with regard to their personal data, the protocol has been assessed for compliance with a reference methodology, and the Sponsors have made a subsequent declaration of compliance to CNIL.

This means that the data collected will correspond strictly to the field of application of the CNIL reference methodology MR-003 and the Sponsors commit to following this methodology, which will be added to the study documents.

The use of indirectly nominative data (patients identified by a number following the order of entry into the study) is justified because there will be a need to send requests for additional information to the participating doctors after the questionnaires have been received and entered in order to guarantee the quality of the data, and if checks are needed in the event of a dispute on computerisation of the data, the investigator will be able to identify patients from whom data needs to be collected at a later stage.

The doctors will have to fill in and keep a correlation table so that they can return to the patient's file by their entry number in the study and respond to these requests.

Under the French data protection law of 6th January 1978, amended, the patient will be informed of his/her right to access, object to and seek corrections to data recorded as part of this study, and that this right may be exercised at any time through his/her doctor.

Nominative information concerning the participating doctors will be declared and the doctors will be informed in the financial agreement of their rights to access, object to and seek corrections to this information.

11.4. Document for the patient

In accordance with French data protection law of 6th January 1978, amended, the patient will be informed in writing of the nature and objective of the study, as well as his/her right to access, object to and seek corrections to the data collected as part of this study (see Appendix 1: Patient information).

11.4.1. Patient information

All parties will comply with the legislation in force, in particular through the implementation of organisational and technical measures to ensure that patients' personal data is protected. These measures will consist of the omission of patient names and other data that will allow them to be identified directly from all reports, publications and any other disclosures, with the exception of the requirements imposed by the legislation in force.

Personal data will be stored at the study site (in an encrypted electronic form and/or hard copy) and will be password protected and/or kept securely in a room locked with a key in order to ensure that only authorised study staff can access them. Each participating site will put in place appropriate technical and organisational measures to ensure that personal data can be recovered in the event of a loss. In the event of a potential breach of personal data, the participating site will be responsible for determining whether this breach has actually occurred and, if so, to make such notifications as are required by law.

In order to protect the rights and freedoms of private persons with regard to their personal data, when the study data are compiled for submission to the Sponsors and other agreed parties, patient names will be removed and replaced with a unique and specific numeric code using a numbering system that will be defined by the Sponsors.

All other data that allows patients to be identified that is to be sent to the Sponsors or to other agreed parties will be identified by this unique code that is specific to each patient. Each participating doctor's site will keep a confidential list of patients that have participated in the study with a link between the numeric codes for each patient and their true identity.

If the data is transferred, the Sponsors will ensure compliance with high levels of confidentiality and a protection of patients' personal data, in accordance with the provisions of the study contract and the laws in force on the protection of privacy.

11.4.2. Consent

The consent forms and all material intended for patient recruitment must comply with local regulatory and legislative requirements, in particular the laws in force concerning the protection of privacy.

The informed consent form*s* used for the process of obtaining informed consent and all materials for patient recruitment must be examined and approved by the Sponsors, approved by an Ethics Committee (EC) (if applicable) before they are used, and they must be available for inspection.

The participating doctor must ensure that all patients in the study are fully informed about the nature and objectives of the study, how data connected to the study will be communicated and any risks associated with their participation, in particular the risks associated with the processing of patients' personal data.

The participating doctor must also ensure that all patients in the study are fully informed about their rights to access and correct their personal data, and to withdraw their consent for their personal data to be processed.

The participating doctor, or a person designated by the participating doctor, will obtain the written informed consent of every patient before any action specifically connected to the study is carried out. The participating doctor will keep the original informed consent form of each of his/her patients.

11.4.3. Early withdrawal of the patient

Patients can withdraw from the study early at any time at their own request, or they can be excluded at any time at the discretion of the participating doctor or the sponsors for reasons of safety, behaviour or administrative issues. In all cases, every effort must be made to document the outcome of the patient, if possible. The participating doctor must ask about the reason for early withdrawal and any follow-up of all unresolved adverse events.

If the patient withdraws from the study early, and also withdraws his/her consent for any future information to be disclosed, no further assessment may be carried out and no

additional data may be collected. The sponsors will be able to keep and continue to use all data collected before the patient withdrew his/her informed consent.

11.5. Agreement with participating doctors

This protocol will be presented to prospective participating doctors before they are asked to confirm whether they will participate. Participation will be confirmed by signing the financial agreement offered by Novartis Pharma and Pfizer.

In accordance with article R.5120 of the French public health code, doctors and all persons invited to work on this study will be held under professional confidentiality with regard to the way the study is carried out, the people participating and the results obtained. Without the prior agreement of the sponsors, they may not give information about the study to anyone other than the Health Authorities.

11.6. Archiving

The study data collection forms will be archived in hard copy by Novartis Pharma and Pfizer for 15 years.

12. Final report and publication of the results

An analysis report of the results will be sent to the participating doctors.

The process for scientific publication of the results, and the authors participating in these publications and communications, will be defined by Novartis Pharma and Pfizer who will retain the copyright at an international level to all significant publications, including translations into other languages.

The scientific committee will play a part in communicating the results of the study. Novartis Pharma and Pfizer also reserve the right to:

- Use the study results for the purposes of any regulatory procedure, on their own behalf or on behalf of subsidiaries
- Present the results in their medical information about medications
- Distribute printed copies of publications

Nobody may make use of these rights without the prior written agreement of Novartis Pharma and Pfizer.

13. List of documents/Material issued to participating doctors

The following documents will be issued to each participating doctor:

- The financial agreement in triplicate (one for the regional branch of CNOM, one for Novartis Pharma and Pfizer, one for the doctor to keep)
- The opinion from CNOM or in the event of a tacit favourable opinion, a copy of the letter stating that the financial agreement has been submitted to CNOM for approval and, if

applicable, all correspondence between CNOM and the pharmaceutical companies further to submission of the file

- A copy of the scientific protocol
- A study data collection form and an information letter (CNIL wording) and consent form for each patient recruited.

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15. APPENDICES

15.1. APPENDIX 1: Information letter for the patient and consent form

Document unchanged since version 9.3 of the protocol

- PATIENT INFORMATION -

Dear Sir/Madam,

Your doctor is inviting you to participate in a national observational study in France that is being carried out in response to a request from the Health Authorities. This study, named Opaline, is being carried out for research purposes in patients with a neuroendocrine tumour of the pancreas. The aim of this study is to describe the care and outcome of adult patients in France who, like you, have a neuroendocrine tumour of the pancreas.

Your doctor wishes to collect some information about your disease, treatments that you are receiving and have received in the past, and the safety of these treatments. The data that will be collected in this study will allow us to describe the care and outcome of your illness.

These data will be taken from your medical records and will concern the following:

- Demographic data and characteristics at the time of enrolment (medical history, treatments)
- Imaging examinations (assessments of the tumour)
- The outcome of your illness
- Treatments
- Side effects

Your doctor will complete a questionnaire with your medical information when you are enrolled in the study and then again at each of your usual follow-up appointments for a period of two years. This study is not a clinical trial, which means that if you participate there will be no additional or different treatments or examinations from those that you receive or will have to receive as part of your usual care and there is no risk. If your doctor loses contact with you during the study, he/she may have to attempt to contact you by telephone, email, letter or another means.

You are free to agree or refuse to participate in this study and this will have no effect on your continued medical care that your doctor provides. You can decide to stop participating at any time, and this will in no way influence the quality of the care that your doctor provides. Your role in this project will be to give your agreement to your doctor for him/her to complete the questionnaires. You will not need to do anything else.

<u>If you agree to participate:</u>
The study has been set up by the pharmaceutical companies Novartis and Pfizer in response to a request from the Health Authorities. As part of the process of entering the data, ensuring that the study is good quality and following the schedule, your doctor may entrust someone else who will be held to professional confidentiality with accessing your medical records and the collection of the medical data required by the protocol. The data collected are strictly confidential and only the medical team, persons duly instructed by the research sponsor or any other person invited to work on the study will be able to access them, and strictly for the purposes of the task assigned to them. Your medical data that are collected as part of this study will be processed by computer and sent to the pharmaceutical companies Novartis and Pfizer under conditions that will guarantee they remain secure and confidential. You will be identified in the files by a patient number and there will be no mention of your first name or surname.

If you refuse to participate:

Your doctor will have to complete a document with some data about you: sex, year of birth, your general health. No other information about you will be recorded. You have the right to refuse to allow this minimal information to be recorded; simply inform your doctor.

Your refusal to participate in the study will not have any impact on your usual medical follow-up. You will continue to receive care and follow-up as usual from your doctor.

We thank you in advance for your cooperation with this epidemiological research and we remain at your disposal if you need any further information.

The scientific committee and the medical team responsible for the Opaline study.

PATIENT CONSENT

I agree that the data recorded during this research may be subject to computerised processing by the pharmaceutical companies Novartis and Pfizer or their behalf.

I am free to agree or refuse to participate in this observational study and this will have no effect on my continued medical care that my doctor provides.

By adding my signature below, I agree voluntarily to participate in this observational study under the conditions set out in the information letter and I give the abovementioned parties direct access to my medical records.

I have taken note that my right of access, as laid down in the law of 6th January 1978 relating to data protection (article 39), can be exercised at any time via the doctor who is treating me as part of this research and who knows my identity. I will be able to exercise my right to seek corrections and to object through this same doctor.

I will receive a signed copy of the information letter.

PATIENT ***(Section to be completed by the patient)***	**INVESTIGATING DOCTOR** ***(Section to be completed by the doctor obtaining consent)***
SURNAME:……	SURNAME:……
FIRST NAME:……..	FIRST NAME:……..
DATE:…….	DATE:…….
SIGNATURE:……..	SIGNATURE:……..

15.2. APPENDIX 2: Non-Inclusion Register

Document amended in version 13 of the protocol

Non-Inclusion Register

Version 15 of 17th July 2018

OBJECTIVES OF THE NON-INCLUSION REGISTER

The non-inclusion register will allow for a comparison of patients who are included in the OPALINE study with patients who are not included.

This comparison will allow for an evaluation of selection bias and its impact on how representative the study population is.

This means that there will be no barrier to full use and publication of the statistical results.

GUIDELINES FOR COMPLETION OF THE NON-INCLUSION REGISTER

The non-inclusion register needs to be completed during the inclusion phase of the OPALINE study for all adult patients who meet the inclusion and exclusion criteria but who do not wish to participate in the study

We remain at your disposal for any further information on:

0800 940 170 (free from a landline)

The data collected in this document will be declared to CNIL. Under the provisions of articles 34 and subsequent articles of the French data protection law of 6th January 1978, amended, you have a right to access, seek corrections to and removal of data through the pharmaceutical company Pfizer.

CHARACTERISTICS OF PATIENTS NOT INCLUDED IN THE STUDY

SITE NUMBER |__|__|__|__|

HAVE ALL ELIGIBLE PATIENTS BEEN INCLUDED IN THE STUDY? ☐ Yes ☐ No, if no, please complete the register

	Date of appointment	Age of patient	Sex	Reason for non-inclusion
1.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
2.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
3.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
4.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
5.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
6.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
7.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
8.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____

	Date of appointment	Age of patient	Sex	Reason for non-inclusion
9.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
10.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
11.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
12.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
13.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
14.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
15.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____
16.	|_|_|/|_|_|/|_|_|_|_| *day month year*		☐ Male ☐ Female	☐ Patient refusal ☐ Other, please state: _____

Please enter the date and electronically sign the non-inclusion register:

Date: |___|___||___|___||_2_|_0_|___|___|

CASE REPORT FORM

"An observational real-world study of the systemic treatment of well-differentiated, unresectable or metastatic, progressive pancreatic neuroendocrine tumours (pNET): a study of morbidity and mortality at 2 years"

OPALINE

CASE REPORT FORM

Site identity number ⌊_⌊_

Patient identity number ⌊_⌊_

Version 15 of 17th July 2018

Summary

1. Data collected

During patients' usual appointments at the sites (i.e. at enrolment and at visits for tumour assessment, carried out in practice every two to three months) the following data will be collected retrospectively and/or prospectively, depending on whether the patient is a "prevalent case" (started the study treatment before the enrolment visit) or "incident case" (started study treatment on the day of the enrolment visit):

	Before the treatment	On initiation of the treatment	At the enrolment visit	At the follow-up visits	Anticipated end of study
Patient reference data					
Compliance with inclusion and exclusion criteria			X		
Social and demographic characteristics (sex, age)			X		
Medical and treatment history					
Initial diagnosis: date of diagnosis, type of tumour (localised, metastatic)	X				
Description of previous treatments: chemotherapy (type, number of cycles, name of treatments), somatostatin analogue, radionuclide therapy, interferon-alpha	X				
Characteristics of the tumour at treatment initiation (metastases and localisation, symptoms)		X			
Clinical parameters					
Comorbidities and history: renal function, diabetes, heart failure, coronary heart disease, history of cerebrovascular accident, hypertension, hypercholesterolaemia, lung disease (asthma, COPD etc.)		X			
ECOG performance status (score, examination date)			X	X	
Status of patient (living, lost to follow-up, deceased and cause of death)					X
Study treatments					
Description of the initiation of treatment: which treatment (targeted therapy or other treatment), date of initiation, dose and treatment regimen, monotherapy/combined treatment		X			
Changes to current treatment: dose changes, temporary interruption, discontinuation and reason for discontinuation			X*	X	X
New treatment line(s) since last visit: which treatment (targeted therapy or other treatment), date of initiation, dose and treatment regimen, monotherapy/combined treatment, dose changes, temporary interruptions, discontinuation and reasons for discontinuation				X	X
Tumour assessment					
Examinations performed to assess the tumour (imaging and/or histology)			X	X	
Radiological and clinical responses as judged by the investigator				X	X
Safety					
Retrospective safety (adverse events that occurred prior to inclusion in the study) as follows: **- If the treatment ongoing at enrolment is Everolimus,** adverse events will be recorded retrospectively: - If they are clearly related to Everolimus and occurred after it was started and before enrolment. - If they are clearly related to a Pfizer product and occurred after the first treatment line was started and before enrolment. **- For all other treatments ongoing at enrolment** (Sunitinib, chemotherapy, somatostatin analogues, radionuclide therapy or interferon alpha), adverse events will be recorded retrospectively: - If they are clearly related to a Pfizer product and occurred after the first treatment line was started and before enrolment.			X*		
Prospective safety (all adverse events observed during the study)				X	X

**Recorded for ALL prevalent case patients*

2. Enrolment visit

Date of the enrolment visit: __/__/____ (DD/MM/YYYY)

2.1 Checking eligibility criteria

INCLUSION CRITERIA		
Patient aged 18 years or over	❑ Yes	❑ No
Patients treated by a targeted therapy (sunitinib or everolimus) or another treatment (chemotherapy, somatostatin analogues, interferon alpha or radionuclide therapy), as a 1st, 2nd, 3rd or 4th line therapy.	❑ Yes	❑ No
Patients treated for: A neuroendocrine tumour of the pancreas that is unresectable or metastatic and confirmed by histology, Well-differentiated, With disease progression prior to initiation of treatment in the investigator's opinion (clinical or radiological progression)	❑ Yes ❑ Yes ❑ Yes	❑ No ❑ No ❑ No
Patient has been informed of the study plan	❑ Yes	❑ No
Patient has signed the informed consent form	❑ Yes	❑ No

A "no" to any one of these criteria means that the patient is not eligible for the study

EXCLUSION CRITERIA		
Patients receiving a targeted therapy (everolimus or sunitinib) that they have already received in an earlier treatment line (patient in rechallenge)	❑ Yes	❑ No
Patients with a diagnosis of poorly differentiated neuroendocrine carcinoma or adeno-neuroendocrine carcinoma	❑ Yes	❑ No
Patients on their fifth or higher line of systemic treatment	❑ Yes	❑ No
Patients who refuse to give consent	❑ Yes	❑ No
Patients participating in a clinical trial and in an arm in which the treatment is not validated by an MA and by the TNCD in the versions of December 2013	❑ Yes	❑ No
Patients who have been randomised to the placebo arm in a placebo-controlled trial or who are taking part in a double-blind clinical trial.	❑ Yes	❑ No

A "yes" to any one of these criteria means that the patient is not eligible for the study

2.2 Social and demographic characteristics
Month and year of birth __/____ (mm/yyyy)
Sex ❑ Male ❑ Female

2.3 Characteristics of patients on initiation of the current treatment line or treatment line initiated at enrolment

2.3.1 Type of treatment ongoing or initiated at the enrolment visit

(*will allow checks of distribution across the groups and will point the user to the screens to be completed §2.5*)

Targeted therapy ❑ Yes ❑ No

If yes: ❑ everolimus
❑ sunitinib

Other treatment ❑ Yes ❑ No

If yes: ❑ Chemotherapy
- ❑ 5 FU
- ❑ Capecitabine (Xeloda®)
- ❑ Doxorubicin (Adriamycin®)
- ❑ Streptozocin (Zanosar®)
- ❑ Temolozomide (Temodal®)
- ❑ Dacarbazine (Deticene®)
- ❑ Oxaliplatin (Eloxatin®)
- ❑ Gemcitabine (Gemzar®)
- ❑ Cisplatin
- ❑ VP-16
- ❑ Other, please state: _____

❑ Somatostatin analogues
- ❑ Octreotide
- ❑ Lanreotide

❑ Interferon alpha

❑ Radionuclide therapy

Anti-secretory drugs since initiation of the current treatment line

Is the patient receiving or has he/she received an anti-secretory drug? ☐ Yes ☐ No ☐ NK

If yes, ❑ Diazoxide
❑ Proton pump inhibitor
❑ Other, please state: _____
☐ NK

Treatment line at the enrolment visit: (maximum 4th line)

❑ Treatment started on the day of the enrolment visit as ⌊_⌋ line
❑ Treatment started before enrolment visit as ⌊_⌋ line

Treatment decision made in: ❑ French NET network MDTM ❑ Other MDTM ☐ NK

2.3.2. Characteristics of the pancreatic neuroendocrine tumour on starting the current treatment line or treatment line initiated at enrolment

Metastases present on starting the treatment line ongoing or initiated at enrolment?
☐ Yes ☐ No ☐ NK

If yes, Localisation of metastases (*tick more than one if applicable*):

Lungs ☐ Yes ☐ No ☐ Not known
Bones ☐ Yes ☐ No ☐ Not known
Liver ☐ Yes ☐ No ☐ Not known
If yes, % of liver invaded: ☐ ≤ 50% ☐ > 50% ☐ NK
Peritoneum ☐ Yes ☐ No ☐ Not known
Other ☐ Yes: _____ ☐ No

2.3.3. Comorbidities and history on starting the current treatment line or treatment line initiated at enrolment

Lung disease (COPD, Asthma etc.) ☐ Yes ☐ No
If yes, on treatment for lung disease? ☐ Yes ☐ No
Heart failure ☐ Yes ☐ No
if yes, on treatment for heart failure? ☐ Yes ☐ No
Left Ventricular Ejection Fraction (LVEF) if available: _____ % or ☐ Not available
Coronary heart disease ☐ Yes ☐ No
if yes, on treatment for coronary heart disease? ☐ Yes ☐ No
Cerebrovascular accident ☐ Yes ☐ No
if yes, on treatment for CVA? ☐ Yes ☐ No
Hypertension ☐ Yes ☐ No
if yes, on treatment for HT? ☐ Yes ☐ No
Hypercholesterolaemia ☐ Yes ☐ No
if yes, on treatment for hypercholesterolaemia? ☐ Yes ☐ No
Diabetes ☐ Yes ☐ No
If yes, Type of diabetes: ☐ Type I on treatment for type I diabetes? ☐ Yes ☐ No
☐ Type II on treatment for type II diabetes? ☐ Yes ☐ No
If yes, Insulin ☐ Yes ☐ No
Oral anti-diabetics ☐ Yes ☐ No
Renal function Clearance (ml/min): ☐ < 30 ☐ [30; 60] ☐ >60
Other ☐ Yes, *please state*_____ ☐ No

Symptoms of functioning pNET present on starting the current treatment line or treatment line initiated at enrolment?
☐ Yes ☐ No
Related to:
❑ Gastrinoma
❑ Insulinoma
❑ Glucagonoma
❑ VIPoma
❑ Other, please state: _____

2.3.4 ECOG performance status at enrolment: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unknown

2.4 History of the illness

Initial diagnosis of pancreatic neuroendocrine tumour
Date of diagnosis: _|_|/_|_|_|_| (MM/YYYY)

Tumour at diagnosis: ☐ Localised tumour
☐ Metastatic tumour

Previous local and/or regional cancer treatments
During the course of the disease, has the patient received local and/or regional treatments? ☐ Yes ☐ No ☐ NK
If yes, ❑ Surgery to primary cancer
❑ Surgery to liver metastases
❑ Radiofrequency ablation
❑ Chemoembolization/embolization
❑ Other, please state: _____

Most recent examinations
Octreoscan® ☐ Yes ☐ No ☐ Not known
If yes, Octreoscan, Date: _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)
Octreoscan, Uptake: ☐ Yes ☐ No ☐ NK
PET scan ☐ Yes ☐ No ☐ Not known
If yes, PET scan, Date: _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)
PET scan, Uptake: ☐ Yes ☐ No ☐ NK
Histology

Ki67 Value obtained ☐ Yes ☐ No *if yes*, Ki67 value: ___ % or ☐ NK
Mitotic index Value obtained ☐ Yes ☐ No
if yes, mitotic index value: ___ mitoses/field or ☐ NK
French NET pathology network 2nd opinion ☐ Yes ☐ No ☐ Not known

History of previous tumour-directed systemic treatments

Please describe all previous treatment lines:

Table 1 - Previous tumour-directed cancer treatments

Name	Treatment line	Combined with somatostatin analogues	Duration	Reason for stopping
Chemotherapy: ❑ 5 FU ❑ Capecitabine (Xeloda®) ❑ Doxorubicin (Adriamycin®) ❑ Streptozocin (Zanosar®) ❑ Temolozomide (Temodal®) ❑ Dacarbazine (Deticene®) ❑ Oxaliplatin (Eloxatin®) ❑ Gemcitabine (Gemzar®) ❑ Cisplatin ❑ VP-16 ❑ Other, please state: _____ ❑ **Interferon Alpha** **Targeted therapies** ❑ Everolimus ❑ Sunitinib **Somatostatin analogues** ❑ Octreotide ❑ Lanreotide ❑ **Radionuclide therapy** ❑ **Other, please state:** _____	❑ First line ❑ Second line ❑ Third line	❑ Yes ❑ No ❑ Octreotide ❑ Lanreotide	*(eCRF display: Duration recorded only if the treatment is a TT)* __|__| months	❑ Adverse event* ❑ Progression ❑ Scheduled treatment discontinuation ❑ Patient decision ❑ Other, please state: _____ ☐ NK

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF** *(lines may be added if there have been more treatments, up to a limit of 3 previous lines)*

2.5 Treatment line ongoing at the enrolment visit

Depending on the treatment ticked in 2.3 the corresponding screen will be displayed
SUNITINIB screen – Treatment initiation
EVEROLIMUS screen – Treatment initiation
CHEMOTHERAPY screen – Treatment initiation
INTERFERON ALPHA screen – Treatment initiation
SOMATOSTATIN ANALOGUE screen – Treatment initiation
RADIONUCLIDE THERAPY screen – Treatment initiation

SUNITINIB screen Treatment initiation

For all cases of treatment with sunitinib initiated on the day of enrolment or before the enrolment visit (treatment line ongoing)

Treatment with sunitinib initiated as:

☐ Monotherapy
☐ Combination therapy with:
☐ A somatostatin analogue
Please state: ☐ Octreotide
☐ Lanreotide
☐ Other, please state: 1) _____
2) _____

Date of d1 of cycle 1: _|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)
Dose and dosage regimen: ☐ 37.5 mg/day
☐ 25 mg/day
☐ Other, please state: _|_|._| mg/day

For all cases of treatment with sunitinib initiated before the enrolment visit (treatment line ongoing)

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2a – Stepwise dose changes (sunitinib)		
Date	**New dose step (mg/day)**	**Reason for change**
_|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)	☐ 25 ☐ 37.5 ☐ 50 ☐ 62.5 ☐ Other: _|_|	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

Has treatment with sunitinib been interrupted (interruption > 7 consecutive days) between treatment initiation and enrolment in the study? ☐ Yes ☐ No

If yes, please describe each interruption:

Table 3a – Temporary treatment interruptions (sunitinib)		
Start date of interruption	**Duration (days)**	**If yes, reason for interruption**
_|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)	_|_|_	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more interruptions)

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

EVEROLIMUS screen - Treatment initiation

For all cases of treatment with everolimus initiated on the day of enrolment or before the enrolment visit (treatment line ongoing)

Treatment with everolimus initiated as:

☐ Monotherapy
☐ Combination therapy with:
☐ A somatostatin analogue
Please state: ☐ Octreotide
☐ Lanreotide
☐ Other treatment, please state: 1) _____
2) _____

Date of initiation: _|_|/_|_|/_|_|_|_| (DD/MM/YYYY)

Dose and dosage regimen: ☐ 5 mg/day
☐ 10 mg/day
☐ Other, please state: _|_| mg/day

For all cases of treatment with everolimus initiated before the enrolment visit (treatment line ongoing)

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2b – Stepwise dose changes (everolimus)		
Date	**New dose step (mg/day)**	**Reason for change**
_|_|/_|_|/_|_|_|_| (DD/MM/YYYY)	☐ 5 ☐ 10 ☐ Other _|_|	☐ Adverse event ☐ Related to everolimus * ☐ Not related to everolimus** ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an AE related to a everolimus, please complete the safety section of the CRF**

**** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

Has treatment with everolimus been interrupted (interruption > 7 consecutive days) between treatment initiation and enrolment in the study? ☐ Yes ☐ No

If yes, please describe each interruption:

Table 3b – Temporary treatment interruptions (everolimus)		
Start date of interruption	**Duration (days)**	**If yes, reason for interruption**
_|_|/_|_|/_|_|_|_| (DD/MM/YYYY)	_|_|_|	☐ Adverse event ☐ Related to everolimus * ☐ Not related to everolimus** ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more interruptions)

*** In the event of an AE related to a everolimus, please complete the safety section of the CRF**

**** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

CHEMOTHERAPY screen - Treatment initiation

For all cases of treatment with chemotherapy initiated on the day of enrolment or before the enrolment visit (treatment line ongoing)

Treatment: *[Pre-completed with the treatment entered in 2.3.1]*

Treatment initiated as:

☐ Chemotherapy only

☐ Combination therapy with:

☐ A somatostatin analogue

Please state: ☐ Octreotide

☐ Lanreotide

☐ Other treatment, please state: 1) _____

2) _____

Date of initiation of the first treatment: _|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)

Number of cycles delivered: _|_|_

Cycle schedule: ☐ 7 days ☐ 14 days ☐ 21 days ☐ 28 days ☐ other, please state: _|_|_ days

For all cases of treatment with chemotherapy initiated before the enrolment visit (treatment line ongoing)

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2c – Stepwise dose changes (chemotherapy)

Date	Dose change	Reason for change
_|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)	☐ Increase ☐ Decrease	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

Has treatment with *"name of treatment"* been postponed by more than 7 consecutive days from the scheduled date of treatment between initiation and enrolment in the study? ☐ Yes ☐ No

If yes, reason for postponing:

☐ Adverse event*

☐ Patient's decision

☐ Doctor's decision

☐ Other, please state:_____

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

INTERFERON ALPHA screen - Treatment initiation

For all cases of treatment with interferon alpha initiated on the day of enrolment or before the enrolment visit (treatment line ongoing)

Treatment with interferon initiated as:

☐ Monotherapy
☐ Combination therapy with:
☐ A somatostatin analogue
Please state: ☐ Octreotide
☐ Lanreotide
☐ Other, please state: 1) _____
2) _____

Type of treatment: ☐ Pegylated
☐ Standard

Date of initiation: _|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)

Initial dose: _|_|_| MIU/day

For all cases of treatment with interferon alpha initiated before the enrolment visit (treatment line ongoing)

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2d – Stepwise dose changes (IFN-a)	
Date	**Reason for change**
_|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

Has treatment with IFN-α been postponed by more than 7 consecutive days from the scheduled date of treatment between initiation and enrolment in the study? ☐ Yes ☐ No

If yes, reason for postponing:

☐ Adverse event
☐ Patient's decision
☐ Doctor's decision
☐ Other, please state:_____

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

SOMATOSTATIN ANALOGUE screen - Treatment initiation

For all cases of treatment with somatostatin analogues initiated on the day of enrolment or before the enrolment visit (treatment line ongoing)

Treatment with somatostatin analogues as:

☐ Monotherapy
☐ Combination therapy, please state: 1) _____
2) _____

Treatment: *[Pre-completed with the treatment entered in 2.3.1]*
Date of initiation: _|_|_ / _|_|_ / _|_|_|_|_ (DD/MM/YYYY)
Dose: *(Screen displayed depends on the treatment)*
If Octreotide: ☐ 10 mg/28days ☐ 20 mg/28days ☐ 30 mg/28days ☐ other, please state:_____
If Lanreotide: ☐ 60 mg/28days ☐ 90 mg/28days ☐ 120 mg/28days ☐ other, please state:_____

For all cases of treatment with somatostatin analogues initiated before the enrolment visit

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No
If yes, please describe the stepwise changes in dose:

Table 2e – Stepwise dose changes (SA)	
Date	**Reason for change**
_|_|_ / _|_|_ / _|_|_|_|_ (DD/MM/YYYY)	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

Has treatment with *"name of treatment"* been postponed by more than 7 consecutive days from the scheduled date of treatment between initiation and enrolment in the study? ☐ Yes ☐ No
If yes, reason for postponing:

☐ Adverse event*
☐ Patient's decision
☐ Doctor's decision
☐ Other, please state:_____

*** In the event of an AE related to a Pfizer product, please complete the safety section of the CRF**

RADIONUCLIDE THERAPY screen - Treatment initiation

For all cases of treatment with radionuclide therapy initiated on the day of enrolment or before the enrolment visit (treatment line ongoing)

Treatment with radionuclide therapy initiated as:

☐ Monotherapy

☐ Combination therapy with:

☐ A somatostatin analogue

Please state: ☐ Octreotide

☐ Lanreotide

☐ Other treatment, please state: 1) _____

2) _____

Date of initiation: __/__/__/__/__/__/__/__ (DD/MM/YYYY)

Place of treatment: ☐ France

☐ Netherlands

☐ Switzerland

☐ Other, please state: _____

Number of treatments administered since initiation: __/__

Radioisotope: ☐ Lutetium

☐ Indium

☐ Ytrium

2.6 Safety – onset of adverse events (recorded retrospectively)

Safety data are only recorded retrospectively for "prevalent case" patients, which is any patient whose treatment had already been started before enrolment irrespective of the treatment (targeted therapies or other treatments)

- **For all treatment initiated before the enrolment visit:**

  Has the patient presented with serious or non-serious adverse events **related to a Pfizer product since the first treatment line for this disease**? ☐ Yes ☐ No

  If yes, please state:
  Please complete the adverse events table below for all serious or non-serious adverse events related to a Pfizer product reported by the patient since **the first treatment line for this disease**

- **For all cases of treatment with everolimus initiated before the enrolment visit (treatment line ongoing):**

  Has the patient presented with serious or non-serious adverse events related to everolimus since initiation of the current treatment line? ☐ Yes ☐ No

  If yes, please state:
  Please complete the adverse events table below for all serious or non-serious adverse events related to everolimus reported by the patient since initiation of the current treatment line

Description of the adverse event:

Table 4 – Safety

Description of the event	Date of onset	Outcome	Severity	CTCAE grade	Seriousness	Causality	Action concerning the suspected treatment
…… …… ……	--/--/----	☐ Resolved If resolved, Date of resolution: --/--/-- ☐ Resolved with sequelae If resolved, Date of resolution: --/--/-- ☐ Resolution ongoing ☐ Not resolved ☐ Unknown	☐Mild ☐Moderate ☐Severe	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5	☐ Serious ☐ Not serious	(Pre-ticked not changeable) ☐ Sunitinib ☐ Everolimus	☐ Stopped temporarily ☐ Stopped definitively ☐ Dosage increase ☐ Dosage decrease ☐ Continue unchanged ☐ Unknown

(Lines may be added if more AE have been reported)

Tumour assessment visit

At each follow-up visit, to take place approximately every 2 - 3 months in line with the site's usual practices for tumour assessment, the following data will be recorded:

Date of the tumour assessment visit: _|_| / _|_| / 20_|_| (DD/MM/YYYY) or ☐ Not done
At the end of study visit, to take place approximately 2 years after enrolment:
The patient has been monitored for 2 years: ☐ Last follow-up visit (scheduled end of study)

3.1 Tumour assessment

Examination date: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

Imaging examination performed for tumour assessment (tick all that apply):
☐ CT scan ☐ MRI ☐ PET scan ☐ Octreoscan® ☐ Ultrasound ☐ Other, please state: ___

Radiological response to treatment in the investigator's opinion (based on RECIST criteria)
☐ CR (Complete response)
☐ PR (Partial response)
☐ SD (Stable disease)
☐ PD (Progressive disease) Date of progression: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)
☐ NE (Not Evaluable) Reason: _____

Clinical response in investigator's opinion: ☐ Yes ☐ No
☐ Progressive disease Date of progression: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)
☐ Stable disease
☐ Response

3.2 Clinical parameters

ECOG performance status

Value obtained: ☐ Yes ☐ No
If yes, Value: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unknown

3.3 Therapeutic management since last tumour assessment

Since the last documented visit, the cancer treatment may have been continued or may have changed on one or more occasions. The participating doctor must enter all of the cancer treatment lines prescribed to the patient, and then complete the corresponding screens.

Therapeutic management since the last documented tumour assessment visit on [date of the last documented visit] and up to and including today's visit:

If a treatment was "ongoing" at the end of the previous visit (will be checked by the eCRF):

❑ Treatment with *[name of treatment]* that was ongoing at the previous visit continued

If treatment continued:

***Is** [combined treatment entered]* **being continued?** ☐ **Yes** ☐ **No**

If no, reason for stopping [combined treatment entered]: ☐ Adverse event*
☐ Patient's decision
☐ Doctor's decision
☐ Other, please state: ___

Have any new combined treatments been started since the last visit? ☐ **Yes** ☐ **No**

If yes, which ones? ☐ A somatostatin analogue
Please state: ☐ Octreotide
☐ Lanreotide
☐ Other treatment, please state: 1) _____
2) _____

❑ Treatment with *[name of treatment]* that was ongoing at previous visit stopped definitively

If stopped, Date stopped definitively *(see Table 5)*
Reason for stopping treatment *(see Table 5)*
Was [*combined treatment entered*] **still ongoing on the date when** *[name of the treatment line stopped]* **was stopped?** ☐ **Yes** ☐ **No**

If no, Reason for stopping [combined treatment entered]: ☐ Adverse event*
☐ Patient's decision
☐ Doctor's decision
☐ Other, please state: ____

Have any new combined treatments been started between the last visit and the date of stopping [*name of the treatment line stopped*]: ☐ **Yes** ☐ **No**

If yes, which ones?: ☐ A somatostatin analogue
Please state: ☐ Octreotide
☐ Lanreotide
☐ Other treatment, please state: 1) _____
2) _____

Has a new treatment line been put in place? ❑ Yes ❑ No

If yes, please describe all new lines of cancer treatment put in place since the last tumour assessment visit, including the treatment in place at the end of today's visit *(see Table 5).*

If No, if a period of treatment abstention is extended, the patient continues to be followed for 2 years as planned (unless deceased or lost to follow-up).

If no treatment was "ongoing" at the end of the previous visit (will be checked by the eCRF):

❑ Treatment abstention extended (apart from temporary treatment interruptions)

If Extended, if a period of treatment abstention is extended, the patient continues to be followed for 2 years as planned (unless deceased or lost to follow-up).

❑ New treatment line resumed

If Resumed, please describe all new lines of cancer treatment put in place since the last tumour assessment visit, including the treatment in place at the end of today's visit *(see Table 5).*

Table 5 – Therapeutic management			
Treatment	**Start date**	**Date stopped definitively**	**If stopped, reason**
Treatment ongoing at previous visit (auto)	*Start date (auto)*	- *If stopped,* date stopped __/__/____ - *If not,* Ongoing.	*If stopped,* Reason ❑ Disease progression ❑ AE **If AE**, has an AE reporting form been completed?: ❑ Yes ❑ No **If no,** please report the AE* ❑ Patient's decision ❑ Doctor's decision, if so please state why: ❑ Cumulative dose reached ❑ Scheduled stop ❑ Optimum response ❑ Other, please state: _____ ❑ Lost to follow-up ❑ Death → *redirects to the Anticipated end of study questionnaire*
Targeted therapy ❑ everolimus ❑ sunitinib **Chemotherapy** ❑ 5 FU ❑ Capecitabine (Xeloda®) ❑ Doxorubicin (Adriamycin®) ❑ Streptozocin (Zanosar®) ❑ Temolozomide (Temodal®) ❑ Dacarbazine (Deticene®) ❑ Oxaliplatin (Eloxatin®) ❑ Gemcitabine (Gemzar®) ❑ Cisplatin ❑ VP-16 ❑ Other, please state: _____ **Somatostatin analogues** ❑ Octreotide ❑ Lanreotide **Interferon alpha** ❑ Interferon alpha **Radionuclide therapy** ❑ Radionuclide therapy **Other** ❑ Other, please state:_____	__/__/____	- *If stopped,* date stopped __/__/____ - *If not,* Ongoing.	*If stopped,* Reason ❑ Disease progression ❑ AE **If AE**, has an AE reporting form been completed? ❑ Yes ❑ No **If no,** please report the AE* ❑ Patient's decision ❑ Doctor's decision, if so please state why: ❑ Cumulative dose reached ❑ Scheduled stop ❑ Optimum response ❑ Other, please state: _____ ❑ Lost to follow-up ❑ Death → *redirects to the Anticipated end of study questionnaire*

(lines may be added if there are more treatments to enter)

*** If there has been an adverse event, please complete the safety section of the CRF within the stated timeframe**

If no "ongoing" treatment is entered and if the patient is not deceased or lost to follow-up (will be checked by the eCRF):

Is the patient receiving a new treatment line targeting the tumour at the end of today's visit? ☐ Yes ☐ No

If yes, please describe the new treatment line targeting the tumour that was put in place at today's visit *(see Table 5)*

If not, the following is displayed:

The patient follow-up phase in the study is set at 2 years. Please repeat the follow-up visit at the next tumour assessment visit.

For each line of cancer treatment entered, the participating doctor will be redirected to the corresponding screen.

If the treatment has been continued since the last documented visit
SUNITINIB screen – Treatment continued
EVEROLIMUS screen – Treatment continued
CHEMOTHERAPY screen – Treatment continued
INTERFERON ALPHA screen – Treatment continued
SOMATOSTATIN ANALOGUE screen – Treatment continued
RADIONUCLIDE THERAPY screen – Treatment continued

If the treatment has been started since the last documented visit
SUNITINIB screen – New treatment line
EVEROLIMUS screen – New treatment line
CHEMOTHERAPY screen – New treatment line
INTERFERON ALPHA screen – New treatment line
SOMATOSTATIN ANALOGUE screen – New treatment line
RADIONUCLIDE THERAPY screen – New treatment line

SUNITINIB screen - Treatment continued

If treated with sunitinib:

Has there been a stepwise dose change since the last tumour assessment visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2a - Stepwise dose changes (sunitinib)		
Date	**If yes, new dose step (mg/day)**	**Reason for change**
___ / ___ / _____ (DD/MM/YYYY)	☐ 25 ☐ 37.5 ☐ 50 ☐ 62.5 ☐ Other: ___	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with sunitinib been interrupted temporarily (interruption > 7 consecutive days) since the last tumour assessment visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No

If yes, please describe each interruption:

Table 3a – Temporary treatment interruptions (sunitinib)		
Start date of interruption	**Duration (days)**	**If yes, reason for interruption**
___ / ___ / _____ (DD/MM/YYYY)	____	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more interruptions)

*** In the event of an adverse event, please complete the safety section of the CRF**

SUNITINIB screen - New treatment line

For all cases of treatment with sunitinib initiated since the last documented visit

Treatment with sunitinib initiated as:

☐ Monotherapy

☐ Combination therapy with:

☐ A somatostatin analogue

Please state: ☐ Octreotide

☐ Lanreotide

☐ Other treatment, please state: 1) _____

2) _____

Date of d1 of cycle 1: ___ / ___ / _____ (DD/MM/YYYY)

Dose and dosage regimen: ☐ 37.5 mg/day

☐ 25 mg/day

☐ Other, please state: ___._ mg/day

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2a - Stepwise dose changes (sunitinib)		
Date	**New dose step (mg/day)**	**Reason for change**
___ / ___ / _____ (DD/MM/YYYY)	☐ 25 ☐ 37.5 ☐ 50 ☐ 62.5 ☐ Other: ___	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with sunitinib been interrupted (interruption > 7 consecutive days) since treatment initiation?

☐ Yes ☐ No

If yes, please describe each interruption:

Table 3a – Temporary treatment interruptions (sunitinib)		
Start date of interruption	**Duration (days)**	**If yes, reason for interruption**
___ / ___ / _____ (DD/MM/YYYY)	____	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more interruptions)

*** In the event of an adverse event, please complete the safety section of the CRF**

EVEROLIMUS screen - Treatment continued

If treated with everolimus:

Has there been a stepwise dose change since the last tumour assessment visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2b - Stepwise dose changes (everolimus)		
Date	**If yes, new dose step (mg/day)**	**Reason for change**
___ / ___ / _____ (DD/MM/YYYY)	☐ 5 ☐ 10 ☐ Other ___	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with everolimus been interrupted temporarily (interruption > 7 consecutive days) since the last tumour assessment visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No

If yes, please describe each interruption:

Table 3b – Temporary treatment interruptions (everolimus)		
Start date of interruption	**Duration (days)**	**If yes, reason for interruption**
___ / ___ / _____ (DD/MM/YYYY)	____	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more interruptions)

*** In the event of an adverse event, please complete the safety section of the CRF**

EVEROLIMUS screen - New treatment line

For all cases of treatment with everolimus initiated since the last documented visit

Treatment with everolimus initiated as:

☐ Monotherapy

☐ Combination therapy with:

☐ A somatostatin analogue

Please state: ☐ Octreotide

☐ Lanreotide

☐ Other treatment, please state: 1) _____

2) _____

Date of initiation: _|_|_ / _|_|_ / _|_|_|_|_ (DD/MM/YYYY)

Dose and dosage regimen: ☐ 5 mg/day

☐ 10 mg/day

☐ Other, please state: _|_|_ mg/day

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2b - Stepwise dose changes (everolimus)		
Date	**New dose step (mg/day)**	**Reason for change**
_|_|_ / _|_|_ / _|_|_|_|_ (DD/MM/YYYY)	☐ 5 ☐ 10 ☐ Other _|_|_	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with everolimus been interrupted (interruption > 7 consecutive days) since treatment initiation?

☐ Yes ☐ No

If yes, please describe each interruption:

Table 3b – Temporary treatment interruptions (everolimus)		
Start date of interruption	**Duration (days)**	**If yes, reason for interruption**
_|_|_ / _|_|_ / _|_|_|_|_ (DD/MM/YYYY)	_|_|_	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more interruptions)

*** In the event of an adverse event, please complete the safety section of the CRF**

CHEMOTHERAPY screen - Treatment continued

If treated with chemotherapy:

If treatment with chemotherapy has been initiated and continued as a combination treatment since last visit:

Has there been a stepwise dose change since the last tumour assessment visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2c - Stepwise dose changes (chemotherapy)		
Date	**Dose change**	**Reason for change**
_|_|_ / _|_|_ / _|_|_|_|_ (DD/MM/YYYY)	☐ Increase ☐ Decrease	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with *"name of treatment"* been postponed by more than 7 consecutive days from the scheduled date of treatment since the last tumour assessment visit on *[date of the last tumour assessment visit entered]?*

☐ Yes ☐ No
If yes, reason for postponing:
☐ Adverse event*
☐ Patient's decision
☐ Doctor's decision
☐ Other, please state:_____
*** In the event of an adverse event, please complete the safety section of the CRF**

CHEMOTHERAPY screen - New treatment line
For all cases of treatment with chemotherapy initiated since the last documented visit
Treatment of: *[Pre-completed with the treatment entered in 3.3]*
Treatment initiated as:
☐ Chemotherapy only
☐ Combination therapy with:
☐ A somatostatin analogue
Please state: ☐ Octreotide
☐ Lanreotide
☐ Other treatment, please state: 1) _____
2) _____
Date of initiation of the first treatment: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)
Number of cycles delivered: _|_|

Cycle schedule: ☐ 7 days ☐ 14 days ☐ 21 days ☐ 28 days ☐ other, please state: _|_| days

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No
If yes, please describe the stepwise changes in dose:

Table 2c - Stepwise dose changes (chemotherapy)		
Date	**Dose change**	**Reason for change**
_|_| / _|_| / _|_|_|_|_| (DD/MM/YYYY)	☐ Increase ☐ Decrease	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)
*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with *"name of treatment"* been postponed by more than 7 consecutive days from the scheduled date of treatment since initiation? ☐ Yes ☐ No
If yes, reason for postponing:
☐ Adverse event*
☐ Patient's decision
☐ Doctor's decision
☐ Other, please state:_____
*** In the event of an adverse event, please complete the safety section of the CRF**

INTERFERON ALPHA screen - Treatment continued

If treated with interferon alpha:

If treatment with Interferon alpha has been initiated and continued as a combination treatment since last visit:

Has there been a stepwise dose change since the last tumour assessment visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2d - Stepwise dose changes (IFN-a)	
Date	**Reason for change**
___ / ___ / _____ (DD/MM/YYYY)	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with interferon alpha been postponed by more than 7 consecutive days from the scheduled date of treatment since the last tumour assessment visit on *[date of the last tumour assessment visit entered]?*

☐ Yes ☐ No

If yes, reason for postponing:

☐ Adverse event
☐ Patient's decision
☐ Doctor's decision
☐ Other, please state:_____

*** In the event of an adverse event, please complete the safety section of the CRF**

INTERFERON ALPHA screen - New treatment line

For all cases of treatment with interferon alpha initiated since the last documented visit

Treatment with interferon initiated as:

☐ Monotherapy
☐ Combination therapy with:
☐ A somatostatin analogue
Please state: ☐ Octreotide
☐ Lanreotide
☐ Other treatment, please state: 1) _____
2) _____

Type of treatment: ☐ Pegylated
☐ Standard

Date of initiation: __ / __ / _____ (DD/MM/YYYY)

Initial dose: ____ MIU/day

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2d - Stepwise dose changes (IFN-a)	
Date	**Reason for change**
__ / __ / _____ (DD/MM/YYYY)	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with IFN-α been postponed from more than 7 consecutive days from the scheduled date of treatment since initiation? ☐ Yes ☐ No

If yes, reason for postponing:
- ☐ Adverse event*
- ☐ Patient's decision
- ☐ Doctor's decision
- ☐ Other, please state:_____

*** In the event of an adverse event, please complete the safety section of the CRF**

SOMATOSTATIN ANALOGUES screen - Treatment continued

If treated with a somatostatin analogue:

If treatment with a somatostatin analogue has been initiated and continued as a combination treatment since last visit:

Has there been a stepwise dose change since the last tumour assessment visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2e - Stepwise dose changes (SA)	
Date	**Reason for change**
___/___/_____ (DD/MM/YYYY)	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with *"name of treatment"* been postponed by more than 7 consecutive days from the scheduled date of treatment since the last tumour assessment visit on *[date of the last tumour assessment visit entered]?* ☐ Yes ☐ No

If yes, reason for postponing:
- ☐ Adverse event*
- ☐ Patient's decision
- ☐ Doctor's decision
- ☐ Other, please state:_____

*** In the event of an adverse event, please complete the safety section of the CRF**

SOMATOSTATIN ANALOGUES screen - New treatment line

For all cases of treatment with somatostatin analogues initiated since last documented visit

Treatment: *[Pre-completed with the treatment entered in 2.3.1]*

Date of initiation: _|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)

Dose: *(Screen displayed depends on the treatment)*

If Octreotide: ☐ 10 mg/28days ☐ 20 mg/28days ☐ 30 mg/28days ☐ other, please state:_____

If Lanreotide: ☐ 60 mg/28days ☐ 90 mg/28days ☐ 120 mg/28days ☐ other, please state:_____

Treatment with somatostatin analogues initiated as:

☐ Monotherapy

☐ Combination therapy, please state: 1) _____

2) _____

Has there been a stepwise change in dose since treatment was started? ☐ Yes ☐ No

If yes, please describe the stepwise changes in dose:

Table 2e - Stepwise dose changes (SA)	
Date	**Reason for change**
_|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)	☐ Adverse event* ☐ Patient's decision ☐ Doctor's decision ☐ Other, please state:_____

(Lines may be added if there have been more changes)

*** In the event of an adverse event, please complete the safety section of the CRF**

Has treatment with *"name of treatment"* been postponed by more than 7 consecutive days from the scheduled date of treatment since initiation? ☐ Yes ☐ No

If yes, reason for postponing:

☐ Adverse event*

☐ Patient's decision

☐ Doctor's decision

☐ Other, please state:_____

*** In the event of an adverse event, please complete the safety section of the CRF**

RADIONUCLIDE THERAPY screen - Treatment continued

If treated with radionuclide therapy:

If treatment with radionuclide therapy has been initiated and continued as a combination treatment since last visit:

Number of cycles administered since the last visit on *[date of last tumour assessment visit entered]*: _|_|

RADIONUCLIDE THERAPY screen - New treatment line

Treatment with radionuclide therapy initiated as:

☐ Monotherapy

☐ Combination therapy with:

☐ A somatostatin analogue

Please state: ☐ Octreotide

☐ Lanreotide

☐ Other treatment, please state: 1) _____

2) _____

Date of initiation: _|_|_ / _|_|_ / _|_|_|_| (DD/MM/YYYY)

Place of treatment: ☐ France

☐ Netherlands

☐ Switzerland

☐ Other, please state: _____

Number of cycles administered since initiation: ⎵⎵

Radioisotope: ☐ Lutetium
☐ Indium
☐ Ytrium

3.4 Safety – onset of adverse events

Has the patient experienced adverse events since the last documented visit on *[date of last tumour assessment visit entered]*? ☐ Yes ☐ No
If yes, please describe <u>all</u> adverse events experienced in the Safety section of the eCRF *(see 5. Adverse events recording module)*

4. Anticipated end of study form

STATUS OF PATIENT

❑ Alive date of last contact: ⎵⎵ / ⎵⎵ / ⎵⎵⎵⎵ (DD/MM/YYYY)

Main reason for stopping the study

- ❑ Does not meet the inclusion criteria at enrolment - exclusion
- ❑ Patient's decision
- ❑ Transferred to another treatment centre not participating in the study
- ❑ Other reason, please state:_____

❑ Lost to follow-up date of last contact: ⎵⎵ / ⎵⎵ / ⎵⎵⎵⎵ (DD/MM/YYYY)

❑ Deceased*

☛ *<u>If deceased, please state</u>*

Date of death ⎵⎵ / ⎵⎵ / ⎵⎵⎵⎵ (DD/MM/YYYY)

Study medication(s) at the time of death

- ☐ Sunitinib
- ☐ Everolimus
- ☐ Octreotide
- ☐ Other treatment, please state:
  - ☐ Chemotherapy
  - ☐ Interferon alpha
  - ☐ Somatostatin analogue other than Octreotide
  - ☐ Radionuclide therapy

Cause of death

- ❑ Disease progression
- ❑ Adverse event* **not related to a study medication**
- ❑ Adverse event* **related to a study medication**

***Please complete the safety section of the CRF**

TREATMENT ONGOING WHEN PATIENT LAST SEEN

If the anticipated end of study form is completed at a time other than a follow-up visit:
Therapeutic management between the last documented tumour assessment visit on [date of the last documented visit] and up to the anticipated end of study date:
→ *Display section 3.3 Therapeutic management since last tumour assessment*
→ *Display Table 5 and the screens corresponding to each recorded treatment line*

DISEASE OUTCOME

Best response to treatment when patient last seen

❑ Complete response ❑ Stable disease

❑ Partial response ❑ Disease progression

Date of the last disease assessment: _|_| / _|_| / _|_|_|_| (DD/MM/YYYY)

5. Adverse events recording module (recorded prospectively)

Please complete the adverse events table for all events reported since inclusion in the study:

Description of the adverse event:

Table 4 - Safety

Description of the event	Date of onset	Outcome	Severity	CTCAE grade	Seriousness	Causality of the study treatment	Action concerning the study treatment
--- History of previously described adverse events ---							
.....	--/--/----	☐ Resolved If resolved, Date of resolution: --/--/-- ☐ Resolved with sequelae If resolved, Date of resolution: --/--/-- ☐ Resolution ongoing ☐ Not resolved ☐ Unknown	☐Mild ☐Moderate ☐Severe	☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5	☐ Serious ☐ Not serious	☐ Not related to treatment ☐ Related to treatment If related, please state: ☐ Related to Sunitinib ☐ Related to Everolimus ☐ Other treatment, please state: ☐ Chemotherapy ☐ Interferon alpha ☐ Somatostatin analogue ☐ Radionuclide therapy	☐ Stopped temporarily ☐ Stopped definitively ☐ Dosage increase ☐ Dosage decrease ☐ Continue unchanged ☐ Unknown ☐ None

(Lines may be added if more AE have been reported)

Appendix AE reporting form

Non-interventional study adverse events reporting form

For internal usage by Pfizer /Novartis	
Premises n°	Date of declaration

AE declaration number (*please state if known)*

												0	*0*			*0*	*0*	*0*	*0*	*0*	*0*		

PROTOCOL/STUDY NUMBER **SITE NUMBER** **PATIENT IDENTITY NUMBER**

Study title:			
☐ Initial declaration ☐ Follow-up declaration			**Country of onset of the event: France**
Patient details	Age ☐ Male ☐ Female	Height ☐ cm Weight ☐ kg	**Ethnic origin**: ☒ No requirement to enter in accordance with local regulation
If patient deceased:	Date of death	Cause(s) of death	Determined by autopsy: Y ☐ N ☐ Unknown ☐ *If yes, cause of death determined by autopsy:*

Patient medical history ☐ None ☐ Unknown *State the relevant medical history below. Include other diseases present at the time of the event and pre-existing conditions. If more space is needed, use copies of this page*.

Disease (please state)	Date of onset	End date	*Tick here if ongoing*	Relevant details *Include surgical interventions and dates*
			☐	
			☐	
			☐	
			☐	

Study medication (brand name and generic name) formulation, route of administration, indication	*Tick if the medication is by* *Pfizer*	*Novartis*	Dose	Units	Frequency	Date of onset	End date	*Tick here if ongoing*
	☐	☐						☐
	☐	☐						☐
	☐	☐						☐
	☐	☐						☐

Treatments received in the 28 days preceding the onset of the AE

In the 28 days preceding the onset of the AE, did the patient receive at least one dose of Sunitinib?	☐**Yes**	☐**No**	
In the 28 days preceding the onset of the AE, did the patient received at least one dose of a Pfizer study product (other than Sunitinib)?	☐**Yes**	☐**No**	☐ NK
In the 28 days preceding the onset of the AE, did the patient receive at least one dose of Everolimus?	☐**Yes**	☐**No**	
In the 28 days preceding the onset of the AE, did the patient receive at least one dose of Octreotide?	☐**Yes**	☐**No**	

Concomitant medications ☐ None ☐ Unknown *State below any concomitant medications taken in the two weeks preceding the onset of the event. Exclude all medications that were only administered over two weeks before the event, and any medication used to treat the event or taken after onset of the event. If more space is needed, use copies of this page*.

Name of the medication (brand and generic names)	Reason for use	Administration route	Date of onset	End date	*Tick here if ongoing*
					☐
					☐
					☐
					☐

Relevant tests	*State only the results of tests relevant to confirmation of the adverse event(s), for example blood tests or diagnostic imaging. If more space is needed, use copies of this page.*					
Test	Date	Result	Units	Normal values Min	Max	Comments

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Non-interventional study adverse events reporting form

AE declaration number (*please state if known)*

For internal usage by Pfizer /Novartis	
Premises n°	Date of declaration

PROTOCOL/STUDY NUMBER | SITE NUMBER *0 0* | PATIENT IDENTITY NUMBER *0 0 0 0 0 0*

ADVERSE EVENTS *(if more than two, please use copies of this page)*
State the diagnosis if known rather than symptoms or signs

Designation of the adverse event ____________

Date of onset: ____________

Was the event serious? ☐ **Yes** ☐ **No**
If yes, please state the serious event criteria below:

Serious event criteria (tick all that apply):
☐ Death
☐ Life threatening
☐ Hospitalisation/prolonged existing hospitalisation
☐ Persistent/significant incapacity/disability
☐ Congenital anomaly/birth defect
☐ Medically important event

Status on the date of reporting or of death:
☐ Resolution
☐ Resolution with sequelae } Date of resolution: ____________
☐ Resolution ongoing
☐ Not resolved
☐ Unknown

Is there a reasonable possibility that the event may have been linked to a study medication? ☐ **Yes** ☐ **No**

If yes, please state the study medication:

____

Is there a reasonable possibility that the event may have been linked to a concomitant medication? ☐ **Yes** ☐ **No**

If yes, please state the concomitant medication:

____

Last step taken in response to the event(s); please state medication name:

Designation of the adverse event ____________

Date of onset: ____________

Was the event serious? ☐ **Yes** ☐ **No**
If yes, please state the criteria for seriousness below:

Serious event criteria (tick all that apply):
☐ Death
☐ Life threatening
☐ Hospitalisation/prolonged existing hospitalisation
☐ Persistent/significant incapacity/disability
☐ Congenital anomaly/birth defect
☐ Medically important event

Status on the date of reporting or of death:
☐ Resolution
☐ Resolution with sequelae } Date of resolution: ____________
☐ Resolution ongoing
☐ Not resolved
☐ Unknown

Is there a reasonable possibility that the event may have been linked to a study medication? ☐ **Yes** ☐ **No**

If yes, please state the study medication:

____

Is there a reasonable possibility that the event may have been linked to a concomitant medication? ☐ **Yes** ☐ **No**

If yes, please state the concomitant medication:

____

Last step taken in response to the event(s); please state medication name:

Study medication	***Concomitant medication***	***Study medication***	***Concomitant medication***
☐ Stopped (temporarily or permanently, or administration deferred)	☐ Stopped (temporarily or permanently, or administration deferred)	☐ Stopped (temporarily o permanently, o administration deferred)	☐ Stopped (temporarily or permanently, or administration deferred)
☐ Dose reduced	☐ Dose reduced	☐ Dose reduced	☐ Dose reduced
☐ Dose increased	☐ Dose increased	☐ Dose increased	☐ Dose increased
☐ No change to dose	☐ No change to dose	☐ No change to dose	☐ No change to dose
☐ Unknown	☐ Unknown	☐ Unknown	☐ Unknown
☐ None taken	☐ None taken	☐ None taken	☐ None taken
Did an AE/SAE develop again on reintroduction of the medication? ☐ Yes ☐ No ☐ Unknown ☐ Not applicable If yes, which medication?		Did an AE/SAE develop again on reintroduction of the medication? ☐ Yes ☐ No ☐ Unknown ☐ Not applicable If yes, which medication?	

Non-interventional study adverse events reporting form

For internal usage by Pfizer /Novartis	
Premises n°	Date of declaration

AE declaration number (*please state if known)*

PROTOCOL/STUDY NUMBER | **SITE NUMBER** | **PATIENT IDENTITY NUMBER**

Description of the event

State all information not given elsewhere on the form relating to the circumstances, chronology, diagnosis and treatment of the event(s). If more space is needed, use copies of this page.

Reporter's comments:			
Reporter:			- -
First name	Surname (*Please write in* BLOCK CAPITALS)		Date: DD-MM-YYYY
Address:	/		
Street	Town	Postcode	Country
Telephone:	Fax:	Email:	

Name of participating doctor: _____	**Signature of participating doctor/doctor's representative:**
Date participating doctor/representative became aware of the event: - - DD-MM-YYYY	
Send this form to Pfizer within 24 hours of becoming aware of the event or immediately in the event of death or a life-threatening SAE.	
INCLUDE ALL RELEVANT INFORMATION ON THE FORM. DO NOT ATTACH SOURCE DOCUMENTS.	