# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

## NDA 21-938 (GIST)
## NDA 21-968(MRCC)

# Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# Statistical Review and Evaluation

CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 21-938 / N000 |
| **Drug Name:** | Sutent (sunitinib) |
| **Indication(s):** | Patients with imatinib mesylate-resistant or intolerant malignant Gastrointestinal Stronak Tumor (GIST) |
| **Applicant:** | Pfizer |
| **Date(s):** | Submission Date: August 11, 2005<br>PDUFA Date: February 11, 2006 |
| **Review Priority:** | Priority. |
| **Biometrics Division:** | Division of Biometrics I (HFD-710) |
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| **Medical Division:** | Division of Oncology Drug Product (HFD-150) |
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**Keywords:** Superiority, log-rank test.

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# 1 EXECUTIVE SUMMARY

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion, the results from the study A6181004 support the sponsor's claim of treating with SUTENT (SU011248) combined with best supportive care for GIST patients with resistant to or intolerant of imatinib Mesylate statistically significantly prolonging time to progression (TTP) comparing to the treatment with placebo plus best supportive care. There were also clinically and statistically significant improvements in progression free survival (PFS) by treating with SU011248. The study A6181004 was a randomized, double-blind, multi-center, phase III study evaluating the efficacy and safety of single-agent SU011248 in patients with imatinib mesylate-resistant or intolerant malignant GIST. This study randomized 312 patients with ratio 2:1 to SU011248 treatment, 50 mg or matching placebo. Both treatment groups received best supportive care. The results presented are based on the second interim analysis (first interim analysis for efficacy) with 149 TTP events based on the central radiologist assessment and about maximum of 1 year duration of treatment and follow-up. It may need adequate treatment and follow-up time to allow data mature to show the overall survival benefit of SUTENT.

## 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA submission, efficacy data were collected by the sponsor from the trial: A6181004. This study was a randomized, double-blind, multi-center, Phase 3 study of SUTENT (SU011248) verse placebo in patients with GIST who had experienced disease progression on or intolerance of imatinib mesylate therapy. This study was conducted at 56 centers, which most centers were in the United States, Australia and other 9 countries in Europe, North America and Asia. The primary objective of this study was to compare the time to tumor progression (TTP) associated with SU011248 plus best supportive care (Arm A) versus that associated with placebo plus best supportive care (Arm B) for the treatment of patients with imatinib mesylate-resistant or intolerant malignant GIST.

A total of 312 patients were randomized as of the data cutoff date (1 January 2005) for this report and comprised of ITT population; 207 patients (66%) were randomized to SU011248 and 105 (34%) were randomized to placebo. At the time of this interim report, 168 patients (134 vs. 34 patients in SU011248 group vs. Placebo group) were ongoing in double-blind treatment, 78 patients (19 vs. 59 patients in SU011248 group vs. Placebo group) had crossed over to open-label treatment, and 56 patients died in both treatment groups, 29 (14% of 207 randomized patients) vs. 27 patients (26% of 105 randomized patients) in SU011248 and Placebo group, respectively.

Study A6181004 included patients with malignant GIST who had experienced objectively confirmed disease progression on prior imatinib mesylate therapy or who were intolerant of imatinib mesylate were eligible if they were at least 18 years of age, had adequate organ function, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. This

study randomized patients with ratio 2:1 to SU011248 treatment, 50 mg or matching placebo. Both treatment groups received best supportive care. Per sponsor, the 2:1 randomization was used to minimize the number of patients treated with placebo.

Per protocol, death due to cancer was included as a TTP event. Having an agreement with FDA, the definition of TTP was revised in this NDA submission. According to the revised definition of TTP, TTP for death due to cancer was censored at the time of last tumor evaluation demonstrating lack of progression prior to death. The definition of TTP through this statistical review refers to the revised definition of TTP unless further notice. The sponsor concluded that at a starting dose of 50 mg daily for 4 weeks in repeated 6-week cycles, SU011248 combined with best supportive care resulted in statistically and clinically significant improvement in the primary endpoint time to progression (TTP) (27.3 vs. 6.4 weeks; $p<0.0001$) compared with placebo plus best supportive care; there were also clinically and statistically significant improvements in progression free survival (PFS).

## 1.3 STATISTICAL ISSUES AND FINDINGS

In this NDA, Study A6181004 was the randomized, placebo-control phase III study conducted to establish efficacy of SU011248. A total of 312 patients were randomized at the ratio 2:1 to this study at the data cutoff date for this interim analysis. Of those, 207 patients were randomized to the SU011248 and 105 were randomized to placebo. The primary efficacy endpoint was time to progression (TTP). The sponsor clams the efficacy analyses of SU011248 indicate a highly clinically meaningful, statistically significant, and robust improvement in the primary endpoint time to progression (TTP) for SU011248 combined with best supportive care compared with placebo plus best supportive care; there were also clinically and statistically significant improvements in the secondary endpoints progression free survival (PFS), overall survival (OS) and objective response rate (ORR).

**Statistical Issues:**

There is no substantial statistical issue in this NDA except following changes from the protocol

- Per protocol,
  - Death due to cancer was included as a TTP event according to the protocol defined TTP.
  - The primary analysis was planning to perform on the MITT population, defined as all ITT patients with disease progression on prior imatinib mesylate confirmed by the core radiology laboratory.

  Having an agreement with FDA in the preNDA meeting, the definition of TTP was revised and the population for primary analysis was changed from MITT to ITT.
  - According to the revised definition of TTP, death due to cancer was censored at the time of last tumor evaluation demonstrating lack of progression prior to death. The submitted analysis results of TTP for this NDA were based on this revised definition.
  - The results of TTP based on the protocol definition also show consistent with the results based on the revised TTP definition.

**Findings**

- Per sponsor, there are 41 patients (29 in Su011248 group and 12 in placebo group) do not have the objective tumor progression assessment available. The sponsor primary results for TTP were based on the data excluded those 41 (13%) patients with missing objective tumor's assessment. The FDA results of TTP analysis, which included these 41 patients by censoring their TTP at the date of randomization, show similar results as the sponsor.

- Per protocol, the primary analysis was planning to perform on the MITT population, defined as all ITT patients with disease progression on prior imatinib mesylate confirmed by the core radiology laboratory. Upon FDA request, the sponsor provided the primary analyses of TTP based on MITT and ITT population. This statistical reviewer verified the sponsor's analysis results. The results of TTP analysis on both populations show that SU011248 combined with best supportive care for GIST patients with resistant to or intolerant of imatinib Mesylate statistically significantly prolongs time to progression comparing to the treatment with placebo plus best supportive care.

Following Table A and B display the sponsor's and FDA's results on ITT and MITT population separately. There was statistically significant difference between Su0011248 group and Placebo group in favor of Su0011248 with respect to time to progression both on ITT and MITT populations. Moreover, there was about 67% reduction in the risk of developing progression disease for patients receiving Su0011248 comparing to the patients receiving placebo.

**Table A: Summary of the Sponsor's and FDA's Results of Time to Progression (ITT Population)**

| Treatment | Number of TTP Events (%) | Median Survival Time (weeks, 95% CI) | Hazard Ratio (Su0011248/Placebo) (95% CI ) | p-value (log-rank test) |
|---|---|---|---|---|
| ***Sponsor's analysis (Based on Central Radiologist Assessment)*** | | | | |
| Su011248 (N=207) | 82 (39.61) | 27.29(16.00,32.14) | 0.329 (0.233-0.466) | 0.0001 |
| Placebo (N=105) | 67 (63.81) | 6.43 ( 4.43, 10.00) | | |
| ***FDA sensitivity Analysis (Based on Central Radiologist Assessment)*** | | | | |
| Su011248 (N=207) | 87 (42.02) | 24.14(12.14,28.29) | 0.363 (0.258-0.511) | 0.0001 |
| Placebo (N=105) | 67 (63.81) | 5.14 ( 4.29, 9.86) | | |

**Table B: Summary of the Sponsor's and FDA's Results of Time to Progression**

**(MITT Population)**

| Treatment | Number of TTP Events (%) | Median Survival Time (weeks, 95% CI) | Hazard Ratio (Su0011248/Placebo) (95% CI ) | p-value (log-rank test) |
|---|---|---|---|---|
| ***Sponsor's analysis (Based on Central Radiologist Assessment)*** | | | | |
| Su011248 (N=170) | 73 (42.94) | 27.29(16.00,32.14) | 0.319 (0.221-0.460) | 0.0001 |
| Placebo (N=91) | 64 (70.32) | 6.00 (4.42, 10.00) | | |
| ***FDA sensitivity Analysis (Based on Central Radiologist Assessment)*** | | | | |
| Su011248 (N=207) | 87 (42.02) | 24.14(10.43,28.29) | 0.354 (0.247-0.507) | 0.0001 |
| Placebo (N=105) | 67 (63.81) | 5.14 ( 4.29, 10.00) | | |

- Table C displays the sponsor's results of secondary endpoints. The results in the Table C are from the interim analysis. For the primary endpoint TTP, the nominal alpha-level is 0.0031. Therefore the p-values for the secondary endpoints should be compared with 0.0031 not 0.05. There is no multiplicity adjustment among secondary endpoints.

- Since there are 41 patients (about 13%) who did not have independent's assessment available, the sponsor's PFS results were based on the data without those 41 patent entries. Among those 41 patients, 7 patients died. 5 out of 7 deaths resulted in 5 PFS events per the definition of PFS. After FDA statistical reviewer requested, the sponsor resubmitted the PFS results which including the extra 5 PFS events and censoring PFS time at the date of randomization for remaining 36 patients with missing independent's assessment. This statistical reviewer verified the resubmitted PFS results, which showed SU011248 combined with best supportive care for GIST patients with resistant to or intolerant of imatinib Mesylate statistically significantly improvement in progression free survival comparing to the treatment with placebo plus best supportive care, which consisting with the previous submitted PFS results. Please see following Table C.

- There were 56 deaths (including cross-over patients) among 312 ITT patients by the time of analysis. The trial stopped based on satisfactory efficacy results of the first interim analysis for efficacy. With about 1 year of maximum duration of treatment and follow-up, the data were not mature enough to determine the survival benefit offered by this therapeutic approach.

- There were 56 deaths (29 in Su011248 group and 27 in the placebo group) by the time of data cut-off, January 1, 2005. With about 1 year of maximum duration of treatment and follow-up, data were not mature enough to determine the survival benefit offered by this therapeutic approach.

**Table C: Summary of Sponsor's Results of Secondary Endpoints ***

**(ITT Population)**

| Endpoints | Median Survival Time (weeks) (95% CI) | | Hazard Ratio (Su0011248/Placebo) (95% CI) | p-value (log-rank test) |
|---|---|---|---|---|
| | Placebo (N = 105) | SU011248 (N =207) | | |
| PFS (originally submitted) | 6.4 ( 4.4, 10.0) | 24.6 ( 12.1, 28.3) | 0.333 (0.238, 0.467) | <0.0001 |
| PFS (resubmitted after FDA requested) | 6.0 (4.4, 9.9) | 24.1 (11.1, 28.3) | 0.334 (0.240, 0.465) | <0.0001 |
| ORR [% (95% CI)] | 0 | 6.8 (3.7, 11.1) | | 0.006[a] |
| OS (including open-label treatment) | 15.86[b] (11.28, **) | 40.00[b] (29.71, **) | 0.491 (0.290,0.831) | 0.007 |

* *A comparison is considered statistically significantly different if the p-value < 0.0031;*

***upper limit could not be calculated because the data were not mature.*

[a] *Pearson chi-square test.*

[b] *The first quartile of survival time for OS*

- This statistical reviewer performed 3 sensitivity analyses on primary endpoint TTP based on the data including 15 patients' alternative progression date adjudicated by the medical reviewer and excluding 3 patients based on protocol deviations that may have influenced efficacy. The results of these TTP sensitivity analyses show SU011248 combined with best supportive care for GIST patients with resistant to or intolerant of imatinib Mesylate statistically significantly robust improvement in time to progression comparing to the treatment with placebo plus best supportive care, which consisting the sponsor's TTP results. Table D shows the results of these TTP sensitivity analyses.

**Table D: Summary of FDA's TTP Sensitivity Analysis Results**

| Population | Median survival time (week) (95% CI) | | Hazard Ratio (Sutent / Placebo) (95% CI) | p-value (log-rank test) |
|---|---|---|---|---|
| | Placebo | SU011248 | | |
| ITT (with alternative PD for 15 patients) | 5.14 ( 4.29, 9.86) | 24.14 (12.14,28.29) | 0.363 (0.258-0.511) | <0.0001 |
| MITT (with alternative PD for 15 patients) | 5.14 (4.29, 10.00) | 24.14 (10.43,28.29) | 0.354 (0.247-0.507) | <0.0001 |
| ITT (excluded 3 patients based on protocol deviations) | 5.14 (4.29, 10.00) | 27.29 (16.00,32.14) | 0.359 (0.254-0.508) | <0.0001 |

- This reviewer performed several subgroup exploratory analyses on the primary endpoint TTP. Table E summarizes the results of these subgroup analysis results. These subgroups included subgroups of patients with different age and sex groups. The results of patients who were in subgroups of all male, all female, older than or equal to 65 and younger than 65 were similar to ITT population.

**Table E: Summary of Results of Time to Progression in Subgroups**

**(FDA's Analysis)**

| Subgroup | Sample size | | Hazard Ratio (Sutent / Placebo) (nominal 95% CI) | p-value (log-rank Test) |
|---|---|---|---|---|
| | Sutent | Placebo | | |
| Age >= 65 | 64 | 29 | 0.241 (0.123, 0.473) | <0.0001 |
| Age <65 | 143 | 76 | 0.373 (0.248, 0.561) | <0.0001 |
| Male | 132 | 64 | 0.322(0.211, 0.491) | <0.0001 |
| Female | 75 | 41 | 0.332 (0.179, 0.616) | <0.0001 |
| White | 183 | 92 | 0.324 (0.224, 0.469) | <0.0001 |
| U.S. and Canada | 96 | 47 | 0.375 (0.233, 0.603) | <0.0001 |
| Other Counties | 111 | 58 | 0.293 (0.176,0.489) | <0.0001 |

# 2 INTRODUCTION

## 2.1 OVERVIEW

Sunitinib malate (SU011248 L-malate) is an oral, multi-targeted tyrosine kinase inhibitor that targets and blocks the signaling pathways of selected receptor tyrosine kinases (RTKs) involved in tumor biology. Sunitinib is a small molecule inhibitor of multiple RTKs that are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer.

The sponsor submitted this NDA to seek an approval on the indication: "*sunitinib malate for the treatment of gastrointestinal stromal tumor (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.*" The proposed dose and schedule is 50 mg daily, 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). There is no standard therapy for patients with GIST who have progressed on imatinib mesylate

In this NDA submission, efficacy data were collected by the sponsor in the trial: A6181004. Trial A6181004 was a multicenter, international, randomized, double-blind phase III study. This Phase III trial was conducted at 367 sites in 37 countries. By the time of data cutoff date, a total of 312 patients with GIST who had experienced disease progression on or intolerance of imatinib mesylate therapy had been randomized in the trial A6181004. In this trial, Patients received treatment in repeated 6-week cycles, consisting of 4 weeks of daily SU011248 or placebo administration followed by 2 weeks of rest (Schedule 4/2).

This statistical reviewer reviewed the study A6181004 for efficacy. The study A6181004 enrolled the first patient on December 10, 2003. January 1, 2005 was the date for the data cut-off date for the second interim analysis. The results for this NDA were based on this interim analysis. A more detailed summary of milestones can be deferred to the FDA Dr. Rock's clinical review.

**Reviewer Comments**:

[1] The Sponsor submitted original protocol for Trial A6181004 under IND No. 62,382 SN128 with the protocol entitled *"A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of SU011248 in the Treatment of Patients with Imatinib Mesylate (Gleevec™, Glivec®)-Resistant or Intolerant Malignant Gastrointestinal Stromal Tumor"*. Since then, the sponsor submitted five amendments. Following are some of the changes addressed in the amendments:

- Modifying the definition of the primary endpoint TTP.
- Increasing number of interim analysis of efficacy and safety from one to three (approximately 25%, 50%, and 75% of the total number expected, respectively), where one interim analysis would be performed (at the time about 25% of the total events expected) for safety assessment and other two (at the time about 50% and 50% of the total events expected, respectively) for efficacy and safety.
- Adding PFS as a secondary endpoint.
- Specifying p-values rather than hazard ratios using in the statistical analysis of primary endpoints derived from O'Brien-Fleming stopping boundaries (Amendment 3).

[2] The sponsor changed some planned definitions and analysis population in the submitted analysis results for this NDA.

- The primary analysis population was changed from the MITT population to the ITT population.
- The definition of TTP was revised (death due to cancer was considered tumor progression in protocol, but in the final analysis TTP was censored at the time of last tumor evaluation prior to death).
- The definition of DR was revised (death due to cancer was considered tumor progression in protocol, but in the analysis death from any cause was considered progression).

## 2.2 DATA SOURCES

Data used for review are from the electronic submission received in August 2005. The network path is "\\Cdsesub1\EVSPROD\n021938\N000\2005-8-10" in the EDR.

# 3 STATISTICAL EVALUATION

This review focuses on the study A6181004. Section 3.1 includes efficacy evaluation for the study A6181004.

## 3.1 EVALUATION OF EFFICACY

This section provides the description of Study A6181004 based on the sponsor's study report. Any difference between the sponsor's study report and the protocol is also discussed in this section.

### 3.1.1 STUDY OBJECTIVES

The primary objective of this study was to compare the time to tumor progression (TTP) associated with SU011248 plus best supportive care (Arm A) versus that associated with placebo plus best supportive care (Arm B) for the treatment of patients with imatinib mesylate-resistant or intolerant malignant GIST.

The secondary objectives of this study were as follows:

- To compare other measures of antitumor efficacy in both treatment arms of the study
- To compare pain control, analgesic usage, tumor-related signs and symptoms, health status,
- and performance status in both treatment arms of the study
- To evaluate the safety and tolerability of SU011248
- To evaluate exposure levels of SU011248 (plus its SU012662 active metabolite) and to correlate these plasma concentrations with efficacy and safety parameters
- To explore the correlations of potential biomarkers with clinical outcomes

### 3.1.2 STUDY DESIGN

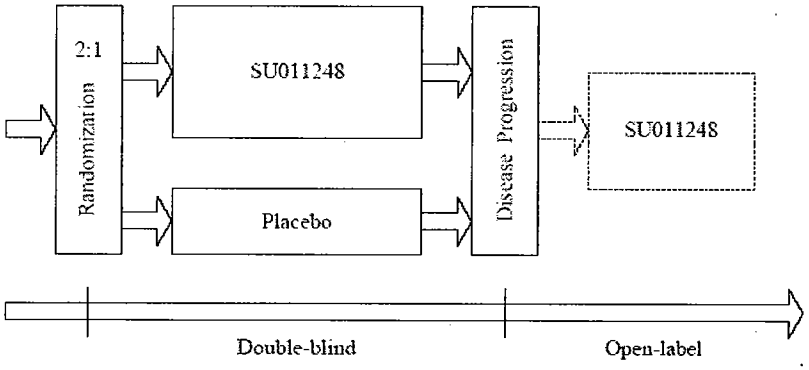
This study was designed as a randomized, double-blind, multi-center, Phase 3 study of SUTENT (SU011248) verse placebo in patients with GIST who had experienced disease progression on or intolerance of imatinib mesylate therapy. Patients on both treatment arms received best supportive care in addition to the study treatment. Patients received treatment in repeated 6-week cycles, consisting of 4 weeks of daily SU011248 or placebo administration followed by 2 weeks of rest (Schedule 4/2). Per the sponsor, placebo control is ethical in this case because there is no standard therapy for patients with GIST that has progressed on imatinib mesylate and because patients on both treatment arms received best supportive care in addition to the study treatment. Neither investigators nor patients will be apprised of treatment arm assignment until RECIST-defined disease progression or at the conclusion of the study. Patients experiencing disease progression could be unblinded, and patients who had been receiving placebo could crossover to open-label treatment with SU011248; patients who had been receiving SU011248 during the blinded phase study could continue to do so after unblinding if, in the opinion of the investigator, there was sufficient evidence of clinical benefit.

After completing screening and after having recorded pain symptoms in the MPQ-PPI for 7 days, consenting patients were randomly assigned to receive either SU011248, 50 mg (Arm A), or matching placebo (Arm B) based on ratio 2:1. Per the sponsor, the 2:1 randomization was used to minimize the number of patients treated with placebo. The randomization were stratified by Prior imatinib mesylate response or intolerance (PD within 6 months of the start of imatinib treatment vs PD beyond 6 months from the start of imatinib treatment vs intolerance), Baseline MPQ score (0 vs >1). Baseline MPQ score (0 vs >1) were based on the median value of the worst daily pain over a 7-day period prior to randomization.

The study design is presented in following Figure

**Figure 1: Study Design**

[*Source: Figure 1. in Sponsor's Study Report*]




*[Source: sponsor's study report]*

Please refer to Dr. Rock' s FDA clinical review for more detail of inclusion and exclusion criterion for this study population.

### 3.1.3 EFFICACY ENDPOINTS

#### 3.1.3.1 Primary Efficacy Endpoint

Per protocol, the primary endpoint time to tumor progression (TTP) was defined as the time from randomization to first documentation of objective tumor progression, or to death due to cancer (on treatment or within 28 days of last dose). TTP data would be censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who a) do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment, b) removed from treatment prior to documentation of objective tumor progression, or c) die of non-cancer-related symptoms including death due to an unknown cause in the absence of documented disease progression. Patients having no tumor assessments after randomization would have TTP censored on the date of randomization. Imaging studies demonstrating progression of disease would be reviewed by an independent third-party imaging core laboratory for verification.

**Reviewer Comments**:

[1] Per the sponsor, the definition of TTP was revised as the time from randomization to first documentation of objective tumor progression. Death due to cancer was considered tumor progression in the protocol, but in the submitted results of analyses TTP was censored at the time of last tumor evaluation prior to death. FDA agrees the change of TTP definition (refer to pre-NDA Meeting Minutes on February 10, 2005)

[2] In assessing time to progression, if deaths are included as events, then deaths due to all causes should be included. The sponsor added PFS, which includes all deaths as events, as the secondary endpoint in one of the protocol amendments.

### 3.1.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints were progress free survival (PFS), overall survival (OS), overall response rate (ORR), time to tumor response (TTR), duration of response (DR), and duration of performance status maintenance (DPSM).

- **Progress free survival (PFS),** defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause (on treatment or within 28 days of last dose) whichever comes first. PFS data will be censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment, or are removed from treatment follow-up prior to documentation of objective tumor progression. Patients having no tumor assessments after randomization will have PFS censored on the date of randomization.

- **Overall survival (OS)**, defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond randomization will have their survival times censored on the date of randomization.

- **Overall confirmed objective response rate (ORR),** defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST), relative to the total population of randomized patients. Confirmed responses are those that persist on repeat imaging study ε4 weeks after initial documentation of response. Imaging studies of responders (PR or CR) will be reviewed by an independent third-party imaging core laboratory for verification.

- **Time to tumor response (TTR),** defined as the time from date of randomization to first documentation of objective tumor response. TTR will only be calculated for the subgroup of patients with an objective tumor response.

- **Duration of response (DR),** defined as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to cancer. DR data will be censored on the day following the date of the last

tumor assessment documenting absence of progressive disease for patients who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment, are removed from study follow-up prior to documentation of objective tumor progression, died of non-cancer-related causes including death due to an unknown cause in the absence of documented disease progression. DR will only be calculated for the subgroup of patients with an objective tumor response.

- **Duration of performance status maintenance (DPSM),** defined as the time from randomization until the last time the performance status was no worse than at baseline or to death due to cancer in the absence of previous documentation of performance status worsening. For patients who do not have performance status worsening, who are either removed from study or are given antitumor treatment other than the study treatment, or who die of non-cancer-related symptoms including death due to an unknown cause in the absence of documented disease progression, performance status maintenance will be censored at the time of the last performance status assessment.

**Reviewer Comments**:

[1] Per sponsor, the definition of DR was revised (death due to cancer was considered tumor progression in protocol, but in the analysis death from any cause was considered progression). Analyses of those post-hoc secondary endpoints are considered supportive.

### 3.1.4 SAMPLE SIZE CONSIDERATIONS

The study A6181004 was originally designed to have 90% power to detect a 50% improvement (hazard ratio 0.67 [Arm A:Arm B]) in median TTP from 4 months to 6 months in patients randomized to receive SU011248 is considered to be clinically relevant. Adopting a sequential monitoring procedure with 2 interim and a final analyses, a total of 281 patients with disease progression are required for a 2-sided, unstratified log-rank test with an overall 2-sided significance level of 0.05 and 90% power. Applying a 2:1 randomization and a planned accrual period of 18 months, a minimum follow-up period of 6 months, and an expectation that approximately 5% of patients may be lost to follow-up, it is estimated that 357 patients (238 in Arm A and 119 in Arm B) will need to be enrolled in order to observe 281 patients with progressive disease by the end of the minimum follow-up period. The final analysis will take place when the 281st patient has documented progressive disease. The nominal significance level for the final analysis is 0.044.

### 3.1.5 INTERIM ANALYSIS

Per sponsor's protocol, three interim analyses were planned when approximately 25%, 50% and 75% of the total events expected. When the first 70 patients had documented progressive disease (approximately 25% of the total events expected), one interim assessment of safety was conducted. No adjustment for the overall type I error rate for this interim analysis because this

was for safety assessment. Another two interim analyses for efficacy and safety were to be conducted after the first 141 and 211 patients had documented progressive disease (approximately 50%, and 75% of the total number expected, respectively). The nominal significance level for the interim and final efficacy analyses were determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule. The nominal levels of significance for the interim analyses were to be determined at the time of the interim analysis (if exactly 141 and 211 expected number of events have occurred at the time of the interim analysis, then the nominal significance levels will be 0.0031 and 0.0183, respectively). The nominal significance level for the final analysis was to be adjusted to 0.044.

**Reviewer's Comments:**

[1] Per the sponsor's study report, this NDA submission summarized the results of the second interim analysis with 312 randomized patients with 152 TTP events based on investigator's assessment and 149 TTP events based on the central radiologist assessment.

[2] The sponsor planned one interim analysis in the original protocol, and increased number of interim analysis of efficacy and safety to three (approximately 25%, 50%, and 75% of the total number expected, respectively) after accepting FDA's statistical recommendation.

### 3.1.6 STATISTICAL METHODOLOGIES

#### 3.1.6.1 Sponsor's Protocol/Statistical Analysis Plan

Per sponsor's protocol, the primary endpoint TTP, based on the assessment of an independent, third-party imaging laboratory, would be analyzed by using the Kaplan-Meier method in the modified intent-to-treat (MITT) population and compared with a 2-sided unstratified log-rank test at the $\alpha = 0.05$ overall significance level. In addition, a stratified log-rank test and Cox regression models were used to explore the potential influences of the stratification factors (Prior imatinib mesylate response or intolerance, Baseline MPQ score (0 vs $\geq$1)) on the primary endpoint TTP.

The secondary time-to-event endpoints (including OS and PFS) were also analyzed by applying Kaplan-Meier methods and log-rank test. The proportion of patients who achieved an objective tumor response (PR or CR) were computed for each arm and compared by means of a Chi-square test or the Cochran-Mantel-Haenszel (CMH) method stratified by baseline stratification factors.

**Reviewer's Comments:**

[1] The sponsor changed the primary analysis population from the protocol planned MITT population to the ITT population.

### 3.1.7 SPONSOR'S RESULTS AND STATISTICAL REVIEWER'S COMMENTS/FINDINGS

This section summarizes the sponsor's major results of the second interim analysis for the pivotal study A6181004 and provides the statistical reviewer's comments and findings. Per the pre-specified statistical analysis plan, the second interim analysis was to be performed when 50% (141 events) of the required total number of events 281 occurred. However, the actual number of occurred events was 149 based on the central radiologist assessment.

#### 3.1.7.1 Data Sets

Started from December 10, 2003 to January 1, 2005, the data cutoff date for the planned second interim analysis, a total of 312 patients were randomized to the study A6181004 at 56 centers, which most centers were in the United States, Australia and other 9 countries in Europe, North America and Asia. The data cut-off date for this NDA submission was January 1, 2005.

Table 1 is the sponsor's summary of analysis populations. Per sponsor, three populations intent-to-treat (ITT), modified intent-to-treat (MITT) and as treated (AT) were planned for the efficacy analyses. MITT population was defined as all randomized patients having imatinib mesylate-resistance (confirmed by the independent third-party imaging core laboratory) or intolerance, with study drug assignment designated according to initial randomization, regardless of whether patients received any study drug or received a different drug from that to which they were randomized. The sponsor submitted the results of time to progression performed on ITT and MITT population from the second interim analysis (first interim analysis for efficacy).

**Table 1: Sponsor's Summary of Data Set Analyzed**

| Population | SU011248 | Placebo |
|---|---|---|
| ITT population (all randomized patients) | 207 | 105 |
| MITT population | 170 | 91 |
| AT (safety) population | 202 | 102 |

*[Source: Table 10 in Sponsor's Study Report]*

**Reviewer's Comment:**

[1] This reviewer has verified Table 1.
[2] Sample size appeared balanced between treatment groups with respect to each analysis population.
[3] The sponsor used MITT as the protocol planned primary analysis population but a secondary population for evaluating all efficacy endpoints and patient characteristics in the results for this NDA submission.

### 3.1.7.2 Disposition of Patients

The following Table is the sponsor's summary of patient disposition. As seen in this table, at the date (January 1, 2005) of the cut-off for the analysis, 78 patients had crossed over to open-label treatment (59 (56%) patients from placebo group and 19 (9%) patients from SU011248). Of those 312 randomized patients, 168 patients (53.8%) were still on the blinded treatment, with 134 (79.8%) in the SU011248 group and 34 (20.2%) in the placebo group. In the ITT population (312 randomized patients), 51 patients in the SU011248 group and 65 in the placebo group were discontinuous from the study due to lack of efficacy (including disease progression).

**Table 2: Sponsor's Summary of Patient Disposition at Cut-off Date for Analysis (ITT Population)**

| Reason for Discontinuation | SU011248 (N = 207) | Placebo (N = 105) |
|---|---|---|
| Adverse events | 15 (7) | 3 (3) |
| Consent withdrawn | 6 (3) | 3 (3) |
| Lost to follow-up | 1 (1) | 0 (0) |
| Lack of efficacy (disease progression) | 51 (25) | 65 (62) |
| Crossed over to open-label treatment | 19 (9) | 59 (56) |
| Ongoing in blinded treatment | 134 (65) | 34 (32) |

*[Source: Sponsor's Study Report Table 7. ]*

## Reviewer's Comment:

[1] Table 2 has been verified.

### 3.1.7.3 Demographic and Baseline Characteristics

Table 3 shows the demographic and baseline characteristics for the 312 patients in the study A6181004.

**Table 3: Sponsor's Summary of Demographic and Baseline Characteristics (ITT Population)**

| Variable | SU011248 (N = 207) | Placebo (N = 105) |
|---|---|---|
| Sex [n (%)] | | |
| Male | 132 (64) | 64 (61) |
| Female | 75 (36) | 41 (39) |
| Race [n (%)] | | |
| White | 183 (88) | 92 (88) |
| Black | 8 (4) | 4 (4) |

| | | |
|---|---|---|
| Asian | 10 (5) | 5 (5) |
| Not allowed/not listed | 6 (3) | 4 (4) |
| Age (years) | | |
| Mean (std) | 57.1 (12.5) | 55.2 (12.6) |
| Median (range) | 58 (23 - 84) | 55 (23 - 81) |
| < 65 [n (%)] | 143 (69) | 76 (72) |
| ≥ 65 [n (%)] | 64 (31) | 29 (28) |
| Weight (kg) | | |
| Mean (std) | 74.0 (16.8) | 72.5 ( 18.5) |
| Median (range) | 72.7 (38.5 - 140.2) | 69.0 (40.5 - 130.0) |
| ECOG performance status [n (%)] | | |
| 0 | 92 (44) | 48 (46) |
| 1 | 113 (55) | 55 (52) |
| 2[a] | 2 (1) | 2 (2) |

a. *All patients had ECOG performance status of 0 or 1 at the time eligibility was determined; some patients' condition deteriorated such that ECOG was 2 at the last pre-treatment assessment, which is summarized here.*
*[Source: Sponsor's Study Report Table 11.]*

**Reviewer Comments:**

[1] This reviewer verified Table 3.
[2] As seen in Table 3, male patients in this study are almost twice of female patients and 88% of patients were white.
[3] Demographic and baseline characteristics appeared balanced between the two treatment groups.

### 3.1.7.4 Time to Progression (Primary Endpoint)

Per sponsor, the primary endpoint Time to Progression (TTP) was defined as the time from randomization to first documentation of objective tumor progression. If tumor progression data include more than 1 date, the first date was used. Time-to-tumor progression (weeks) was calculated as [(first event date − the date of randomization +1)/7]. TTP data was censored on the day following the date of the last on study tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression while on treatment and were still on study at the time of an analysis, were given antitumor treatment other than the study treatment, or removed from treatment prior to documentation of objective tumor progression, or die. Patients having no tumor assessments after randomization had TTP censored on the date of randomization.

ITT population includes all patients who are randomized, with study drug assignment designated according to initial randomization, regardless of whether patients receive any study drug or receive a different drug from that to which they were randomized. Per sponsor, MITT was defined to include all randomized patients having imatinib mesylate-resistance (confirmed by the independent third-party imaging core laboratory) or intolerance, with study drug assignment

designated according to initial randomization, regardless of whether patients receive any study drug or receive a different drug from that to which they were randomized. Data cutoff date was January 1, 2005. The following table summarizes the sponsor's results of TTP analysis.

**Table 4: Sponsor's Summary of Analyses of Time to Progression**

| Population, Data Source<br>Variable | SU011248 | Placebo | p-value |
|---|---|---|---|
| **ITT population, central radiologist**<br>Progression status [n (%)] | **(N = 207)** | **(N = 105)** | |
| Progressed | 82 (40) | 67 (64) | |
| Did not progress | 96 (46) | 26 (25) | |
| Data not available | 29 (14) | 12 (11) | |
| Median (95% CI) TTP (weeks) | 27.3 (16.0 - 32.1) | 6.4 (4.4 - 10) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.329 (0.233 - 0.466) | | <0.001 |
| **MITT population, central radiologist**<br>Progression status [n (%)] | **(N = 170)** | **(N = 91)** | |
| Progressed | 73 (43) | 64 (70) | |
| Did not progress | 78 (46) | 22 (24) | |
| Data not available | 19 (11) | 5 (6) | |
| Median (95% CI) TTP (weeks) | 27.3 (16.0 - 32.1) | 6.0 (4.4 - 10.0) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.319 (0.221 - 0.460) | | <0.001 |
| **AT population, central radiologist**<br>Progression status [n (%)] | **(N = 202)** | **(N = 102)** | |
| Progressed | 82 (41) | 67 (66) | |
| Did not progress | 96 (48) | 26 (25) | |
| Data not available | 24 (12) | 9 (9) | |
| Median (95% CI) TTP (weeks) | 27.3 (16.0 - 32.1) | 6.4 (4.4 - 10.0) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.329 (0.233 - 0.466) | | <0.001 |
| **ITT population, investigative site radiologist**<br>Progression status [n (%)] | **(N = 207)** | **(N = 105)** | |
| Progressed | 77 (37) | 67 (64) | |
| Did not progress | 130 (63) | 38 (36) | |
| Median (95% CI) TTP (weeks) | 28.9 (21.3 - 34.1) | 5.1 (4.4 - 10.1) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.281 (0.198 - 0.399) | | <0.001 |
| **MITT population, investigative site radiologist**<br>Progression status [n (%)] | **(N = 170)** | **(N = 91)** | |
| Progressed | 69 (41) | 64 (70) | |
| Did not progress | 101 (59) | 27 (30) | |
| Median (95% CI) TTP (weeks) | 29.7 (18.6 - 34.1) | 5.1 (4.4 - 10.1) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.283 (0.196 - 0.408) | | <0.001 |
| **AT population, investigative site radiologist**<br>Progression status [n (%)] | **(N = 202)** | **(N = 102)** | |

| | | | |
|---|---|---|---|
| Progressed | 77 (38) | 67 (66) | |
| Did not progress | 125 (62) | 35 (34) | |
| Median (95% CI) TTP (weeks) | 28.9 (21.3 - 34.1) | 5.1 (4.4 - 10.1) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.281 (0.198 - 0.399) | | <0.001 |

**Table 5: Reviewer's Summary of Analyses of Time to Progression (Based on sponsor's data)**

| Population, Data Source | SU011248 | Placebo | P-value |
|---|---|---|---|
| **ITT population, central radiologist** | **(N = 207)** | **(N = 105)** | |
| Progression status [n (%)] | | | |
| Progressed | 82 (40) | 67 (64) | |
| Did not progress | 96 (46) | 26 (25) | |
| Data not available | 29 (14) | 12 (11) | |
| Median (95% CI) TTP (weeks) | 27.3 (16.0 - 32.1) | 6.4 (4.4 - 10) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.329 (0.233 - 0.466) | | <0.001 |
| **MITT population, central radiologist** | **(N = 170)** | **(N = 91)** | |
| Progression status [n (%)] | | | |
| Progressed | 73 (43) | 64 (70) | |
| Did not progress | 78 (46) | 22 (24) | |
| Data not available | 19 (11) | 5 (6) | |
| Median (95% CI) TTP (weeks) | 27.3 (16.0 - 32.1) | 6.0 (4.4 - 10.0) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.319 (0.221 - 0.460) | | <0.001 |
| **AT population, central radiologist** | **(N = 202)** | **(N = 102)** | |
| Progression status [n (%)] | | | |
| Progressed | 82 (41) | 67 (66) | |
| Did not progress | 96 (48) | 26 (25) | |
| Data not available | 24 (12) | 9 (9) | |
| Median (95% CI) TTP (weeks) | 27.3 (16.0 - 32.1) | 6.4 (4.4 - 10.0) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.329 (0.233 - 0.466) | | <0.001 |
| **ITT population, investigative site radiologist** | **(N = 207)** | **(N = 105)** | |
| Progression status [n (%)] | | | |
| Progressed | **80 (39)** | **72 (69)** | |
| Did not progress | **127(61)** | **33 (31)** | |
| Median (95% CI) TTP (weeks) | 28.9 (**18.57** - 34.1) | 5.1 (4.4 - 10.1) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | **0.328 (0.236 - 0.455)** | | <0.001 |
| **MITT population, investigative site radiologist** | **(N = 170)** | **(N = 91)** | |
| Progression status [n (%)] | | | |
| Progressed | **72 (42)** | **68 (75)** | |
| Did not progress | **98 (58)** | **23 (25)** | |
| Median (95% CI) TTP (weeks) | **28.86 (17.4** - 34.1) | **5.29** (4.4 - 10.1) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | **0.333 (0.236 - 0.470)** | | <0.001 |
| **AT population, investigative site radiologist** | **(N = 202)** | **(N = 102)** | |

| | | | |
|---|---|---|---|
| Progression status [n (%)] | | | |
| Progressed | **80 (40)** | **72 (71)** | |
| Did not progress | **122 (60)** | **30 (29)** | |
| Median (95% CI) TTP (weeks) | **28.9 (18.6 - 34.1)** | **5.1 (4.4 - 10.1)** | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | **0.328 (0.236 - 0.455)** | | <0.001 |

*[Source: sponsor's study report section 7.2. Table 15]*

**Figure 2: Reviewer's Kaplan-Meier Plot of Time to Progression (ITT Population with Central Radiologist Assessments provided by the Sponsor)**

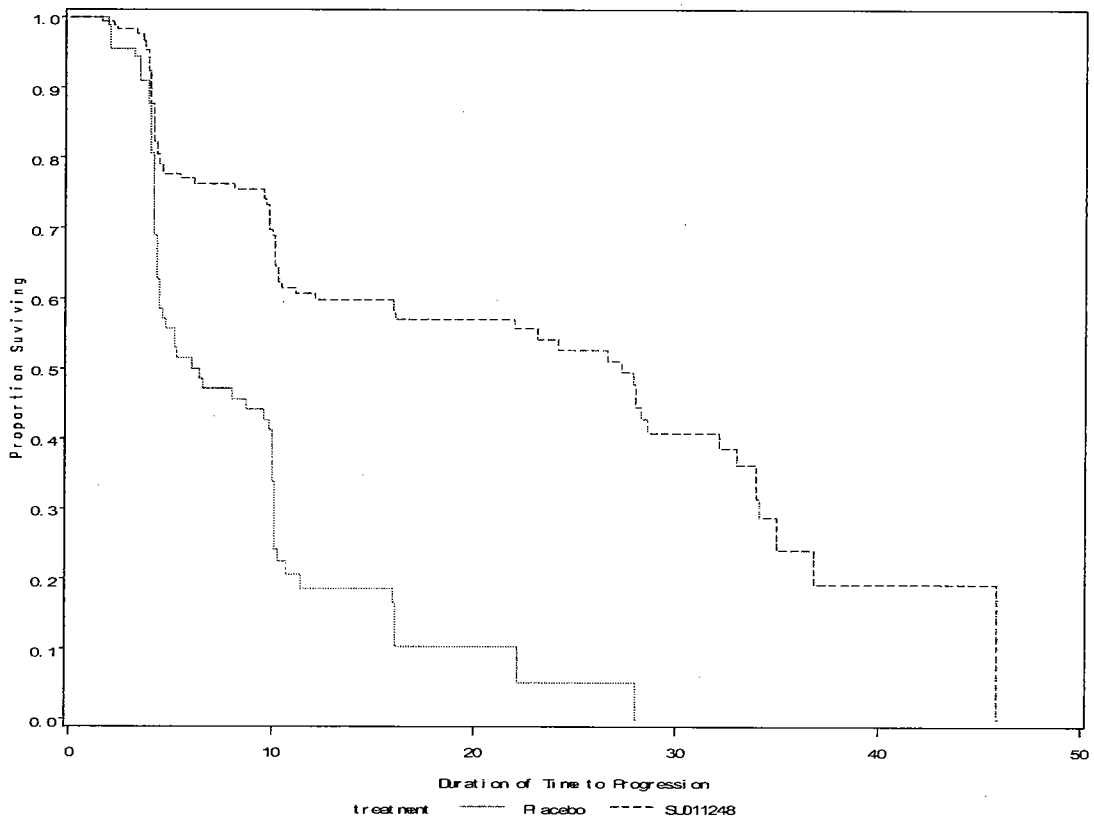
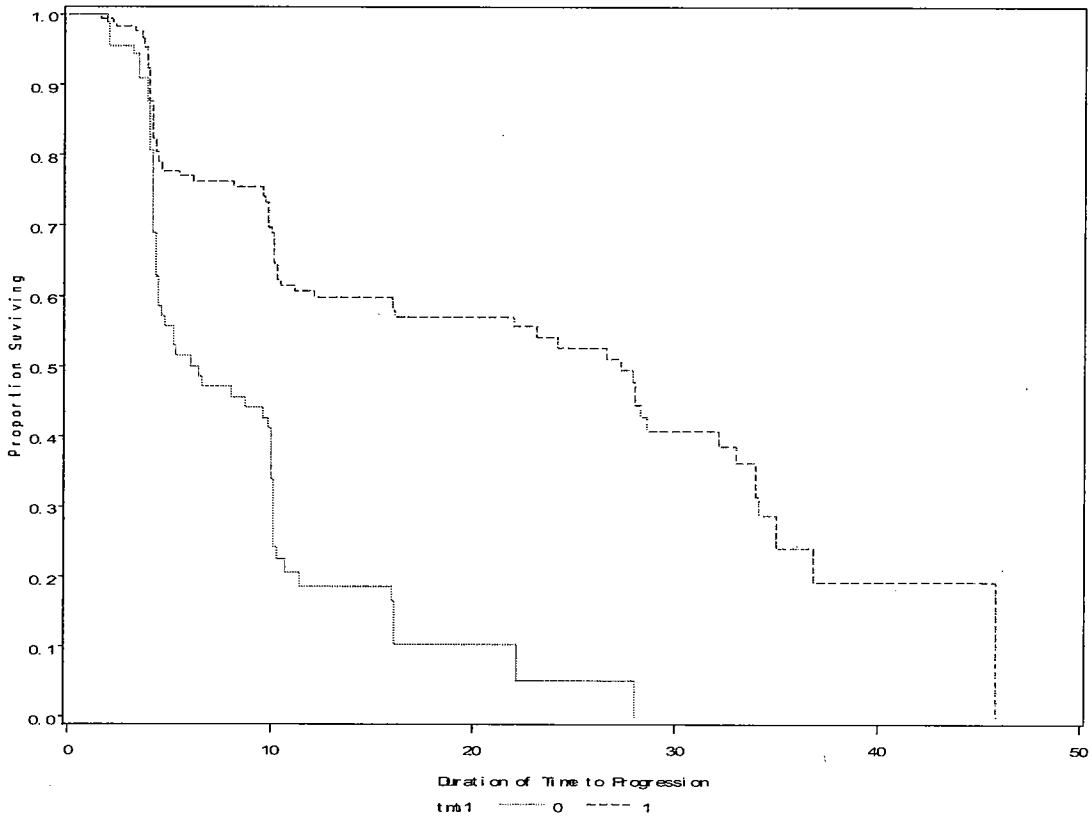


**Figure 3: Reviewer's Kaplan-Meier Plot of Time to Progression (ITT Population with Investigator's assessments)**




**Reviewer Comments:**

[1] Since the results presented here are based on the second interim analysis, the p-value should be compared with the pre-specified nominal significance level of 0.0031, not 0.05.

[2] The primary analysis should be performed on ITT and based on the objective assessment. The results of analyses performed on any other populations and based on investigator's assessment should be considered as supportive.

[3] There are some discrepancies between the sponsor's results of time to progression and the reviewer's. The Table 5 shows this reviewer's summary of time to progression analyses results. The bold numbers indicate the discrepancies deviated from the sponsor's results. Per sponsor's statistician, the discrepancies were introduced due to the updated dataset(s).

[4] There 41 patients (about 13%) who do not have central radiologist assessments records. This reviewer performed an analysis of TTP by adding those patients with censoring TTP at the date of randomization. The results are similar with the sponsor's results.

[5] Per protocol, the primary endpoint Time to Progression (TTP) was defined in the sponsor's protocol as the time from randomization to first documentation of objective tumor progression, or to death due to cancer (on treatment or within 28 days of last dose). Also, the primary analysis was planned to perform on MITT population. However, death due to cancer was censored at the time of last tumor evaluation prior to death in the TTP analysis results which were submitted for this NDA according to the sponsor's study report. This change of TTP definition was agreed with FDA in the pre-NDA meeting minutes. Following table 6 summaries the sponsor result based on protocol defined TTP and MITT population.

**Table 6: Sponsor's Summary of Analyses of Time to Progression in MITT (Including Death Due to Cancer as Defined in the Protocol)**

| Population, Data Source | SU011248 | Placebo | P-value |
|---|---|---|---|
| **MITT population, central radiologist** Progression status [n (%)] | **(N = 170)** | **(N = 91)** | |
| Progressed | 79 (40) | 70 (64) | |
| Did not progress | 74 (46) | 19 (25) | |
| Data not available | 17 (14) | 2 (11) | |
| Median (95% CI) TTP (weeks) | 27.3 (16.0 - 32.1) | 6.4 (4.4 - 10) | |
| Hazard ratio (SU011248 vs placebo; 95% CI) | 0.341 (0.241 - 0.483) | | <0.001 |

*[Source: sponsor's study report Table A10.3.1]*

**Reviewer Comments:**

[1] This reviewer performed several sensitivity analyses on the primary endpoint TTP. Two sensitivity analyses were performed on ITT, MITT population separately by using the alternative progression dates for 15 patients (4 patients in placebo group and 11 patients in SU011248 group). Those alternative progression dates were adjudicated by the FDA clinical reviewer. The third sensitivity analysis was performed on the ITT population excluded 3 patients based on protocol deviations that may have influenced efficacy. Table 7 summarizes the results of these three TTP sensitivity analyses.

[2] Figure 4 shows the distributions of TTP were statistically significantly different between the two treatment groups with log-rank p-value < 0.0001, as compared to the nominal significance level of 0.0031. Results of the TTP sensitivity analysis on ITT suggested that SU011248 treatment provided substantial improvement in time to progression and was associated with an estimated 64% reduction in the risk of developing progression disease comparing to Placebo (HR = 0.363 with a nominal 95% CI of 0.258-0.511).

[3] This statistical reviewer performed 3 sensitivity analyses on primary endpoint TTP based on the data including 15 patients' alternative progression date

adjudicated by the medical reviewer and excluding 3 patients based on protocol deviations that may have influenced efficacy. The results of these TTP sensitivity analyses show that SU011248 combined with best supportive care for GIST patients with resistant to or intolerant of imatinib Mesylate demonstrate highly statistically significantly improvement in time to progression comparing to the treatment with placebo plus best supportive care, which consisting with the sponsor's TTP results. The results of three TTP sensitivity analyses show the sponsor's TTP results are robust. Table 7 shows the results of these TTP sensitivity analyses.

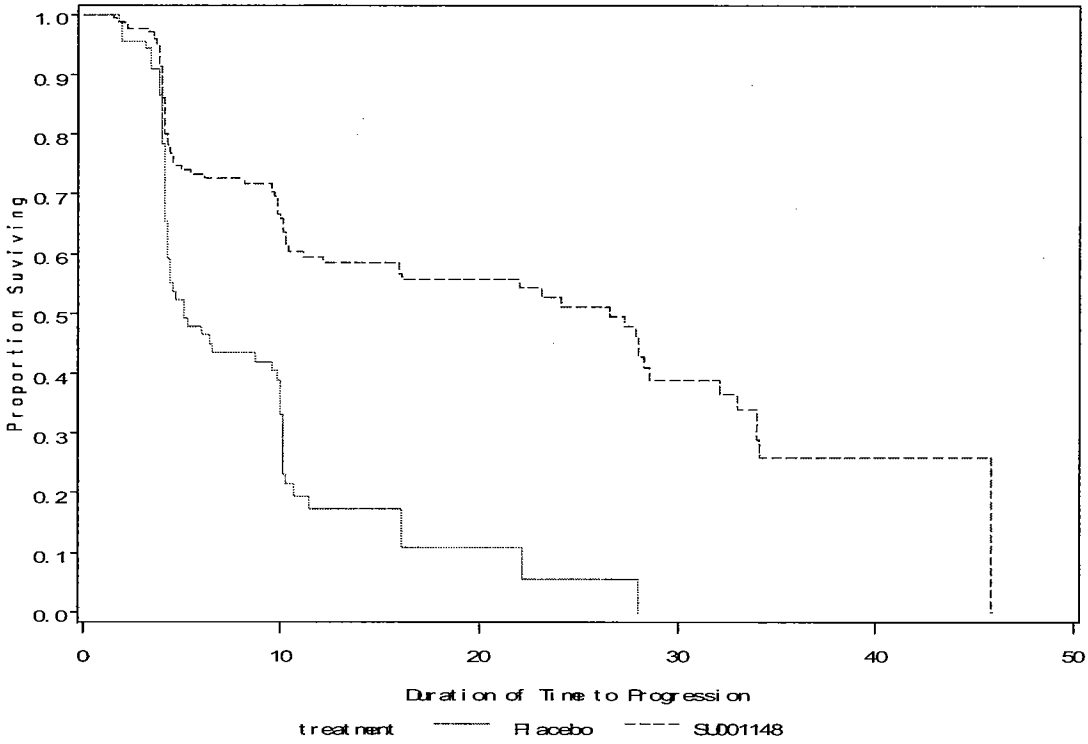
**Table 7: Summary of Sensitivity Analyses of Time to Progression (FDA Analysis)**

| Population | Median survival time (weeks) (95% CI) | | Hazard Ratio (Su011248/Placebo) (95% CI) | p-value (log-rank test) |
|---|---|---|---|---|
| | Placebo | SU011248 | | |
| ITT (with alternative PD* for 15 patients) | 5.14 ( 4.29, 9.86) | 24.14(12.14,28.29) | 0.363 (0.258-0.511) | <0.0001 |
| MITT(with alternative PD* for 15 patients) | 5.14(4.29, 10.00) | 24.14(10.43,28.29) | 0.354(0.247-0.507) | <0.0001 |
| ITT (excluded patients #70, 82 and 86) | 5.14(4.29, 10.00) | 27.29(16.00,32.14) | 0.359 (0.254-0.508) | <0.0001 |

* Those alternative progression dates for 15 patients were provided by the FDA clinical reviewer. The list of ids for those 15 patients can be found in the Appendices.

**Figure 4: Kaplan-Meier Plot of Time to Progression (ITT Population)**

**(FDA Sensitivity Analysis*)**




* The statistical reviewer produced this Kaplan-Meier Plot based on the central radiologist assessment data with alternative progression dates for 15 patients.

### 3.1.7.5 Secondary Endpoints

Secondary efficacy endpoints were PFS, OS, overall ORR, TTR, DR, and DPSM. The sponsor conducted two OS analyses. There were 56 deaths (27 from placebo group and 29 in Sutent group) by the data cut-off date.

The following Tables summarize the sponsor's results of the secondary endpoints based upon the central radiologist assessments

**Table 8: Sponsor's Summary of Results of Some Secondary Endpoints (ITT Population)**

| Endpoints | Median Survival Time (weeks) (95% CI) | | Hazard Ratio (Su011248/Placebo) (95% CI) | p-value (log-rank test) |
|---|---|---|---|---|
| | Placebo (N = 105) | SU011248 (N =207) | | |
| PFS (originally submitted) | 6.4 ( 4.4, 10.0) | 24.6 ( 12.1, 28.3) | 0.333 (0.238, 0.467) | <0.0001 |
| PFS (resubmitted upon FDA's request) | 6.0 (4.4, 9.9) | 24.1 (11.1, 28.3) | 0.334 (0.240, 0.465) | <0.0001 |
| ORR [% (95% CI)] | 0 | 6.8 (3.7, 11.1) | | 0.006[a] |
| OS (including open-label treatment) | 15.9[b] (11.3, 33.7) | 40.0[b] (29.7, **) | 0.491 (0.290,0.831) | 0.007 |

*[Source: Sponsor's study report section 7.3.1 and 7.3.2.]*

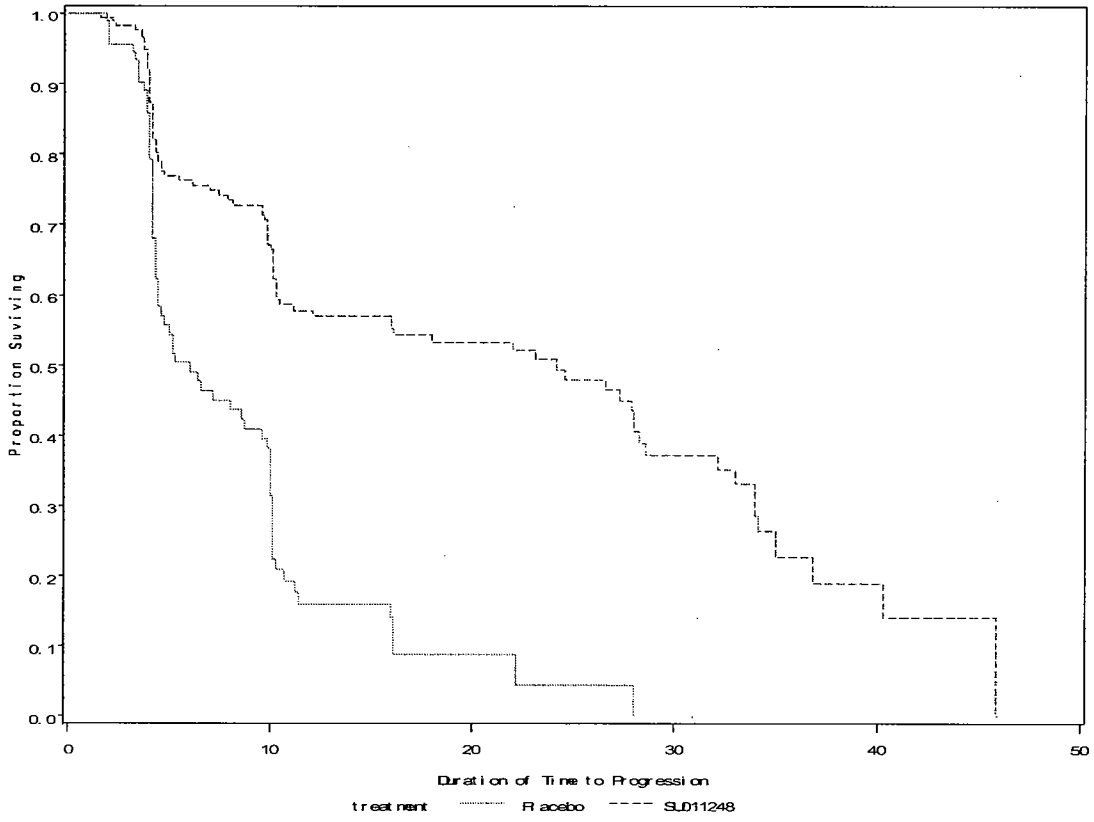
***Upper limit could not be calculated because the data were not yet mature.*

[a] *Pearson chi-square test.*

[b] *The first quartile of survival time for OS*

**Figure 5: Reviewer's Kaplan-Meier Plot of Progression Free Survival ***

**(ITT Population with Central Radiologist Assessments)**




* The statistical reviewer produced this Kaplan-Meier Plot based on the central radiologist assessment data resubmitted by the sponsor.

**Table 9: Sponsor's Summary of Results of Secondary Endpoint ORR (ITT population)**

| Variable (N=207) (N=105) | SU011248 | Placebo |
|---|---|---|
| Patients with Baseline Assessment [n (%)] | 178 ( 86.0) | 93 ( 88.6) |
| Patients with Measurable Disease at Baseline [n (%)] | 177 ( 85.5) | 91 ( 86.7) |
| Core Radiology Laboratory Data not Applicable [n (%)] | 29 ( 14.0) | 12 ( 11.4) |
| Best Overall Response During Blinded Phase [n (%)] | | |
| Complete Response | 0 ( 0.0) | 0 ( 0.0) |
| Partial Response | 14 ( 6.8) | 0 ( 0.0) |
| Stable Disease | 120 ( 58.0) | 50 ( 47.6) |
| Progressive Disease | 39 ( 18.8) | 39 ( 37.1) |
| Unable to Evaluate | 0 ( 0.0) | 0 ( 0.0) |
| Missing | 5 ( 2.4) | 4 ( 3.8) |
| Overall Confirmed Objective Response Rate (CR+PR) | 14 ( 6.8) | 0 ( 0.0) |
| 95% Exact CI [1] | ( 3.7, 11.1) | |
| Duration of Progression Free [n (%)] | | |
| < 6 Months | 101 ( 48.8) | 49 ( 46.7) |
| >= 6 Months | 33 ( 15.9) | 1 ( 1.0) |

[*Source: Study Repot Table 13.4.3.1.1.]* [1] % = (n/N)*100,

## Reviewer's Comment:

[1] Since this was the result of the second interim analysis and the pre-specified nominal alpha-level for the primary endpoint TTP is 0.0031, the p-values for the secondary endpoints should be compared with 0.0031, not 0.05.

[2] Per sponsor, the originally submitted results of PFS were based on the central objective radiologist assessment data where 41 patients did not have data available. PFS for those 41 patients were censored at the date of randomization. In fact, among these 41 patients, 7 patients died. Per protocol, 5 (2 in Su011248 group and 3 in placebo group) out of 7 deaths should be considered as PFS events and should not be censored in the PFS analysis. After FDA statistical reviewer requested, the sponsor resubmitted PFS results with another censoring scheme for those 41 patients. There were 164 PFS events (73 in Placebo group and 91 in Su011248 group). This reviewer verified the resubmitted PFS results.

[3] The results of ORR in Table 9 were verified by this reviewer. The p-value for testing treatment difference is 0.006, which is derived from Chi-squared test and should be interpreted with caution.

[4] Overall survival is an important endpoint even though it is the secondary endpoint in this study. The sponsor presented two overall survival analysis results. One OS analysis based on the data excluded deaths after patient's cross-over. Another OS analysis analyzed patients as they were originally randomized. In other words, this OS included 56 deaths with twenty-nine (14% of 207) vs. 27 patients (26% of 105) on SU011248 vs. placebo, respectively, who died by the time of this interim analysis. This OS analysis was contaminated when patients in placebo arm switched to open-label treatment arm. As indicated in Table 8, at that time, median OS had not been reached for either

treatment arm because the data were not yet mature. The first quartile for OS was 40.0 (95% CI: 29.7 weeks to **) [** upper limit could not be calculated because the data were not yet mature] vs. 15.9 weeks (95% CI: 11.3 to 33.7 weeks). The hazard ratio (SU011248 vs placebo) was 0.491 (95% CI: 0.290 to 0.831; p = 0.007), indicating decreased risk of dying for SU011248 plus best supportive care vs placebo plus best supportive care. The risk of dying in the SU011248 group was approximately half that when compared to the placebo group. The trial stopped based on satisfactory efficacy results of the first interim analysis for efficacy. With about 1 year of maximum duration of treatment and follow-up, the data were not mature enough to determine the survival benefit offered by this therapeutic approach

### 3.2 EVALUATION OF SAFETY

Please refer to FDA clinical reviewer Dr. Rock's review for safety evaluation of Sutent (Su0011248).

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section will be focused on the reviewer's results of the exploratory subgroup analyses of the primary endpoint, time to progression (TTP).

### 4.1 GENDER, RACE, AGE AND REGION

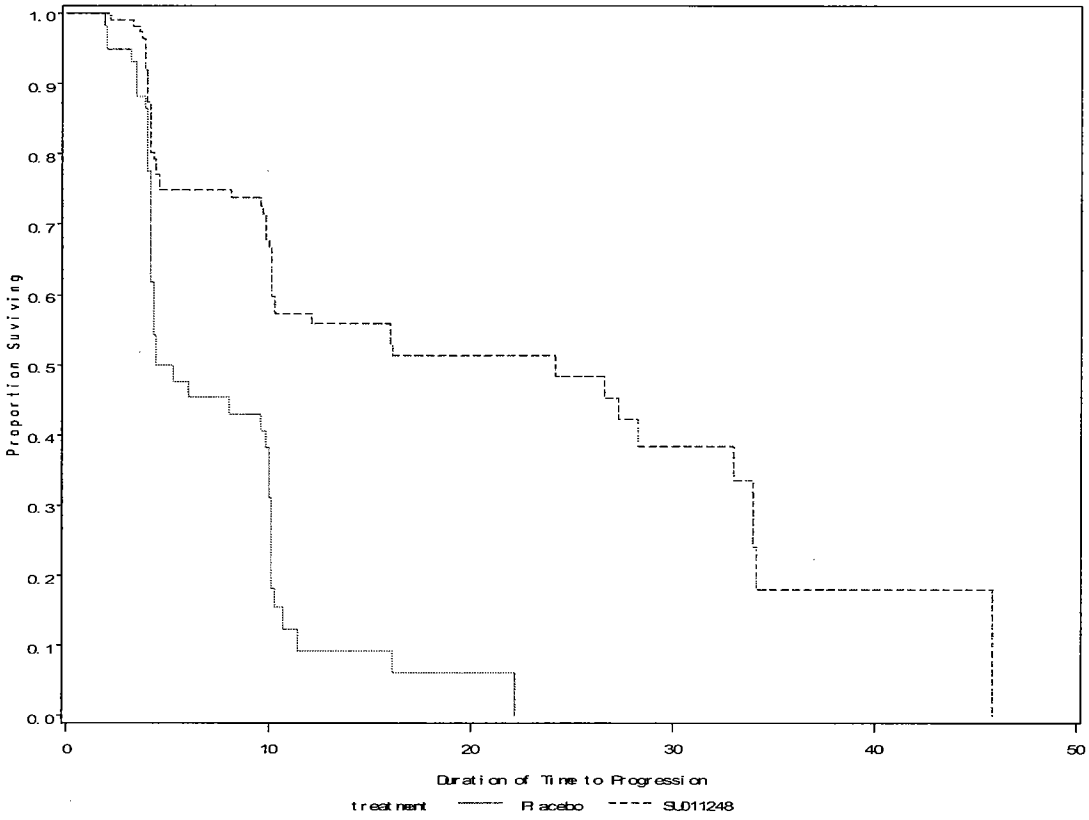
The following table is this reviewer's summary of subgroup analysis by gender, age, race and region. In this study, about 88% (275 out of 312) of patients were white and two thirds of patients were male. Kaplan-Meier survival curve of time to progression for subgroup of male is presented in the following figure. The subgroup results appeared consistent with the overall ITT population.

**Table 10: Summary of Result of Subgroup Analyses of Time to Progression (FDA's Analysis)**

| Subgroup | Sample size | | Hazard Ratio (Sutent / Placebo) (nominal 95% CI) | p-value (log-rank Test) |
|---|---|---|---|---|
| | Sutent | Placebo | | |
| Age >= 65 | 64 | 29 | 0.241 (0.123, 0.473) | <0.0001 |
| Age <65 | 143 | 76 | 0.373 (0.248, 0.561) | <0.0001 |
| Male | 132 | 64 | 0.322(0.211, 0.491) | <0.0001 |
| Female | 75 | 41 | 0.332 (0.179, 0.616) | <0.0001 |
| White | 183 | 92 | 0.324 (0.224, 0.469) | <0.0001 |
| U.S. and Canada | 96 | 47 | 0.375 (0.233, 0.603) | <0.0001 |
| Other Counties | 111 | 58 | 0.293 (0.176,0.489) | <0.0001 |

**Figure 6: Kaplan-Meier Plot of Time to Progression (Subgroup of all Male in ITT)**

**(FDA's Analysis*)**




## Reviewer's Comment:

[1] The results of primary endpoint, time to progress in subgroups of patients with age great than or equal to 65, age less than 65, female patients, male patients, White patients, North America (Canada and the United States) and other non-North America counties are consistent to overall ITT population, which indicate treating SU011248 combined with best supportive care for GIST patients with resistant to or intolerant of imatinib Mesylate statistically significantly prolonging time to progression comparing to the treatment with placebo plus best supportive care.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 SPONSOR'S EFFICACY CONCLUSIONS AND REVIEWER'S CONCLUSION/COMMENTS

The study A6181004 was designed as a multicenter, international, randomized double-blind phase III study in 312 patients with GIST who had experienced disease progression on or intolerance of imatinib mesylate therapy. The primary objective of this study was to compare the time to tumor progression (TTP) associated with SU011248 plus best supportive care (Arm A) versus that associated with placebo plus best supportive care (Arm B) for the treatment of patients with imatinib mesylate-resistant or intolerant malignant GIST. Per protocol, the primary efficacy endpoint was time to progression, and was defined as the time from randomization to first documentation of objective tumor progression or to death due to cancer (on treatment or within 28 days of last dose). Agreed with FDA in the preNDA meeting, the definition of TTP was revised (the death due to cancer was considered tumor progression in protocol, but in the submitted analysis results of TTP was censored at the time of last tumor evaluation prior to death). The sponsor concludes that SU011248 treatment for GIST patients resistant to or intolerant of imatinib mesylate prolongs statistical significantly time to progression (27.3 vs. 6.4 weeks; $p<0.0001$) comparing to the treatment with placebo plus best supportive care. An effect that was consistent for many subgroups of patients evaluated. Further, statistically significant improvement was seen in progression free survival (24.1 vs. 6.0 weeks; $p<0.0001$). Although the data was not mature to show the significance of survival advantage of SU011248 at the time of interim analysis, the overall survival analysis results show consistent with the results of TTP. Following are the reviewer's comments.

- This statistical reviewer verified the results of the study A6181004. The results of this study support the efficacy claimed by the sponsor based on primary endpoint TTP.
- Any comparison will be considered as statistically significant different if the p-value is less than 0.0031, since the results submitted for this NDA were from the interim analysis and the nominal alpha-level for the primary endpoint is 0.0031. No multiplicity adjustment among the secondary endpoints.
- Since this trial stopped based on satisfactory efficacy results of the second interim analysis (first interim analysis for the efficacy), the treatment period and follow up for some patients were too short to determine the survival benefit offered by this therapeutic approach.

## 5.2 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion, the results from the study A6181004 support the sponsor's claim of SU011248 treatment for GIST patients resistant to or intolerant of imatinib mesylate statistically significantly prolonging time to progression comparing to the treatment with placebo plus best supportive care. This study shows that treating with SU011248 combined with best supportive care statistically significant prolongs time to progression (27.3 vs. 6.4 weeks; $p<0.0001$),) compared with placebo plus best supportive care. The A6181004 was a multicenter, international, randomized, double-blind phase III study. The results of efficacy are based on the second interim analysis (first interim analysis for efficacy) with 149 TTP events

(based on the central radiologist assessment) and maximum of about 1 year duration of treatment and follow-up. It may need adequate treatment duration and follow-up time to show the efficacy of SU011248 treatment for GIST patients resistant to or intolerant of imatinib mesylate as compared to the treatment with placebo plus best supportive care in terms of overall survival.

APPENDICES

## APPENDIX 1 – Patient ID's whose progression dates were adjudicated by the FDA efficacy medical reviewer

**Table 11: List of IDs for Patients whose Progression Dates were Adjudicated**

| Patient ID | Treatment |
|---|---|
| A618X1004-038733-00002 | 50mg,4/2,QD |
| A618X1004-127449-00018 | 50mg,4/2,QD |
| A618X1004-113649-00039 | Placebo (blinded) |
| A618X1004-129926-00060 | 50mg,4/2,QD |
| A618X1004-127449-00063 | 50mg,4/2,QD |
| A618X1004-133140-00100 | 50mg,4/2,QD |
| A618X1004-133140-00116 | 50mg,4/2,QD |
| A618X1004-086022-00123 | 50mg,4/2,QD |
| A618X1004-130703-00131 | Placebo (blinded) |
| A618X1004-127984-00147 | 50mg,4/2,QD |
| A618X1004-011526-00160 | Placebo (blinded) |
| A618X1004-133140-00174 | 50mg,4/2,QD |
| A618X1004-086022-00180 | 50mg,4/2,QD |
| A618X1004-101149-00183 | Placebo (blinded) |
| A618X1004-029293-00198 | 50mg,4/2,QD |

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