



Protocol A6181196

A PHASE I/II STUDY OF SUNITINIB IN YOUNG PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR

Statistical Analysis Plan (SAP)

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Protocol A6181196 Statistical Analysis Plan - Version 1.0 Final

CONTENTS

| | |
|---|---|
| 1. AMENDMENTS FROM PREVIOUS VERSION | 3 |
| 2. INTRODUCTION | 3 |
| 2.1. Study Design | 3 |
| 2.2. Study Objectives | 3 |
| 3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING..... | 4 |
| 4. STATISTICAL HYPOTHESES..... | 4 |
| 5. ANALYSIS SETS | 4 |
| 5.1. Full Analysis Population | 4 |
| 5.2. Per Protocol Population..... | 4 |
| 5.3. Pharmacokinetic population..... | 4 |
| 5.4. Protocol Deviations | 4 |
| 6. ENDPOINTS | 5 |
| 6.1. PRIMARY ENDPOINT..... | 5 |
| 6.2. Secondary ENDPOINTS..... | 5 |
| 7. COVARIATES AND STRATIFICATION FACTORS..... | 5 |
| 7.1. Covariates..... | 5 |
| 7.2. Stratification Factors | 5 |
| 8. HANDLING OF MISSING VALUES | 5 |
| 9. STATISTICAL METHODOLOGY AND STATISTCAL ANALYSES..... | 6 |
| 9.1. Statistical METHODS AND ANALYSES | 6 |
| 9.1.1. Analysis of Primary Endpoint | 6 |
| 9.1.2. Analysis of Efficacy Endpoints | 6 |
| 9.1.2.1. Objective Response Rate..... | 6 |
| 9.1.2.2. Progression-Free Survival..... | 6 |
| 9.1.2.3. Duration of Response..... | 7 |
| 9.1.2.4. Overall Survival | 7 |
| 9.1.3. Analysis of Safety Endpoints..... | 7 |
| 9.1.3.1. Analysis of Adverse Events | 7 |
| 9.1.3.2. Analysis of Clinical Labs | 8 |
| 9.1.3.3. Concomitant Medications | 9 |
| 9.1.3.4. Vital Signs | 9 |
| 9.1.3.5. Electrocardiograms (ECGs) | 9 |
| 9.1.4. Analysis of Other Endpoints..... | 9 |

1. AMENDMENTS FROM PREVIOUS VERSION

- N/A at this time

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol A6181196 dated 17 June 2011. This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

2.1. Study Design

This study is a single arm, multi-center, multi-national, Phase I/II trial evaluating the PK, safety and preliminary anti-tumor efficacy of sunitinib in chemotherapy-naïve children and young adults diagnosed with metastatic, unresectable (without major morbidity) or recurrent GIST. The study aims to enroll 15 evaluable children aged 6 years to less than 18 years. In addition, up to 15 young adults aged 18 years to less than 21 years may be enrolled. The starting dose of sunitinib in children will be 15 mg/m²/day for 4 weeks followed by 2 weeks with no study drug, the MTD established during the pediatric Phase 1 clinical trial conducted by the Children's Oncology Group. Inpatient dose escalation of sunitinib will be allowed, based on tolerability. Investigators will have the option to access real time PK results to aid in dosing decisions. Sunitinib dosing for the young adults will follow approved guidelines (per current USPI and SmPC). Study treatment for all patients may continue for up to 18 cycles, equaling approximately 2 years of therapy.

2.2. Study Objectives

Primary

- To characterize the plasma PK profile of sunitinib and its active metabolite SU012662 in children and young adults with advanced (defined as unresectable without major morbidity, metastatic or recurrent) GIST.

Secondary:

- To investigate whether doses greater than the established pediatric MTD are tolerated in chemotherapy-naïve pediatric patients with GIST;
- To investigate the safety and tolerability of sunitinib in children and young adults with GIST;
- To investigate the anti-tumor activity of sunitinib in children and young adults with GIST;

Protocol A6181196 Statistical Analysis Plan - Version 1.0 Final

- To explore PK-pharmacodynamic relationships with respect to safety and efficacy in children and young adults with GIST.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned in this study.

4. STATISTICAL HYPOTHESES

The primary objective of this study is to characterize the plasma PK profile of sunitinib and its active metabolite SU012662 in children and young adults with advanced (defined as unresectable without major morbidity, metastatic or recurrent) GIST. Assuming the coefficient of variation of sunitinib clearance among pediatric patients is approximately 35%, with 15 patients, we will be able to detect 35% margin of error in sunitinib oral clearance (CL/F) with 95% confidence and 80% power. Furthermore, assuming the coefficient of variation of sunitinib clearance among young adult patients is also ~35%, a total of 30 patients will allow us to detect 25% margin of error with 95% confidence and 80% power.

5. ANALYSIS SETS

5.1. Full Analysis Population

The full analysis (or intent-to-treat) population will include all enrolled patients regardless of what treatment, if any, was received. The efficacy analysis will be based on the full analysis population.

5.2. Per Protocol Population

The per protocol (or as-treated) population will include all enrolled patients who receive at least one dose of study drug. The safety analysis will be based on per protocol population.

5.3. Pharmacokinetic population

The pharmacokinetic (PK) population will include all treated patients with at least one PK observation. The pharmacokinetic analysis will be based on pharmacokinetic population.

5.4. Protocol Deviations

Changes to the procedures that may impact the quality of the data will be considered significant protocol deviations. These changes would include any circumstances that would alter the evaluation of the pharmacokinetics, safety or efficacy of the study. Examples include but may not be limited to, violations to the inclusion/exclusion criteria, non-compliance to study drug administration, and incomplete tumor assessments.

Protocol A6181196 Statistical Analysis Plan - Version 1.0 Final

In the case of a significant protocol deviation, the situation will be evaluated on a case-by-case basis and data collected during the affected treatment period may be excluded from the analysis.

6. ENDPOINTS

6.1. PRIMARY ENDPOINT

- Pharmacokinetic parameters of sunitinib and its main active metabolite (SU012662) including total plasma exposure (AUC_{24}) and oral clearance (CL/F).

6.2. Secondary ENDPOINTS

- Type, incidence, severity (graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0 [v4.0]), timing, seriousness, and relatedness of adverse events and laboratory abnormalities;
- Objective response rate, duration of response, PFS and OS at 2 years after study enrollment;
- Pharmacokinetic-pharmacodynamic relationships with respect to safety and efficacy in pediatric GIST.

7. COVARIATES AND STRATIFICATION FACTORS

7.1. Covariates

The potential influence of baseline patient characteristics such as age, gender, ethnicity, and tumor characteristics (including *KIT* genotype, etc.) on primary and secondary endpoints may be evaluated if necessary.

7.2. Stratification Factors

None.

8. HANDLING OF MISSING VALUES

Pharmacokinetic and safety endpoints will not be imputed for missing data. For efficacy endpoints, non-event observations will be censored according to the censoring rules specified in Section 9.

Missing Dates: In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to Day one date). In this case, the date resulting in 0 time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration).

9. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

Statistical analysis and data presentation will be performed on the subgroups of patients aged 6 years to less than 18 years, and patients aged 18 years to less than 21 years, respectively. A pooled data analysis including all the patients enrolled in the study will also be performed. Also, analysis of time-to-event efficacy endpoints will be performed only if sufficient number of events permit meaningful estimates.

9.1. Statistical METHODS AND ANALYSES

9.1.1. Analysis of Primary Endpoint

Descriptive statistics for observed and dose-corrected (where appropriate) PK data will be reported for all patients with at least one PK observation by presenting the population size, arithmetic mean, standard deviation, percent coefficient of variation (CV%), median, minimum, maximum values. In addition, geometric mean and the 95% CI for the geometric mean will be reported where appropriate.

The key PK parameters in pediatric patients will be compared to adult patients with GIST based on historical data. The formal comparison will be carried out as part of the NONMEM portion using the historical PK data in adult GIST patients.

9.1.2. Analysis of Efficacy Endpoints

9.1.2.1. Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with a confirmed complete (CR) or partial response (PR) relative to the number of patients in the treatment group according to RECIST criteria (Version 1.1). The number and percent of patients achieving objective response (CR or PR) will be summarized along with the corresponding exact 2-sided 95% CI calculated using a method based on the F distribution.

9.1.2.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the date of enrollment to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurs first. PFS data will be censored on the day following the date of the last

Protocol A6181196 Statistical Analysis Plan - Version 1.0 Final

tumor assessment documenting absence of progressive disease for patients who 1) are given anti-tumor treatment other than the study treatment prior to observing objective tumor progression; 2) are removed from the study prior to documentation of objective tumor progression; 3) are ongoing at the time of the analysis.

Patients who do not have any post-baseline tumor assessments will have their PFS endpoint censored on the date of enrollment. Death or disease progression that occurs after more than one missed visit will be censored on the day following the date of the last tumor assessment as well.

PFS will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. Median PFS and its corresponding 2-sided 95% CI for the median will be provided.

9.1.2.3. Duration of Response

Duration of response (DR) is defined as the time from the first objective documentation of complete or partial response that is subsequently confirmed to the first documentation of disease progression or to death due to any cause, whichever occurs first. DR will be calculated for the subgroup of patients with objective disease response. DR will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 2-sided 95% CI for the median will be provided if appropriate. The number of patients experiencing CR and PR may be small and thereby limit the use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics or listings will be provided.

9.1.2.4. Overall Survival

Overall survival (OS) is defined as the time from enrollment to the date of death due to any cause. OS data will be censored on the day following the date of the last contact at which the patient is known to be alive. OS will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median survival time and 2-sided 95% CI for the median will be estimated.

The 2-year survival probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI will be constructed for the 2-year survival probability.

9.1.3. Analysis of Safety Endpoints

The per protocol population will be the analysis population for evaluating safety endpoints.

9.1.3.1. Analysis of Adverse Events

All AEs reported during the AE reporting period will be considered as treatment-emergent AEs, unless present at baseline with the same severity grade. All AEs will be coded by system organ class (SOC) and preferred term using MedDRA. The severity of all AEs will be coded by the investigator using NCI CTCAE Version 4.0.

Protocol A6181196 Statistical Analysis Plan - Version 1.0 Final

An overall summary of AEs will be provided. The number and percentage of patients who experienced any AE, who experienced any serious adverse event (SAE), who experienced any treatment-related AE, who experienced any treatment-related SAE, and who discontinued because of an AE will be presented. Treatment-related AEs are those judged by the investigator to be at least possibly related to the study drug (with a cause related to the study drug indicated on the CRF).

All AEs will be summarized by MedDRA SOC and preferred term. A summary of AEs by preferred term and maximum CTCAE grade will also be presented.

Treatment-related AEs will be summarized by MedDRA SOC and preferred term. A summary of treatment-related AEs by preferred term and maximum CTCAE grade will also be presented.

Deaths will be summarized by time period (on-study vs. during follow-up) and cause of death. Deaths that occurred within 28 days after the last dose of study medication are defined as on-study deaths. Death data will also be listed.

Patients who withdraw from study treatment because of an AE will be listed. Patient discontinuation will be determined from the end of study (EOS) evaluation (where reason for termination is "Adverse Event") and the specific AE(s) will be determined from the AE CRF page (where action taken is "Permanently Discontinued").

SAEs and treatment-related SAEs will be summarized by MedDRA SOC and preferred term. Patients who experienced a SAE will be listed.

Individual patient listings will be prepared for all AE data.

9.1.3.2. Analysis of Clinical Labs

Hematology and blood chemistry data will be graded according to NCI CTCAE version 4.0 severity grade if applicable. The frequencies of the worst severity grade observed will be displayed for each parameter. Summary tables of laboratory results by maximum CTC grade and shift tables of laboratory results from baseline by maximum CTC grade will be presented. Baseline is defined as the last evaluation prior to the first dose of study drug. For those hematology and blood chemistry tests that do not have CTC grades, summary tables of the laboratory results using flags (high/low) will be presented.

Listing tables will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment.

9.1.3.3. Concomitant Medications

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary; patients who received concomitant medications will be listed.

9.1.3.4. Vital Signs

Vital signs data will be summarized and presented by treatment group. Data will be summarized and presented according to the following categories:

| | |
|------------------|--|
| Pulse Rate | >120 bpm or <50 bpm Change from baseline (increase or decrease) of ≥ 30 bpm |
| Blood Pressure | Systolic BP >150 mmHg / Diastolic BP >100, or Systolic BP >200 mmHg / Diastolic BP >110 Change from baseline (increase) in SBP of ≥ 20 , ≥ 40 , or ≥ 60 mmHg Change from baseline in DBP (increase) of ≥ 10 , ≥ 20 , or ≥ 30 mmHg |
| Respiration Rate | >40/min or <8/min |
| Temperature | >38.3 °C (101 °F) Increase from baseline of $\geq 1.1^{\circ}\text{C}$ ($\geq 2^{\circ}\text{F}$) – if the baseline temperature is $>36.8^{\circ}\text{C}$ (98.2°F) |
| Body Weight | Percent change from baseline (increase or decrease) of $\geq 5\%$ |

9.1.3.5. Electrocardiograms (ECGs)

Triplicate, 12-lead ECGs are performed at Screening, Day 1 of Cycle 2, and at the end of treatment. At each time point, triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data.

Individual patient ECG data listings will be generated. Changes from baseline in corrected QT (QTc) interval will be calculated to describe and display the frequency of patients who experienced QTc interval prolongation, displayed by category according to CTCAE v4.0 grades. QT intervals will be corrected for heart rate using cube root (Fredericia's) conversion.

9.1.4. Analysis of Other Endpoints

Descriptive statistics will be used to summarize study conduct and patient disposition, baseline characteristics, and treatment administration/compliance.

Protocol A6181196 Statistical Analysis Plan - Version 1.0 Final

Study Conduct and Patient Disposition - An accounting of the study patients will be tabulated. Patients not meeting the eligibility criteria and/or who deviate from the protocol will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized. The full analysis population will be used for the summarization of study conduct and patient disposition.

Baseline Characteristics - Demographic characteristics such as patient age, gender, height, weight, ethnicity, prior therapy, medical history, tumor history, Lansky/ECOG performance status and signs and symptoms will be tabulated. The full analysis population will be used for the analysis of baseline characteristics.

Treatment Administration/Compliance - Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose adjustments, dose interruptions, and reasons for the deviations from planned therapy. The per protocol population will be used for the summarization of treatment administration and compliance.

Tumor Genetic Testing Data – Results of tumor genetic testing will be presented descriptively without formal statistical testing.

PET analysis – Results of PET scans will be described but no formal statistical testing will be conducted.