NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**A multi-center, prospective, non-interventional (NI) study of the safety and efficacy of sunitinib in Chinese patients with progressive advanced or metastatic well-differentiated unresectable pancreatic neuroendocrine tumors**
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Date of last version of protocol	**16 JUNE 2014**
Active substance	**L01XE04 Sunitinib malate**
Medicinal product	**SU011248 L-malate salt; Sunitinib malate**
Research question and objectives	**The NI study is designed and conducted to meet China Food and Drug Administration（CFDA） post-marketing commitments for collecting the data on safety and efficacy from every treated patient**
Author	*PPD* *PPD*

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CDD	Continuous daily dosing
CFDA	China Food and Drug Administration
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EDC	Electronic Data Collection
EDP	Exposure during pregnancy
FDA	US Food and Drug Administration
FLK1	VEGF Type 2 Receptor (fetal liver kinase 1)
GCP	Good Clinical Practices
GEP	Good Epidemiological Practice
GGT	Gamma-Glutamyl Transferase
GPP	Good Pharmacoepidemiology Practices
HFS	Hand foot syndrome
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition
NI	Non-Interventional
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall Survival
PD	Progressive Disease
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival

PPE	Palmoplantar erythrodysesthesia
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
TTP	Time to progression
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD , MD	PPD	PPD	PPD
PPD , MD, PhD	PPD	PPD	PPD

3. ABSTRACT

A multi-center, prospective, non-interventional (NI) study evaluating the safety and efficacy of China Food and Drug Administration (CFDA) approved sunitinib in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors.

Version of Protocol: Final Protocol Amendment 1.0

Date of Protocol: 17 September 2015

Main Author: *PPD*

- **Rationale and Background**

Pancreatic neuroendocrine tumors (NET) are rare malignancies with an incidence of approximately 2.5 to 5 cases per 100,000 per year.1 For patients with metastatic disease, the 5-year survival rate is low, and cure is generally not possible.

Pancreatic neuroendocrine tumors are highly vascular tumors. Investigation of angiogenesis inhibitors such as sunitinib and everolimus in patients with pancreatic NET is therefore of great interest. Results from a Phase 2 study of sunitinib (RTKC-0511-015) demonstrated activity, which was confirmed in a Phase 3 study (A6181111). Base on these results, sunitinib was approved for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors with clinical trial waiver by China Food and Drug Administration (CFDA) in Nov. 2012.

There is currently lack of systematic collection and analysis for the efficacy and safety data of sunitinib in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. The sunitinib non-interventional (NI) study is designed to collect data systematically and to assess the safety and efficacy in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. It is designed and conducted to meet CFDA post-marketing commitments. One of post marketing commitments was “Please carry out a post-marketing observational study on the indication in pancreatic Neuro-Endocrine Tumors. A detailed and strict protocol should be designed to collect the data on safety and efficacy from every patient. Data on survival rate should be collected for at least 5 years”.

- **Research Question and Objectives**

The sunitinib non-interventional (NI) study is a real world observational study which represents the usual and customary treatment of patients and being proposed to collect data systematically and to assess the safety and efficacy in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. Primary objective is to evaluate the safety profile of sunitinib in treating Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic

neuroendocrine tumors. Secondary objectives are to assess progression-free survival (PFS), overall survival (OS) and 5-year survival rate.

- **Study Design**

This study is a multi-center, prospective, non-interventional (NI) study evaluating the safety and efficacy of CFDA approved sunitinib in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. Approximately 100 adults with progressive advanced or metastatic well-differentiated unresectable pancreatic neuroendocrine tumors will be recruited in China hospitals. Each subject will be followed up overall survival (OS) time or the date of withdrawal and subjects who remain alive after study completion will have their OS time censored on the last date known to be alive. The dosage of sunitinib is based on individual safety and tolerability in daily clinical practice. Subjects will be treated until disease progress, unacceptable toxicity, withdrawal of subject consent or other withdrawal criteria are met. Subjects with evidence of disease progression may continue on treatment if judged to have clinical benefit. The NI study will capture observations that will be used for evaluating the safety profile of sunitinib, including: subject demographics, medical history and medications. Safety assessments, treatment data and any other laboratory examination results, which were done according to routine clinical practice, will be collected at all visits.

- **Population**

The Chinese adult with progressive advanced or metastatic well-differentiated unresectable pancreatic neuroendocrine tumors is the target population.

Principle Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

2. Subjects who will accept sunitinib therapy, or subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy, and are willing to follow up visits within current clinical practice.

3. Histologically or cytologically proven diagnosis of well-differentiated pancreatic neuroendocrine tumors (according to World Health Organization (WHO) 2000 classification).[2]

4. Unresectable (as assessed by the investigator) or metastatic disease documented on a scan.

5. Age ≥18 years.

Principle Exclusion Criteria:

1. Patients with poorly-differentiated pancreatic neuroendocrine tumors (according to WHO 2000 classification).[2]

- **Variables**

Baseline data include demographic data, medical history, medication history, physical examination, 12-lead Electrocardiogram (ECG), hematology and blood chemistry. If applicable, tumor imaging will also be collected. For the subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy, these key element baseline data will be collected prior to their sunitinib treatment after the subject or their legal representative has provided informed consent. For the subjects who haven't taken sunitinib and will accept sunitinib therapy, they (or a legally acceptable representative) sign on current Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent document.

During treatment period, data collection includes administration of sunitinib, physical examination, 12-lead ECG, hematology and blood chemistry. If applicable, the following will be collected: Multiple gated acquisition (MUGA) or Echocardiography (ECHO) for Left Ventricular Ejection Fraction (LVEF) assessment, thyroid function testing, urine protein assessment and tumor imaging. Safety data collected throughout the treatment period will consist of all Adverse Event (AE) and Serious Adverse Event (SAE) data. For the subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy, they (or a legally acceptable representative) sign on current Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent document on the day that they decide enrollment this study.

During the post-treatment follow-up visit, if applicable, the following will be collected: hematology, blood chemistry, thyroid function testing and physical examination within 28 days (+10 days) after the end of treatment or study withdrawal. The concomitant medications and treatments including antineoplastic therapies will be recorded. The outcome of adverse events with a date of onset during the study period should be reevaluated. All serious adverse events, and those non-serious adverse events assessed by the investigator as possibly related to study drug should continue to be followed even after subject withdrawal from study. These adverse events should be followed until they resolve or until the investigator assesses them to be "chronic" or "stable".

Survival follow-up includes progression free survival, PFS by clinical judgment and overall survival. All subjects will be followed for tumor progression (Computerized Tomography (CT)/Magnetic Resonance Imaging (MRI) or clinical judgment) and overall survival (OS) time or the date of withdrawal. Subjects who remain alive after study completion will have their OS time censored on the last date known to be alive.

- **Data sources**

This NI study data will be recorded by a physician/nurse in the medical records, through subject interview, and in the electronic Case Report Forms (CRF).

- **Study size**

The sample size for this study is not based on statistical considerations. Since the study is designed to observe the clinically relevant outcomes in patients treated in real world and based on discussion with potential investigators, it was decided to have a sample size of approximately 100 patients who would be enrolled over five years.

- **Data analysis**

The results of this study will be presented using descriptive statistics. The primary analysis will be performed on all subjects who receive at least one dose of sunitinib.

- **Milestones**

The planned dates for the start and end of subject data collection plus the planned dates for the annual submission report as well as the planned date for the Sutent pNET licence renewal submission to the China FDA.

Milestone	**Planned date**
Start of data collection	15 December 2014
End of data collection	30 November 2022
Study annual report 1	16 November 2015
Study annual report 2	16 November 2016
Study interim analysis report 1	15 March 2017
Study annual report 3	15 November 2017
Study annual report 4	15 November 2018
Study annual report 5	13 November 2019
Study annual report 6	13 November 2020
Study annual report 7	15 November 2021
Study interim analysis report 2	TBD, upon renewal approval date
Study annual report 8	17 November 2022
Final study report	17 August 2023

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	17 September 2015	Substantial amendment	Inclusion and Exclusion criteria , Endpoints, Baseline Data Colletcion,	Subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy can enroll this study. PFS is defined as the time from the start of sunitinib treatment to first document of objective tumor progression or death due to any cause, whichever occurs first.PFS by clinical judgment is defined as the time from the start of sunitinib treatment to first document of objective tumor progression, or first time tumor progression diagnosed by investigator based on clinical judgment, or death due to any cause, whichever occurs first.Overall Survival (OS) is defined as the time from the start of sunitinib treatment to documentation of death due to any cause.The baseline data must be performed prior to the start of sunitinib treatment.	Recruitment challenge for Pancreatic neuroendocrine tumors (NET) are rare disease

5. MILESTONES

The planned dates for the start and end of subject data collection plus the planned dates for the annual submission report as well as the planned date for the Sutent Pancreatic neuroendocrine tumors licence renewal submission to the China FDA.

Milestone	Planned date
Start of data collection	15 December 2014
End of data collection	30 November 2022
Study annual report 1	16 November 2015
Study annual report 2	16 November 2016
Study interim analysis report 1	15 March 2017
Study annual report 3	15 November 2017
Study annual report 4	15 November 2018
Study annual report 5	13 November 2019
Study annual report 6	13 November 2020
Study annual report 7	15 November 2021
Study interim analysis report 2	TBD, upon renewal approval date
Study annual report 8	17 November 2022
Final study report	17 August 2023

6. RATIONALE AND BACKGROUND

Pancreatic neuroendocrine tumors (NET) are rare malignancies with an incidence of approximately 2.5 to 5 cases per 100,000 per year.1 Because of the relatively indolent nature of this disease, the majority of patients are diagnosed with disseminated metastases. For patients with metastatic disease, the 5-year survival rate is low, and cure is generally not possible. Despite an often slow rate of tumor progression, patients with unresectable metastatic pancreatic NET ultimately develop significant morbidity.

Their indolent nature and resistance to traditional treatment modalities distinguish well-differentiated neuroendocrine tumors from poorly-differentiated carcinoma and small-cell carcinoma. These latter tumors pursue a far more aggressive clinical course, are often responsive to platinum-based chemotherapy regimens, and are characterized histologically by the presence of frequent mitoses and areas of necrosis. Because of biological differences between poorly-differentiated carcinoma and well-differentiated NET, treatment regimens and response to treatment for each differ.

Until recently, with the exception of surgery for localized disease, there was a lack of available therapies with meaningful, clinical benefit for well-differentiated pancreatic NET.3 Available treatment options for unresectable disease have included the use of somatostatin analogs, which may relieve symptoms related to hormonal hypersecretion, but there is little evidence to support a direct antitumor effect. The palliative benefit of interferon-α (IFN-α),

combination chemotherapy, radiotherapy, cryotherapy, and chemoembolization therapy has been questioned, given the resistance of these tumors to traditional treatment modalities and the associated toxicity of many of these treatments. Therefore, newer agents with novel mechanisms of action were desperately needed for the treatment of this disease.

Pancreatic neuroendocrine tumors are highly vascular tumors. A number of tumors, including pancreatic NET, aberrantly express both the vascular endothelial growth factor (VEGF) ligand and its Flk-1/KDR receptor (VEGF receptor), both of which play critical roles in tumor angiogenesis.4 The expression of VEGF up regulates intracellular anti-apoptotic proteins, facilitates tumor growth, and is associated with relatively short disease-free and overall survival. In addition to VEGF receptor, platelet-derived growth factor receptor (PDGFR) is also activated by phosphorylation in a number of tumor types and is also involved in tumor neoangiogenesis. Inhibition of angiogenesis would therefore be expected to result in growth inhibition and regression of these tumors. In one study performed in a mouse model, treatment with the angiogenesis inhibitors angiostatin and endostatin reduced the tumor burden of pancreatic NET by 60%.5 Investigation of angiogenesis inhibitors such as sunitinib and everolimus in patients with pancreatic NET is therefore of great interest.

Sunitinib malate is a small molecule that inhibits the tyrosine kinase enzymatic activities of the receptors for VEGF and Platelet-derived growth factor (PDGF) as well as the KIT, Fms-Related Tyrosine Kinase (FLT)3, and RET pathways. Because sunitinib inhibits receptors that may be important in the biology of pancreatic NET, the rationale for studying sunitinib in this indication was strong. CCI [redacted]

Sunitinib has been evaluated in subjects with pancreatic neuroendocrine tumors in two clinical trials, a pivotal Phase 3 double-blind placebo-controlled study (A6181111) and supportive Phase 2 open-label study with a pancreatic NET cohort (RTKC-0511-015).

Study RTKC-0511-015 was an open-label, single-arm, Simon's Minimax 2-stage, multi-center, Phase 2 clinical trial evaluating the activity and safety of single-agent sunitinib in subjects with NET (small cell carcinoma was excluded). Subjects were enrolled independently into 2 cohorts: subjects with carcinoid tumor and subjects with pancreatic NET. Sunitinib was administered at a starting dose of 50 mg once daily for 4 consecutive weeks followed by a 2-week off treatment period (Schedule 4/2). Subjects received study treatment until disease progression, unacceptable toxicity, or death.

Within the pancreatic NET cohort of subjects, 7 of 38 subjects (18%) enrolled in the first stage experienced a confirmed objective response. Enrollment was expanded to Stage 2, and a total of 66 subjects were treated: 11 (16.7%) experienced a confirmed objective response, 45 (68%) had best response of stable disease (SD), and 37 (56%) maintained SD for at least 6 months. Median time to progression (TTP) among subjects with pancreatic NET was 33.4 weeks.

Study A6181111 was a multinational, randomized, double-blind, Phase 3 study comparing the efficacy and safety of sunitinib versus placebo in subjects with progressive well-differentiated pancreatic NET. Subjects were required to have documented progression of disease within 1 year prior to the start of the study. Subjects were randomized in a 1:1 ratio to either sunitinib at a starting dose of 37.5 mg once daily on a continuous daily dosing (CDD) schedule, or matching placebo with best supportive care. Subjects remained in the study drug until progression of disease, unacceptable toxicity, or death.

The final analysis demonstrated a clear and clinically significant improvement in progression-free survival (PFS) in favor of sunitinib in subjects with progressive, advanced or metastatic, well-differentiated, unresectable pancreatic NET. A median PFS of 11.4 months was observed in the sunitinib arm, and a median PFS of 5.5 months was observed in the placebo arm, with a hazard ratio of 0.418 and p-value of 0.0001 as reported in the SmPC. The effect on PFS was maintained across all subsets analyzed, including demographics and baseline characteristics such as histology, disease burden, number of prior systemic regimens, performance status and time from diagnosis. In regards to subjects in the first-line setting, a median PFS of 11.4 months was observed in the sunitinib arm compared to 5.7 months in the placebo arm with a hazard ratio of 0.460 and p-value of 0.035. There were no confounding effects identified that would alter the interpretation of the improvement in PFS observed. Secondly, sunitinib treatment resulted in a clinically and statistically significantly increase in investigator-assessed objective response rate (ORR) compared with placebo (9.3% vs. 0%, respectively; 95% CI: 3.2 - 15.4; p=0.0066). Additionally, sunitinib treatment was associated with longer survival compared with placebo, with a hazard ratio for overall survival (OS) of 0.409 (95% CI: 0.187 - 0.894; p=0.0204; 30 OS events).

Overall, results of the pivotal Study A6181111 of sunitinib treatment of subjects with well-differentiated pancreatic NET demonstrated a clear and clinically significant improvement in the primary endpoint, PFS, with accompanying improvements in secondary ORR and OS endpoints, and supports findings from study RTKC-0511-015. Additionally, subgroup analysis of subjects treated in the first-line setting identified a similar treatment effect for sunitinib in this treatment setting, albeit based on a limited number of patients.

On 29 November 2010, the European Medicines Agency (EMA) approved sunitinib for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults; experience with SUTENT as first-line treatment is limited. On 20 May 2011, FDA approved sunitinib for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.

Results from a Phase 2 study of sunitinib demonstrated activity, which was confirmed in a Phase 3 study. Based on these results, sunitinib was approved for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors for clinical trial waiver by China Food and Drug Administration (CFDA) in Dec. 2012. There is currently lack of systematic collection and analysis for the efficacy and safety data of sunitinib in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. The sunitinib non-interventional (NI) study is being proposed to collect data systematically, assess and provide the safety and efficacy information on the use of sunitinib in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. It is designed and conducted to meet CFDA post-marketing commitments. One of post marketing commitments was "Please carry out a post-marketing observational study on the indication in pancreatic Neuro-Endocrine Tumors. A detailed and strict protocol should be designed to collect the data on safety and efficacy from every patient. Data on survival rate should be collected for at least 5 years".

7. RESEARCH QUESTION AND OBJECTIVES

The sunitinib non-interventional (NI) study is a real world observational study which represents the usual and customary treatment of patients and is being proposed to collect data systematically and to assess the safety and efficacy in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. Primary objective is to evaluate the safety profile of sunitinib in treating Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors. Secondary objectives are to assess progression-free survival (PFS), overall survival (OS) and 5-year survival rate.

8. RESEARCH METHODS

8.1. Study Design

This study is a multi-center, prospective, Non-interventional (NI) Study evaluating the safety and efficacy of CFDA approved sunitinib in Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors.

Approximately 100 adults with progressive advanced or metastatic well-differentiated unresectable pancreatic neuroendocrine tumors in China hospitals are the target population. Receipt of any previous systemic therapies is not an exclusion criteria. Each subject will be followed up overall survival (OS) time or the date of withdrawal and subjects who remain alive after study completion will have their OS time censored on the last date known to be alive. The dosage of sunitinib is based on individual safety and tolerability in daily clinical practice. Subjects will be treated until disease progress, unacceptable toxicity, withdrawal of subject consent, other withdrawal criteria are met. Subjects with evidence of disease progression may continue on treatment if judged to have clinical benefit. After discontinuation of treatment and mandated 28 day follow-up, subjects will be followed to collect information on further antineoplastic therapy and the time to death as appropriate or until the subjects withdraw their informed consents during the study period. Subjects who

remain alive after study completion will have their OS time censored on the last date known to be alive.

The NI study will capture observations that will be used for evaluating the safety profile of sunitinib, including: subject demographics, medical history and medications. Safety assessments, treatment data and any other laboratory examination results, which were done according to routine clinical practice, will be collected at all visits.

Concomitant medication will be recorded in the case report form.

8.1.1. Study Objectives and Endpoints

Primary Objective

- To evaluate the safety profile of CFDA approved sunitinib in treating Chinese patients with progressive, unresectable, advanced or metastatic well-differentiated, pancreatic neuroendocrine tumors.

Secondary Objectives

- To assess progression-free survival (PFS).
- To assess PFS by clinical judgment.
- To assess overall survival (OS).
- To estimate 5-year survival rate.

Primary Endpoints

Every observed and reported adverse event and all associated laboratory abnormalities, regardless of the causal relationship with the study drug, will be recorded as an adverse event in the CRF. At each visit, patients will be questioned with non-leading questions for example as follows:

"Have you had any health problem since the last visit?"

Assessment of adverse events and SAE data will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria [CTCAE] version 4, see ANNEX 2) and relatedness; and laboratory abnormalities.

Adverse events of particular interest are as follows:

- Infections;
- Cardiac and vascular;

- Skin and subcutaneous tissue;

  The most common skin and subcutaneous tissue related adverse events of interest are rash (includes erythematous, macular, or scaly rash), hand foot syndrome (HFS) or palmoplantar erythrodysesthesia (PPE), dry skin and skin discoloration

- Gastrointestinal;
- Psychiatric and nervous system;
- Musculoskeletal;
- Thyroid function;
- General disorders;
- Others;
- laboratory abnormalities:

  1. Haematologic: hemoglobin, platelet count, white blood cell count, neutrophile granulocyte count.

  2. Non Haematologic: total bilirubin, ALT (Alanine Transaminase), AST (Aspartate Transaminase), alkaline phosphatase, GGT (Gamma-Glutamyl Transferase), total protein, albumin, BUN (Blood Urea Nitrogen), creatinine, uric acid, glucose, hypocalcemia, hyponatremia, hypophosphatemia, hypokalemia.

Secondary Endpoints

Progression-Free Survival:

Investigator assessed PFS according to RECIST 1.1.6 PFS is defined as the time from the start of sunitinib treatment to first document of objective tumor progression or death due to any cause, whichever occurs first.

Progression-Free Survival by clinical judgment:

PFS by clinical judgment is defined as the time from the start of sunitinib treatment to first document of objective tumor progression, or first time tumor progression diagnosed by investigator based on clinical judgment, or death due to any cause, whichever occurs first.

Overall Survival Time:

Overall Survival (OS) is defined as the time from the start of sunitinib treatment to documentation of death due to any cause.

5-Year Survival Rate:

5-year survival rate is defined as the percentage of patients who stay alive till after 5 years from the start of sunitinib treatment.

8.2. Setting

8.2.1. Population

The Chinese adult (Age ≥18 years) who are diagnosed well-differentiated pNET by histologically or cytologically and unresectable (as assessed by the investigator) or metastatic pNET documented on a scan is the target population. This NI study plans to enroll these patients who are eligible and willing to participate in this study.

8.2.2. Duration of Subject Participation

The frequency of the NI study visits may be conducted following the local medical advice and it is usually once in 1 or 2 months. In the post-treatment follow-up visit, in the event a subject is unable to return to the clinic for the visit, telephone contact with the subject to assess adverse events and concomitant medications and treatments is expected and is to be conducted at least 28 calendar (+10 days). If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. All subjects who don't withdraw from the study will be followed for survival status (if permitted).

8.2.3. Definitions of Loss to Follow-up

The investigator should attempts to contact the subject. After three unsuccessful attempts to contact the subject on different dates, the subject should be considered lost to follow-up. All attempts should be documented in the Subject Summary CRF.

8.2.4. Definitions of Subject Withdrawal

Subject may be withdrawn from treatment in the case of:

- Subject lost to follow-up.
- Withdrawal of subject consent (cessation of follow-up).

8.2.5. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

Patient's eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

2. Subjects who will accept sunitinib therapy, or subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy, and are willing to follow up visits within current clinical practice.

3. Histologically or cytologically proven diagnosis of well-differentiated pancreatic neuroendocrine tumors (according to WHO 2000 classification).[2]

4. Unresectable (as assessed by the investigator) or metastatic disease documented on a scan.

5. Age ≥18 years.

8.2.6. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients with poorly-differentiated pancreatic neuroendocrine tumors (according to WHO 2000 classification).[2]

8.3. Variables

This study will collect and analyze the safety and efficacy data from approximately 100 eligible subjects from the time of first subject first visit to the time the study is closed. Since this is primarily an observational study, there are no patient visits specified by virtue of this protocol.

8.3.1. Baseline Data Collection (Day 0)

The baseline data must be performed prior to the start of sunitinib treatment :

- For the subjects who haven't taken sunitinib and will accept sunitinib therapy, they (or a legally acceptable representative) sign on current Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent document.

- Demographic data:

  - Date of birth, height, weight, race.

- Medical history:

  - Cancer history treatment, tumor Ki-67 index(assessment based on previous tumor biopsy results or previous surgical resections to be provided.), response to treatment, ongoing symptoms/events.

- Medication history:

- History of other disease processes (active or resolved), concomitant illnesses and treatments.

- Physical examination:
  - Examination of major body systems, such as general appearance, throat, neck, thyroid, lungs, heart, breasts, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological, others, ECOG performance status, body weight, height, and vital signs (eg, temperature, blood pressure, and heart rate).

- Hematology and blood chemistry (see ANNEX 3 for laboratory tests):
  - Haematologic: hemoglobin, platelet count, white blood cell count, neutrophile granulocyte count.
  - Blood chemistry: total bilirubin, ALT (Alanine Transaminase), AST (Aspartate Transaminase), alkaline phosphatase, GGT (Gamma-Glutamyl Transferase), total protein, albumin, BUN (Blood Urea Nitrogen), creatinine, uric acid, glucose, hypocalcemia, hyponatremia, hypophosphatemia, hypokalemia.

- 12-lead ECG.

- If applicable, tumor imaging should be performed as appropriate within current clinical practice:
  - CT scans/MRI of chest, abdomen, pelvis, brain and bone scan, in addition to any other applicable sites of disease.

For the subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy, these key element baseline data, such as demographic data, medical history, medication history, physical examination, 12 lead Electrocardiogram (ECG), hematology and blood chemistry, tumor imaging, will be collected prior to their sunitinib treatment after the subject or their legal representative has provided informed consent.

8.3.2. Treatment and Efficacy Data Collection (From First Dosage to Last Dosage of Sunitinib)

For the subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy, they (or a legally acceptable representative) sign on current Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent document on the day that they decide enrollment this study.

- Administration of sunitinib:
  - Dose reduction or escalation for any reason.

- Tumor imaging, if applicable:

- CT scans/MRI of chest, abdomen, pelvis, brain and bone scan, in addition to any other applicable sites of disease.

- Concomitant medications and treatments.

8.3.3. Safety Data Collection (From First Dosage to Last Dosage of Sunitinib)

- Physical examination:

  - examination of major body systems, such as general appearance, throat, neck, thyroid, lungs, heart, breasts, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological, others, ECOG performance status, body weight, height, and vital signs (eg, temperature, blood pressure, and heart rate).

- All AE and SAE data

  Data collection includes:

  1. Infections.
  2. Cardiac and vascular:
     - 12-lead ECG.
     - MUGA or ECHO for LVEF assessment (if applicable, within current clinical practice).
  3. Skin and subcutaneous tissue:
     - The most common skin and subcutaneous tissue related adverse events of interest are rash (includes erythematous, macular, or scaly rash), hand foot syndrome (HFS) or palmoplantar erythrodysesthesia (PPE), dry skin and skin discoloration.
  4. Gastrointestinal.
  5. Psychiatric and nervous system.
  6. Musculoskeletal.
  7. Thyroid function (if applicable, within current clinical practice):
     - Thyroid function testing (see ANNEX 3 for laboratory tests).
  8. General disorders.
  9. Others.

10. laboratory abnormalities:

- Haematologic: hemoglobin, platelet count, white blood cell count, neutrophile granulocyte count.

- Blood chemistry: total bilirubin, ALT (Alanine Transaminase), AST (Aspartate Transaminase), alkaline phosphatase, GGT (Gamma-Glutamyl Transferase), total protein, albumin, BUN (Blood Urea Nitrogen), creatinine, uric acid, glucose, hypocalcemia, hyponatremia, hypophosphatemia, hypokalemia. Urine protein assessment, if applicable (see ANNEX 3 for laboratory tests).

This data will be reported on the appropriate electronic CRF and Adverse Event Monitoring (AEM) forms during treatment with sunitinib.

For the subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy, these key element data, such as demographic data, medical history, medication history, physical examination, 12 lead Electrocardiogram (ECG), hematology and blood chemistry, tumor imaging, will be collected after their sunitinib treatment.

8.3.4. The Post-treatment Follow-up Visit Data Collection

- Physical Examination within 28 days (+10 days) after the end of treatment or study withdrawal, if applicable:

  - examination of major body systems (such as general appearance, throat, neck, thyroid, lungs, heart, breasts, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological, others), ECOG performance status, body weight, height, and vital signs (eg, temperature, blood pressure, and heart rate).

- Hematology, blood chemistry, thyroid function testing(see ANNEX 3 for laboratory tests) within 28 days (+10 days) after the end of treatment or study withdrawal, if applicable:

  - Haematologic: hemoglobin, platelet count, white blood cell count, neutrophile granulocyte count.

  - Blood chemistry: total bilirubin, ALT (Alanine Transaminase), AST (Aspartate Transaminase), alkaline phosphatase, GGT (Gamma-Glutamyl Transferase), total protein, albumin, BUN (Blood Urea Nitrogen), creatinine, uric acid, glucose, hypocalcemia, hyponatremia, hypophosphatemia, hypokalemia.

- Assessment of adverse events within 28 days (+10 days) after the end of treatment or study withdrawal.

- Recording of concomitant medications and treatments including antineoplastic therapies.

In the event a subject is unable to return to the clinic for the follow-up visit, telephone contact with the subject to assess adverse events and concomitant medications and treatments is expected. If laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at a local institution close to the subject is acceptable.

The outcome of adverse events with a date of onset during the study period should be reevaluated. All serious adverse events, and those non-serious adverse events assessed by the investigator as possibly related to study drug should continue to be followed even after subject withdrawal from study. These adverse events should be followed until they resolve or until the investigator assesses them to be "chronic" or "stable."

8.3.5. Survival Follow-up

Survival follow-up includes progression-free survival, PFS by clinical judgment and overall survival.

All subjects will be followed for tumor progression (CT/MRI or clinical judgment) and overall survival (OS) time or the date of withdrawal. Subjects who remain alive after study completion will have their OS time censored on the last date known to be alive.

8.4. Data Sources

This NI study data will be recorded by a physician/nurse in the medical records, through subject interview, and in the electronic Case Report Form (CRF).

8.5. Study Size

The sample size for this study is not based on statistical considerations. Since the study is designed to observe the clinically relevant outcomes in patients treated in real world and based on discussion with potential investigators that there are totally about 20 patients per year in their hospitals, it was decided to have a sample size of approximately 100 patients who would be enrolled over five years.

8.6. Data Management

Datalabs is the Electronic Data Collection (EDC) system for the study. Discrepancy management is used to identify and manage potential problems with study data. Datalabs generates discrepancies during data entry and discrepancy management whenever there is a missing or inconsistency between the data entered and the validation specifications. Datalabs identifies a problem and creates a discrepancy entry in the database.

The investigator is responsible to collect study data, including the eCRF data, laboratory data, via the EDC system in a timely manner and to ensure the integrity, accuracy, and completeness of the data.

The investigator should keep accurate records of: identity of all subjects (sufficient information to link the patients to the corresponding study data), serious adverse event forms, all related source documentation, details of treatment disposition, as well as relevant correspondence details (eg, letters, emails, meeting minutes, telephone call reports). The investigator record retention period should comply with the local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The results of this study will be presented using descriptive statistics. The primary analysis will be performed on all subjects who receive at least one dose of sunitinib.

Data will be collected in a standard format electronic CRF as described in the Study Procedures (see 8.3 Variables).

All analyses will be performed on all subjects who receive at least one dose of Sunitinib.

Primary safety outcomes include the frequency of adverse events and serious adverse events. Adverse events of particular interest are as follows:

- Infections and infestations.
- Cardiac and vascular.
- Skin and subcutaneous tissue:
    - The most common skin and subcutaneous tissue related adverse events of interest are rash (includes erythematous, macular, or scaly rash), hand foot syndrome (HFS) or palmo plantar erythrodysesthesia (PPE), dry skin and skin discoloration.
- Gastrointestinal.
- Psychiatric and nervous system.

- Musculoskeletal.
- Thyroid function.
- General disorders.
- Others.
- laboratory abnormalities:
    - Haematologic: hemoglobin, platelet count, white blood cell count, neutrophile granulocyte count.
    - Non Haematologic: total bilirubin, ALT (Alanine Transaminase), AST (Aspartate Transaminase), alkaline phosphatase, GGT (Gamma-Glutamyl Transferase), total protein,albumin, BUN (Blood Urea Nitrogen), creatinine, uric acid, glucose, hypocalcemia, hyponatremia, hypophosphatemia, hypokalemia.

Secondary efficacy endpoints are the progression-free survival time, progression-free survival by clinical judgment, overall survival time and 5-year survival rate.

Progression-Free Survival is defined as the time from the start of sunitinib treatment to first documentation of objective tumor progression or to death due to any cause, whichever occurs first. PFS data will be censored on the date of the last tumor assessment on study for subjects who do not have objective tumor progression and who do not die while on study.

Default start date is date of first treatment, if this date is not available, date of enrollment will be used.

Progression-free survival by clinical judgment is defined as the time from the start of sunitinib treatment to first document of objective tumor progression, or first time tumor progression diagnosed by investigator based on clinical judgment, or death due to any cause, whichever occurs first. PFS by clinical judgment data will be censored on the date of the last tumor assessment on study for subjects who do not have tumor progression (objective or based on clinical judgment) and who do not die while on study.

Subjects lacking an evaluation of tumor response after “start of sunitinib treatment will have their PFS and PFS by clinical judgment time censored on the date of “start of sunitinib treatment. Additionally, subjects who start a new anti-cancer therapy prior to Progressive Disease (PD) will be censored at the date of the last tumor assessment prior to the start of the new therapy.

Overall Survival (OS) is defined as the time from the start of sunitinib treatment to documentation of death due to any cause. Subjects who withdraw from study will have their OS time censored on the date of withdrawal, and subjects who remain alive after study completion will have their OS time censored on the last date known to be alive.

5-year survival rate is defined as the percentage of patients who stay alive till after 5 years from the start of sunitinib treatment.

For secondary efficacy time-to-event endpoints (PFS, PFS by clinical judgment and OS), the Kaplan-Meier method will be used to obtain the estimates of median event-free time. Confidence intervals for the 25^{th}, 50^{th} and 75^{th} percentiles of the event-free time will be reported based on the sign test (produced with "PROC LIFETEST" in SAS).

For 5-year survival rate, the estimate and 95% confidence interval will be calculated from the Greenwood method (produced with "PROC LIFETEST" in SAS).

Safety data will be tabulated and listed according to Pfizer's standard reporting algorithms. Medical Dictionary for Regulatory Activities (MedDRA) and WHO drug dictionary will be used.

Additional details of the analysis will be provided in the statistical analysis plan and/or the clinical study report. This information may include details of missing and, if applicable, unused and spurious data. Deviations from the statistical plan will be reported in the clinical study report.

8.8. Quality Control

During study conduct, Clinical Research Associates (CRAs) or study manager will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow CRAs or study manager monitors and appropriate regulatory authorities direct access to source documents to perform this verification.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

8.9. Limitations of the Research Methods

Due to the real world nature of this study, heterogeneity of clinical judgment and clinical practice may exist which may include but it not limited to the following: timing of imaging/laboratory testing, different measurement techniques/standards for judging tumor change.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where

required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

When subjects are permanently withdrawn from treatment, the primary reason for discontinuation must be provided. Reasons for discontinuation include:

- Death due to any cause.
- Unacceptable toxicity.
- Withdrawal of subject consent.
- Other reason.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Requirements

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.1.1. Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Sunitinib or the time of the patient's informed consent if s/he is already exposed to Sunitinib, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to sunitinib, the SAE also must be reported to Pfizer Safety.

10.1.2. Causality Assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to sunitinib, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that sunitinib caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether sunitinib caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that sunitinib did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

10.2. Definitions of Safety Events

10.2.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;

- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

10.2.2. Serious Adverse Events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.2.3. Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep).
- Administrative admission (eg, for yearly exam).
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).

- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

10.2.4. Scenarios Necessitating Reporting to Pfizer Safety within 24 Hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) sunitinib, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to sunitinib (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to sunitinib prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with sunitinib, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Sunitinib in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with

pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

For non-interventional studies conducted in pregnant women, data on the pregnancy outcome and non-serious AEs are expected to be collected and analyzed in the study database. In such instances, only EDPs associated with a SAE are to be reported.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm

while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

  - An identifiable reporter;

  - A suspect product;

  - The event medication error.

  Overdose, Misuse, Extravasation

  - Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

  Lack of Efficacy

  - Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

  Occupational Exposure

  - Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.3. Single Reference Safety Document

The Sutent® Local Product Label approved by CFDA will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Communication of Issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

Regarding requirement from China Clinical Drug Evaluation(CDE), study progress and interim analysis result will be reported as following timeline.

Items	**Planned date**
Study annual report 1	16 November 2015
Study annual report 2	16 November 2016
Study interim analysis report 1	15 March 2017
Study annual report 3	15 November 2017
Study annual report 4	15 November 2018
Study annual report 5	13 November 2019
Study annual report 6	13 November 2020
Study annual report 7	15 November 2021
Study interim analysis report 2	TBD, upon renewal approval date
Study annual report 8	17 November 2022

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13. LIST OF TABLES

None

14. LIST OF FIGURES

None

15. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

16. ANNEX 2. NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

Detail information of CTCTA 4.0 is described as below. Published: May 28, 2009 (v4.03: June 14, 2010):

http://ctep.cancer.gov/reporting/ctc.html

17. ANNEX 3. LABORATORY TESTS

	Conventional Units	Conversion Factor	SI Units
Hematology			
Hemoglobin (Hgb)	g/dL	x 10	g/L
Platelet count (Plt)	$10^3/mm^3$	x 10^9	10^{12}/L
White blood cell	$10^3/mm^3$	x 10^6	10^9/L
Neutrophils (absolute)	$10^3/mm^3$	x 10^6	10^9/L
Lymphocytes (absolute)	$10^3/mm^3$	x 10^6	10^9/L
Chemistry			
Total bilirubin	mg/dL	x 17.1	µmol/L
Alanine transaminase (ALT)	U/L	N/A	U/L
Aspartate transaminase (AST)	U/L	N/A	U/L
Gamma-glutamyl transferase (GGT)	U/L	N/A	U/L
Alkaline phosphatase	U/L	N/A	U/L
Total protein	g/dL	x 10	g/L
Albumin	g/dL	x 10	g/L
Sodium	MEq/L	x 1.0	mmol/L
Potassium	MEq/L	x 1.0	mmol/L
Chloride	MEq/L	x 1.0	mmol/L
Calcium	mg/dL	x 0.25	mmol/L
Creatinine	mg/dL	x 88.4	µmol/L
Phosphorus	mg/dL	x 0.323	mmol/L
Uric acid	mg/dL	x 0.059	mmol/L
Blood urea nitrogen (BUN)/Urea	mg/dL	x 0.357	mmol/L
Creatinine	mg/dL	x 88.4	mol/L
Glucose	mg/dL	x 0.055	mmol/L
Thyroid function Tests			
Serum Thyrotropin (TSH)	µU/mL		
Free Triiodothyronine (T3)	pg/dL		
Free Thyroxine (T4)	ng/dL		