Protocol A6181215

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

Statistical Analysis Plan (SAP)

Version: 3.0

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Document	Version Date	Summary of Changes
Version 3	29 May 2018	• Changed from "Not applicable" to "Protocol deviations (minor/major) will be" in Section 5.6 on Page 8. • Added censoring rule for patients with documentation of a PFS event after an unacceptably long interval in Section 6.1.1 on Page 8. • Changed the window of censorship for patients died with no on-study disease assessments from "prior to the first planned assessment" to "within 17 weeks post first dose" in Section 6.1.1 on Page 8 and in Section 6.1.2 on Page 9. • Added definition for adequate baseline in Section 6.1.1 on Page 8. • Added censoring rule for patients with documentation of a PFS by clinical judgment event after an unacceptably long interval in Section 6.1.2 on Page 9. • Remove "Patients with inadequate baseline disease assessment are censored at the start date" in Section 6.1.2 on Page 9. • Added "Sensitivity analyses will be conducted for efficacy endpoints by excluding patients with major protocol deviations" in Section 8.2.2 on Page 11.
Version 2	08 June 2016	• Changed from "Eligible subjects…" to "*The dosage of sunitinib…"* in Section 2.1 on Page 5. • Added the "Variables" information from the study Protocol to the Section 2.1 on Page 5-6. • Defined the "default start date" on Page 7. • Deleted the duplicated definitions of "default start date" in Sections 6.1.1, 6.1.2, 6.1.3 and 6.1.4 on Page 7. • Added "All analyses…."in Section 8.1 on Page 10.

		• Deleted "see the list in Section 5.2" on Page 11.
Version 1	16 June 2014	Finalized

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicised***.

Pancreatic neuroendocrine tumors (NET) are rare malignancies with an incidence of approximately 2.5 to 5 cases per 100,000 per year. 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".

2.1. 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 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.

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.

2.2. Study 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

- *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.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Two interim analyses are planned to deliver interim reports to CDE before 15 Mar 2017 and some day in year 2022 for license renewal. The interim analyses will include all the data and analyses that will be reported in the final analysis.

Final analysis will be conducted after the official database is released.

Unblinding is not applicable for this study as it is a non-interventional single arm study, and no DMC is needed.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

This study is non-comparative and no inferential statistical analyses are planned. Analyses will consist of descriptive statistics and corresponding 95% 2-sided confidence intervals when appropriate.

4.2. Statistical Decision Rules

There are no statistical decision rules.

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set (FAS) will be defined as all patients who receive at least one dose of study drug during the study. All efficacy analyses will be performed using the FAS.

5.2. 'Per Protocol' Analysis Set

Not applicable.

5.3. Safety Analysis Set

The safety population will be defined as all enrolled patients who take at least one dose of the study drug; all summaries of safety will be reported within the safety analysis set. The safety analysis set is the same as full analysis set in this study.

5.4. Other Analysis Sets

Not applicable.

5.5. Treatment Misallocations

Not applicable.

5.6. Protocol Deviations

Protocol deviations (minor/major) will be compiled prior to database closure and will be listed for the FAS.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

All efficacy endpoints are secondary endpoints in this study. Default start date is date of first treatment during the study, if the date is not available, date of enrollment will be used.

6.1.1. Progression-Free Survival

Investigator assessed PFS according to RECIST 1.1. PFS is defined as the time from start date *to first document of objective tumor progression or death due to any cause, whichever occurs first.* PFS (in months) will be calculated as (first event date −– start date +1)/30.44.

PFS data will be censored on the date of the last objective *tumor assessment on study for subjects who do not have objective tumor progression and who do not die while on study.* Patients with documentation of a PFS event after an unacceptably long interval (>17 weeks) since the previous objective disease assessment will be censored at the date of the previous assessment. Patients with no on-study objective disease assessments are censored at the start date unless death occurred within 17 weeks post first dose (in which case the death is an event). Patients with inadequate baseline disease assessment are censored at the start date. Adequate baseline is defined using the following criteria:

- Subjects with target lesions: All target lesions had measurement(s) within the baseline window (200 days) and measurable.

- Subjects with non-target lesions only: All non-target lesions had non missing assessments(s) and at least one of the non-target lesions assessed as non-indeterminate within the baseline window (200 days).

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.

6.1.2. Progression-Free Survival by Clinical Judgment

PFS by clinical judgment is defined as the time from start date *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 (in months) will be calculated as (first event date − start date +1)/30.44.

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. Patients with documentation of a PFS by clinical judgment event after an unacceptably long interval (>17 weeks) since the previous disease assessment (objective or based on clinical judgment) will be censored at the date of the previous assessment. Patients with no on-study disease assessments (objective or based on clinical judgment) are censored at the start date unless death occurred within 17 weeks post first dose (in which case the death is an event). *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.*

6.1.3. Overall Survival Time

Overall Survival (OS) is defined as the time from start date *to documentation of death due to any cause.* OS (in months) is calculated as (date of death − start date +1)/30.44.

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.

6.1.4. 5-Year Survival Rate:

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

5-year survival rate will use the same censoring rule as OS.

6.2. Safety Endpoints

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.*

6.3. Other Endpoints

Not applicable.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

Missing data will not be imputed. Subjects with missing value for a given efficacy variable will not contribute to the analysis of that variable.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

This section gives a general overview of the statistical methodology for the efficacy and safety endpoints.

The results of this study will be presented using descriptive statistics.

All analyses will be performed on (a) all FAS subjects who receive at least one dose of Sunitinib, (b) FAS subjects who have not taken sunitinib within the past 6 months (26 weeks) and will accept sunitinib therapy, and (c) FAS subjects who have already taken sunitinib within the past 6 months (26 weeks) and will continue sunitinib therapy.

All analyses will be based on the data collected during the study.

8.1.1. Analyses for Continuous Data

Descriptive summary statistics for continuous variables will include the following: sample size, mean, median, standard deviation, minimum and maximum.

8.1.2. Analyses for Time-To-Event Data

*For time-to-event endpoints, the Kaplan-Meier method will be used to obtain the estimates of median event-free time. Confidence intervals for the 25th, 50th and 75th percentiles of the event-free time will be reported based on the sign test (*Brookmeyer and Crowley 1982, *produced with "PROC LIFETEST" in SAS).* Some time-to-event endpoints will be displayed graphically when appropriate.

8.1.3. Analyses for Categorical and Binary Data

Descriptive statistics for categorical and binary variables will be given as counts and percentages. For proportions with a 95% confidence interval (CI) specified, the CI will be 2-sided with an alpha level of 0.05 using the exact method (Clopper-Pearson interval).

8.2. Statistical Analyses

8.2.1. Analysis of Primary Safety Endpoints

Safety endpoints will be summarized for the safety analysis set.

Safety data, such as AEs, vital signs, ECOG status, laboratory data, physical examination etc., *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.* The severity of all AEs will be coded using NCI CTCAE Version 4.0.

For the adverse events of particular interest, 95% CI will be presented using the exact method (Clopper-Pearson interval).

8.2.2. Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints will be summarized for the FAS.

*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 25th, 50th and 75th percentiles of the event-free time will be reported based on the sign test (*Brookmeyer and Crowley 1982, *produced with "PROC LIFETEST" in SAS).* Some time-to-event endpoints will be displayed graphically when appropriate. Sensitivity analyses will be conducted for efficacy endpoints by excluding patients with major protocol deviations.

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

9. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Derivation of PFS by Clinical Judgment

The following is the IOTA CRF page:

INVESTIGATOR OVERALL OBJECTIVE TUMOR ASSESSMENT - RECIST (VERSION 1.1) IOTA003

☐ (1) NOT DONE

Date of Tumor Assessment (dd-MMM-yyyy): ___ - ____ - ____

Tumor Assessment

Target Lesions (check (X) ONE only):

☐ (0) No Target Lesion At Baseline

☐ (1) Complete Response ☐ (2) Partial Response ☐ (3) Stable Disease

☐ (4) Progressive Disease ☐ (5) Not Assessed ☐ (6) Indeterminate

Non Target Lesions (check (X) ONE only):

☐ (0) No Non-Target Lesion At Baseline

☐ (1) Complete Response ☐ (3) Progressive Disease ☐ (4) Not Assessed

☐ (5) Indeterminate ☐ (6) No Complete Response/No Progressive Disease

New Lesion:

☐ (1) Yes

☐ (2) No

Overall (check (X) ONE only):

☐ (1) Complete Response ☐ (2) Partial Response ☐ (3) Stable Disease

☐ (4) Progressive Disease ☐ (5) Not Assessed ☐ (6) Indeterminate

VARIABLE INFORMATION:

OPTIONAL INFORMATION:

DESIGN GUIDELINE: This page should not be used for RECIST 1.0 assessments.

This DCM should be deployed at post-baseline/screening assessments.

Place the IOTA page in a CPE separate from the general cycle information. If the tumor assessment schedule is based on weeks from randomization, use weeks in the CPE label. If the tumor assessment schedule is based on cycles, cycle may be used in the label, but it should be placed in its own CPE.

On the IOTA page, if "Not Assessed" is checked for both Target Lesions and Non Target Lesions, no option is checked for New Lesion, and "Progressive Disease" is checked for Overall, then tumor progression diagnosed by investigator based on clinical judgment is reached on the Date of Tumor Assessment.