

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-938 (GIST)

NDA 21-968(MRCC)

Medical Review(s)

I. REASON(S) FOR CONSULT REQUEST AND MAJOR FINDINGS:

Reason for consult: This consultation was requested to perform an analysis of the imaging dataset (CT of the chest, abdomen and pelvis) submitted to the NDA. Specifically, this request was to review the submitted images for completeness and to assess the image data integrity based upon a review of subjects identified by the clinical and imaging reviewers.

Major findings: FDA/DMIHP inspection of tumor lesion measurements and other imaging aspects supports the integrity of the independent radiographic review conducted by the sponsor's contractor, [REDACTED]

II. CLINICAL STUDIES

The major clinical study supporting the safety and efficacy of sunitinib was Study A6181004, a Phase 3, randomized, double-blind, placebo-controlled trial of sunitinib versus placebo in patients with gastrointestinal stromal tumor (GIST) who were intolerant of or who had disease progression during prior imatinib treatment. Patients enrolling on this study were randomized in a 2:1 ratio to receive sunitinib or matching placebo. The study design allowed for the crossover to open-label sunitinib for patients experiencing objective disease progression while receiving placebo. Patients randomized to sunitinib who showed evidence of objective progression could continue on open label sunitinib if the patient was deriving clinical benefit.

The primary objective of Study A6181004 was to compare the time to tumor progression (TTP) in patients receiving sunitinib plus best supportive care to patients receiving placebo plus best supportive care. Secondary objectives included comparison of progression free survival (PFS), objective response rate (ORR), and overall survival (OS); evaluation of the safety of sunitinib; evaluation of exposure to sunitinib and its active metabolite (SU012662); and patient reported outcomes for pain control and quality of life.

Patients eligible for Study A6181004 were to have experienced failure during prior imatinib treatment due to disease progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria (confirmed retrospectively by the core imaging laboratory) or intolerance defined as life-threatening toxicity at any dose or unacceptable toxicity at a moderate dose (i.e., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 toxicity or Grade 2 toxicity that was unacceptable to the patient, such as nausea). Eligible patients were also to be at least 18 years of age, have histologically-proven GIST that was not amenable to therapy with curative intent, measurable disease, adequate organ function as defined in the entry criteria and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were not eligible for the study if they had received treatment including chemotherapy, chemoembolization, immunotherapy, or an investigational agent after failure of imatinib or radiotherapy to sites of GIST disease. Females who were pregnant or breastfeeding were to be excluded.

The randomization stratification factors were 1) prior progressive disease (PD) within 6 months of the start of imatinib treatment vs. PD beyond 6 months from the start of imatinib treatment vs. intolerance, and 2) baseline McGill Pain Questionnaire's Present Pain Intensity Scale, MPQ-PPI score (0 vs. ≥ 1).

The sunitinib starting dose was 50 mg once per day using a Schedule 4/2 paradigm (four weeks on treatment/ followed by two weeks off). Dose reduction on an individual basis was permitted depending on treatment tolerability. Patients were to continue blinded treatment on study until documentation of disease progression according to protocol-specified RECIST criteria (Response Evaluation Criteria in Solid Tumors) or withdrawal from study for another reason.

Overall, 207 subjects were randomized to sunitinib and 105 were randomized to placebo. Some subjects (41) did not have evaluable follow-up radiographic images. The study's primary endpoint (time to progression) showed a median of 27 weeks for the sunitinib group versus 6.4 weeks for the placebo group ($p < 0.001$).

This report will focus on the radiographic endpoints of the study

III. RADIOGRAPHIC RESPONSE ASSESSMENT

A. Schedule of Radiographic Assessments

Tumor assessments using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans of the chest, abdomen and pelvis were performed at screening, on Day 28 of the first cycle and then at 6-week intervals, fixed according to the calendar, regardless of treatment delays. For patients without treatment delays, the schedule would equate to disease assessment on Day 28 (± 7 days) of each 6-week cycle. Additional scans were performed whenever disease progression was suspected.

Determination of objective disease response and progression was made according to RECIST criteria, consistent with the clinical protocol and independent radiographic charter pre-specified criteria. The independent radiographic review findings were used in the determination of the study's primary endpoint (time to progression).

B. Definitions of Radiographic Response

The prospectively stated definitions for radiographic response and progression for target and non-target lesions for study A6181004 were as follows:

a. Target Lesions

- **Complete Response Target Lesions (CR):** Disappearance of all target lesions.
- **Partial Response Target Lesions (PR):** At least a 30% decrease in the sum of the longest diameter (SLD) of target lesions, taking as reference the baseline SLD.
- **Stable Disease Target Lesions (SD):** Neither sufficient shrinkage of target lesions

to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the nadir SLD since the treatment started.

- **Progressive Disease Target Lesions (PD):** At least a 20% increase in the SLD of target lesions, taking as reference the nadir SLD recorded since the treatment started or, the presence of one or more new lesions.
- **Unable to Evaluate (UE):** A target lesion present at baseline which was not measured or which was unable to be evaluated (UE) leading to an inability to determine the status of that particular tumor for the time point in question.
- **Not Applicable (NA):** No target lesions were identified at baseline.
- **Not Done (ND):** Scans were not performed at this time point to evaluate the target lesions.

b. Non-Target Lesions

Each non-target lesion was to be qualitatively evaluated at each time point. Response of each lesion at each time point was assessed with respect to the baseline status. Progression was assessed with respect to nadir size of the non-target lesions. The overall non-target lesion response for each time point was assessed as the worst case for the non-target lesions for that particular time point. Response assessments were prospectively defined as follows:

- **Complete Response Non-Target Lesions (CR):** Disappearance of all non-target lesions.
- **Stable Disease (SD)/Incomplete Response (IR)-Decreased Non-Target Lesions:** The persistence of one or more non-target lesions not qualifying for CR or PD.
- **Progressive Disease (PD) Non-Target Lesions:** PD of Non-Target Lesions was defined as the “unequivocal progression” of existing non-target lesions or appearance of one or more new lesion(s). Lesions noted on bone scans will be considered non-target lesions. Regions of increased uptake in pre-existing lesions will not be considered as PD. The appearance of new lesions (i.e. new regions of abnormal uptake) is required to call PD.
- **Unable to Evaluate (UE):** A non-target lesion present at baseline which was not measured or was unable to be evaluated (UE) leading to an inability to determine the status of that particular tumor for the time point in question.
- **Not Applicable (NA):** No non-target lesions were identified at baseline.
- **Not Done (ND):** Scans were not performed at this time point to evaluate the non-target lesions.

c. Best Overall Response

Response at each time point was assessed as a combination of the target and non-target responses as well as the presence of new lesions. The time point responses were assessed with reference to baseline for the determination response and the nadir tumor size for evaluation of disease progression.

d. Primary Endpoint

- **Time to Tumor Progression (TTP)** was defined as the time from randomization to first documentation of objective tumor progression. If tumor progression data included more than one date, the first date was to be used.

e. Secondary Endpoints

- **Progression Free Survival (PFS)** was defined as the time from randomization to first documentation of objective tumor progression or death due to any cause. If PFS data included more than 1 date, the first date was used.
- **Objective Response Rate (ORR)** was defined as the proportion of patients with confirmed CR or confirmed PR according to RECIST.
- **Time to Tumor Response (TTR)** was defined as the time from date of randomization to first documentation of objective tumor response (CR or PR) that was subsequently confirmed TR.
- **Duration of Response (DR)** was defined as the time from the first documentation of objective tumor progression or to death on study.

IV. INDEPENDENT READ PROCEDURE

A. IMAGE HANDLING

The image handling procedures were prospectively described in the radiographic charter. Investigators were instructed to send images to [redacted] in the form of second original images, optical disks or CDs. A [redacted] radiologist was to perform quality assurance of the submitted images. A research assistant at [redacted] was to check daily for mailings from the sites. The research assistant was to perform the following: sort images, check all exam dates, subject's initials and subject numbers, notify the sites and Pfizer of missing images, blind any information pertaining to subject identification, and label all incoming images. A new subject file with label was to be made for a subject's initial submission. The old file was to be updated if a subject's additional submission was received. Detailed image tracking and reading information was to be recorded, consistent with the radiographic charter.

B. READING SESSIONS

Pfizer was to notify [redacted] what cases would be read without revealing subject outcome or treatment assigned (as described within the radiographic charter). Each [redacted] blinded radiologist was to read the Pfizer Protocol and to independently review the Protocol, Charter, Source Document and Instructions for Completion of the Source Document specific for this study. Protocol and tumor-specific training for each radiologist was to be documented and signed by the project manager and radiologist. Independently, two different blinded radiologists were to read all time points for each patient. The reads were to be designated "Radiology Read Number 1" and "Radiology Read Number 2". Neither radiologist (1 or 2) was to have access to the other reader's measurements or assessments. The only history provided to the readers was to be a radiation therapy report, as prospectively defined in the radiographic charter. Each radiologist was to complete standard [redacted] source documents for his or her independent reads. Every source document was to undergo 100% QC. The project manager was to complete the appropriate section of a "Read Comparison Source Document" page that would compare the results of Radiology Read Number 1 and Number 2. If any of the information between the Read Number 1 and Reader Number 2 was discordant, Radiologist Number 3 was to perform an adjudication of the radiology results. The adjudicator was to review, but not re-read, the two prior reads. The adjudicator would choose the read that he or she believed most accurately represented the best overall response, the date of the first radiographic response for those patients whose best responses CR or PR, and the date of progression. The adjudicator may not have agreed with either reader on the overall best response, date of first radiographic response, or date of progression. In this situation the adjudicator was to re-read the case and provide the best overall response, date of first radiographic response, or date of progression, as required. Missing data was not to be imputed.

V. FINANCIAL DISCLOSURE

The sponsor submitted financial disclosure information for all investigators/readers involved in the image assessments. None of these individuals reported financial arrangements with the sponsor.

VI. DESCRIPTION OF THE MATERIAL PROVIDED FOR REVIEW:

Pfizer [redacted] submitted an eight treatment cycle Image Database for Study A6181004. The image database consisted of a computer hard drive that contained digitized radiographs for applicable patient enrolled in these studies.

The following table summaries the number of subjects with radiographs by each cycle:

Table 1. Study A6181004 Image Database
Letter encryptions are supplied below the table

Number of Cycle	Pre-study	Base-line	1	2	3	4	5	6	7	8	Un-scheduled
Number of patients assessed	262	272	254	153	97	62	34	20	6	1	22
I			1	24	22	12	3	3	2	0	2
Number of patients not assessed	50	40	58	159	215	250	278	292	306	311	
B		32									
C			10								
UE			2	3	1	1	2				
E	16	2	2	1							
F	1		4								
M	25	6	9	4	4	5	2	2	2		
N	8										
NA			31	151	210	244	274	290	304	311	
Censor			32	15	13	13	6	5	3		

- A =Assessment performed and complete
- B = Baseline scans received but baseline assessment not performed because no on-study assessments available
- C = No on-study assessments performed because of early patient clinical deterioration, death or discontinuation due to adverse experience
- UE = Scans received but assessment outcome is "Unable to Evaluate"
- E = Scans received but inadequate to attempt assessment
- F = Scan performed by Investigator but not received at [] in time for assessment
- PD = Progression of Disease determined per []
- I = Scans beyond disease Progression received and assessed by []
- K = Withdrawal due to disease progression per Investigator or other reasons but prior to disease progression per []
- M = Missing, not received from the study center
- N = Not required
- NA = Not applicable due to reason described in footnotes PD, K, Censor
- Censor = Censored for analysis beyond the cycle Indicated

[] successfully loaded the Imaging Database at the FDA on August 18, 2005. Dr. David Clunie provided the initial technical orientation on the same day. Mr. Robert Stokes provided formal technical instruction on August 19 and September 1st, 2005. Dr. Robert Ford provided formal training sessions on September 8, 9, 12, and 13, 2005.

VI. FDA CONSULTANT’S REVIEW OF RADIOGRAPHIC DATASET

Dr. Edwin Rock, the FDA clinical reviewer on the GIST file, submitted a random sample of 45 subjects for radiographic review, (30 on study drug, 15 on placebo). The 45 subjects selected all had CT scans of the chest, abdomen, and pelvis. All images submitted to FDA

inspection were digital images; however these images consisted of either cut film which was digitized by [] for radiographic review or film digitally acquired on disc or CD and processed for review (a process performed for the independent radiographic review, consistent with the radiographic charter).

Dr. Rock requested review of the following 45 subjects:

Table 2. Reviewed Subjects

Pfizer Subject ID	[] Subject ID
A618X1004-011526-00009	01008000009
A618X1004-011526-00028	01008000028
A618X1004-011526-00034	01008000034
A618X1004-011526-00177	01008000177
A618X1004-014405-00161	01014000161
A618X1004-034186-00152	01015000152
A618X1004-038733-00002	01006000002
A618X1004-038733-00014	01006000014
A618X1004-038733-00055	01006000055
A618X1004-038733-00064	01006000064
A618X1004-038733-00135	01006000135
A618X1004-038733-00215	01006000215
A618X1004-038733-00261	01006000261
A618X1004-038733-00298	01006000298
A618X1004-039285-00113	01048000113
A618X1004-039285-00204	01048000204
A618X1004-067665-00256	01007000256
A618X1004-086022-00109	01029000109
A618X1004-086022-00141	01029000141
A618X1004-086022-00217	01029000217
A618X1004-088097-00156	01054000156
A618X1004-103556-00092	01034000092
A618X1004-103556-00282	01034000282
A618X1004-110129-00246	01051000246
A618X1004-113649-00076	01013000076
A618X1004-113649-00118	01013000118
A618X1004-125359-00277	01017000277
A618X1004-127449-00023	01019000023
A618X1004-127449-00045	01019000045
A618X1004-127449-00090	01019000090
A618X1004-127449-00130	01019000130
A618X1004-127962-00268	01025000268
A618X1004-127964-00287	01024000287
A618X1004-127982-00305	01022000305
A618X1004-129412-00236	01063000236
A618X1004-129538-00052	01031000052
A618X1004-129538-00182	01031000182
A618X1004-129538-00240	01031000240
A618X1004-130482-00173	01035000173

A618X1004-130706-00072	01040000072
A618X1004-131182-00193	01044000193
A618X1004-131182-00308	01044000308
A618X1004-133140-00100	01056000100
A618X1004-133253-00197	01057000197
A618X1004-138236-00226	01065000226

The FDA radiographic reviewers were able to verify the measurement of the target lesions and description of the non-target lesions of the independent readers for 38 of the 45 selected subjects. Some randomized subjects did not have evaluable follow-up images at the requisite time points for [redacted] to incorporate into the central radiographic review. This included the [redacted] radiographic subject IDs: 01048000113, 01034000092, 01220000305, 01040000072, 01040000308, 01025000268, 01006000298. As noted in the study report, evaluable radiographic data were not available for 41 of the 312 randomized subjects (29 subjects randomized to sunitimib and 12 subjects randomized to placebo).

Radiographs from an additional 22 subjects (randomly chosen by the FDA image inspector) were also reviewed. The additional subjects had the following [redacted] subject ID numbers: 01015000001, 01006000003, 01006000004, 01011000005, 01002000242, 01002000249, 01060000015, 01013000039, 01014000086, 01008000026, 01048000244, 01051000201, 01051000181, 01032000171, 01019000142, 01054000134, 01055000124, 01036000108, 01006000044, 01041000071, 01025000085, 01041000094.

All reviewed subjects had received CT scans of the chest, abdomen, and pelvis. Exams consisted of a mixture of direct digital data and digitized films. While it was not possible to perform the window and leveling process on the digitized films, it was possible to adjust contrast to optimize comparison to the digital films.

Examinations could be loaded into the system as complete studies or as a series where only sections with measurements were loaded. The images could be reviewed for an individual reader or for both readers simultaneously, either by annotation of both readers' measurements onto a single image or by viewing images on adjacent computer screens.

The FDA consultant was able to perform additional limited technical functions on the images to enhance viewing and interpretation to include measuring lesions. Pre-screening, baseline screening, and follow up exams could be viewed simultaneously. The technical quality was very good to excellent overall. The additional technical settings such as the zoom and contrast were occasionally helpful for comparing direct digital data to digitized data for example in evaluating the hepatic parenchyma. Examinations reviewed satisfied the timeline guidelines of the protocol.

Image review for lesions was performed on the complete studies at screening and at the last time point and either on complete studies or studies with measurements only for intermediate scans obtained off cycle (unscheduled) or for scheduled cycle scans. Each subject had a complete read comparison document which correlated to the information on the independent radiology results. Both readers' measurements were reviewed and results

also correlated to the overall independent radiology results.

Sixteen (16/60) of the reviewed cases were adjudicated. The most common discrepancies requiring adjudication were attributed to the choice of lesion to measure and the time point at which a lesion was called “new.” Full studies were reviewed for all adjudicated cases. Some lesions were measured for each adjudicated case. There was no significant difference in lesion size measured by the readers and the FDA consultant.

VII. OVERALL ASSESSMENT

Conclusion

In conclusion, in the performance of the quality check and assessment of the radiographic data integrity, the FDA reviewers were able to verify the independent reading interpretations for all of the 60 subjects queried.

Recommendation on Regulatory Action

The submitted radiographic database supports the integrity of the radiographic review conducted by [redacted]. These data are submitted in support of efficacy of SUTENT for the proposed indication – use in the treatment of patients with Gastrointestinal Stromal Tumor (GIST).

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/s/

Rafel Rieves
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	021938
Submission Code	N000
Letter Date	August 10, 2005
Stamp Date	August 11, 2005
PDUFA Goal Date	February 11, 2006
Reviewer Name	Edwin P. Rock, M.D., Ph.D.
Team Leader	Ramzi Dagher, M.D.
Review Completion Date	January 24, 2006
Established Name	SU011248
(Proposed) Trade Name	SUTENT
Therapeutic Class	Tyrosine kinase inhibitor
Applicant	Pfizer
Priority Designation	P
Formulation	12.5, 25, and 50 mg capsules
Dosing Regimen	50 mg by mouth once daily
Indication	Gastrointestinal stromal tumor (GIST) that has progressed on or is intolerant to imatinib mesylate
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Division of Drug Oncology Products (DDOP), OODP, CDER, FDA recommends that FDA approve SUTENT via the regular approval mechanism for treatment of gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib mesylate. This recommendation follows from assessment of interim results of Study A6181004, an adequate and well-controlled clinical trial that provides substantial evidence of efficacy for this indication. A single-arm Phase 2 study, RTKC-0511-013, provides supportive data. There is no other known effective therapy, either approved or off-label, for this indication.

Study A6181004 is a randomized, double-blind, placebo-controlled, international Phase 3 clinical trial in 56 centers on three continents. This trial compared SUTENT versus placebo for treatment of patients who had progressed on or were intolerant to imatinib mesylate (Gleevec). Patients were randomized 2:1 to SUTENT versus placebo. The primary objective was time to tumor progression (TTP). After 149 progression events occurred, an interim analysis for efficacy revealed that patients on SUTENT experienced a more than four-fold increase in median TTP from 6.4 to 27.3 weeks (HR 0.33, 95% CI 0.23-0.47, log-rank $P < 0.0001$). This result exceeded the O'Brien Fleming stopping boundary of $P < 0.0042$, and the trial was unblinded due to a compelling positive efficacy result. 14 patients experienced partial responses for an objective response rate of 6.8%. Survival data is not mature.

Relative to clinical benefit demonstrated in this indication, SUTENT is safe for use by all tests reasonably applicable to assessment of safety. Common adverse events following from use of SUTENT include increased blood pressure, gastrointestinal disturbances, skin abnormalities, altered sense of taste, asthenia, and laboratory abnormalities. Common laboratory abnormalities include elevated pancreatic enzymes, electrolyte disturbances, lowered neutrophils and platelets.

Two important safety questions persist. First, Study A6181004 revealed an increased incidence of decreased LVEF in patients on SUTENT (11%) versus those on placebo (3%). Although there was no difference in clinical heart failure observed between the two study groups, patients with baseline cardiac abnormalities were excluded from Study A6181004. Cardiac safety of SUTENT in patients with preexisting cardiac abnormalities remains unknown.

Second, adrenal toxicity was seen in rats and monkeys at doses as low as 0.7 times the AUC observed in clinical trials. Although no overt clinically important adrenal suppression was observed in patients taking SUTENT, patients on SUTENT undergoing physiologic stress such as infection, trauma, or surgery may be unable to mount an appropriate adrenal response due to subclinical adrenal toxicity. Such subclinical toxicity would be difficult to detect without unmasking by physiologic stress. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma, or severe infection.

Data submitted are adequate to provide directions for use, including dose, dose adjustment, and safety considerations.

Simultaneous with this application, the sponsor submitted NDA 021968 in support of an additional SUTENT indication for treatment of advanced renal cell carcinoma. Dr. Vicki Goodman of DDOP conducted the primary review of studies under NDA 021968.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activities have been recommended.

1.2.2 Required Phase 4 Commitments

DDOP recommends regular approval of SUTENT for treatment of GIST after progression on or intolerance to imatinib. The following are suggested Phase 4 commitments.

1. Submit the completed report and datasets for study titled "A Phase 1 Study to Evaluate the Effect of SU011248 on Cardiac Repolarization Following Repeat Doses of SU011248 in Patients with Advanced Solid Tumors".
2. Submit the completed report and datasets for study titled "A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function".
3. Submit completed final study report for study titled "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".

1.2.3 Other Phase 4 Requests

No other Phase 4 requests were made.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

SUTENT is an oral inhibitor of multiple receptor tyrosine kinases (RTKs). This agent has been studied in numerous oncologic diseases. Indications have been submitted in advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumor (GIST) following progression on or intolerance to imatinib mesylate (Gleevec). The database submitted in support of the advanced renal cell carcinoma indication is reviewed separately by Dr. Vicki Goodman (NDA 021968).

Study A6181004, “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”, has an intent-to-treat population of 312 randomized patients. This study remains ongoing. Interim results were submitted in support of the efficacy claim for regular approval of SUTENT for the GIST indication.

The safety database covered by this review comprises the As Treated (AT) population enrolled in Study A6181004. The AT population in Study A6181004 includes 202 patients who received SUTENT and 102 patients who received placebo.

1.3.2 Efficacy

Study A6181004 is a randomized, double-blind, placebo-controlled, international Phase 3 clinical trial in 56 centers on three continents. This trial compared SUTENT versus placebo for treatment of patients who had progressed on or were intolerant to imatinib mesylate (Gleevec). Patients were randomized 2:1 to SUTENT versus placebo. The primary objective was time to tumor progression (TTP). Secondary endpoints included response rate (RR), progression-free survival (PFS), overall survival (OS), patient reported outcomes (PROs), safety, exposure levels (AUC), and potential biomarkers of activity.

Radiographic images for establishment of tumor response and tumor progression were assessed by an independent, blinded core radiology laboratory. After 149 progression events had occurred, an interim analysis for efficacy revealed that patients on SUTENT experienced a more than four-fold increase in median TTP from 6.4 to 27.3 weeks (HR 0.33, 95% CI 0.23-0.47, log-rank $P < 0.0001$). This result exceeded the O’Brian Fleming stopping boundary of $P < 0.0042$, and the trial was unblinded due to a compelling positive efficacy result. 14 patients experienced partial responses for an objective response rate of 6.8%. Survival data is not mature. PRO data was not submitted in the NDA reviewed here.

Several factors bolster the credibility of efficacy results from Study A6181004. First, the study was well designed. Double-blinding, regular radiographic assessment for progression, central and blind reading of radiographic images, and an appropriate prospective statistical analysis plan each ameliorated potentially limiting sources of bias in measurement of the primary endpoint.

Second, treatment groups were well balanced at baseline. Third, although survival results remain immature, results for the primary endpoint of TTP were statistically robust. Finally, supportive evidence of SUTENT's efficacy was provided by Study RTKC-0511-013, a single-arm trial of SUTENT in patients with GIST following progression on or intolerance to imatinib. A 9% partial response rate was observed in this latter trial.

In conclusion, there is substantial evidence of efficacy for SUTENT for treatment of GIST that has progressed on or is intolerant to Gleevec. For this indication no other effective therapy is available, either approved or off-label.

1.3.3 Safety

Study A6181004 was designed to collect appropriate clinical and laboratory adverse event (AE) information. The randomized trial design enabled direct comparison of AE rates in groups treated with SUTENT versus placebo. Median duration of blinded study treatment was two cycles for patients on SUTENT (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo.

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 56% vs. 51% of patients on SUTENT versus placebo, respectively. Grade 3 or 4 AEs increased in incidence in patients receiving SUTENT relative to placebo include diarrhea (4% vs. 0%), hypertension (4% vs. 0%), and decreased platelets (5% vs. 0%).

Common (>10%) adverse events following from use of SUTENT relative to placebo include hypertension (15% vs. 11%), diarrhea (40% vs. 27%), constipation (20% vs. 14%), mucositis/stomatitis (29% vs. 18%), skin abnormalities (63% vs. 54%), altered sense of taste (21% vs. 12%), asthenia (22% vs. 11%), and laboratory abnormalities. Common laboratory abnormalities include elevated pancreatic enzymes (35% vs. 30%), electrolyte disturbances (38% vs. 20%), lowered neutrophils (53% vs. 4%) and platelets (38% vs. 4%), and decreased left ventricular ejection fraction (LVEF) (10% vs. 3%). Uncommon (<10%) laboratory abnormalities following from use of SUTENT include hypophosphatemia (9% vs. 0%) and acquired hypothyroidism (4% vs. 1%).

Safety data is limited by the fact that SUTENT has not been studied in patients with liver disease or pre-existing heart disease.

Two important safety questions persist. First, Study A6181004 revealed an increased incidence of decreased LVEF in patients on SUTENT (11%) versus those on placebo (3%). There was no difference in clinical heart failure observed between the two study groups with one death from diagnosed heart failure occurring in both SUTENT and placebo groups. However, patients with baseline cardiac abnormalities were excluded from Study A6181004. It is not clear whether

patients with cardiac abnormalities before starting SUTENT will experience increased incidence of clinical heart failure.

Second, adrenal toxicity was seen in rats and monkeys at doses as low as 0.7 times the AUC observed in clinical trials. No overt clinically important adrenal suppression was observed in patients taking SUTENT. However, if SUTENT is even marginally toxic to the adrenals, patients undergoing stress such as infection, trauma, or surgery may be unable to mount an appropriate adrenal response. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma, or severe infection.

There is negligible abuse potential for SUTENT. Overdosage has not been observed. Use during pregnancy or lactation has not been studied and is not recommended. No pediatric studies have been performed. [

]

In conclusion, there is adequate data to be able to make an appropriate safety assessment of SUTENT, as well as to provide directions for safe use in the approved indication. Given that there is no other therapy known to be effective in treatment of second-line GIST following imatinib, the safety profile of SUTENT on balance is not limiting. Additional information should be collected concerning pharmacokinetics of the drug in hepatic insufficiency, as well as cardiac effects both after longer drug exposures and in patients with pre-existing heart disease.

1.3.4 Dosing Regimen and Administration

The recommended dose of SUTENT[®] is one 50-mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off. SUTENT[®] may be taken with or without food. Dose increase or reduction of 12.5-mg increments is recommended based on individual safety and tolerability.

Five regimens varying in schedule and daily dose were assessed in a Phase 1/2 dose-finding study. Based on tumor responses and adverse events, the dosing regimen listed above was selected. Dose-response evaluation at that time was adequate, as was subsequent exposure-response evaluation based on the datasets submitted in this NDA.

1.3.5 Drug-Drug Interactions

Dosing adjustments for patients on CYP3A4 inhibitors

There was an approximately 50% increase in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with ketoconazole. To adjust for this increase, FDA clinical pharmacology reviewers recommend that sunitinib dose be reduced to 66% of the recommended dose in patients who must receive strong CYP3A4 inhibitors concomitantly.

Dosing adjustments for patients on CYP3A4 inducers

There was an approximately 50% decrease in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with rifampin. To adjust for this decrease, the clinical pharmacology reviewers recommended that the sunitinib dose be increased to 175% of the recommended dose in patients who must receive CYP3A4 inducers concomitantly.

Preliminary pharmacodynamic analysis suggests an exposure-response relationship based on gender. In this analysis likelihood of response correlated directly with exposure. This combined with the generally higher exposures (AUC) found in women by population PK analysis suggests that men treated with SUTENT may benefit from taking a higher dose. However, there is no prospective clinical data to test this hypothesis.

1.3.6 Special Populations

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for age, body weight, creatinine clearance, race, gender or ECOG score.

The pharmacokinetics of sunitinib have not been evaluated in pediatric patients.

Appears This Way
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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

- Established name: SU011248
- Generic drug name: sunitinib
- Proposed trade name: SUTENT
- Chemical class: new molecular entity
- Pharmacological class: tyrosine kinase inhibitor

SUTENT is a small-molecule inhibitor of receptor tyrosine kinases (RTKs). Inhibition of tyrosine kinase activity by sunitinib has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. Table 1 summarizes these data for the primary RTKs inhibited by SUTENT. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Table 1. Inhibition of Target Receptor Tyrosine Kinases by Sunitinib

(Source: Sponsor's proposed label, NDA 021938, SN#000)

Tyrosine Kinase	Biochemical Ki ^a (µM)	Cellular IC ₅₀ (µM)	
		RTK Phosphorylation ^b	Cell Proliferation ^d
VEGFR1	0.002	ND	ND
VEGFR2	0.009 (Flk-1)	0.004 (KDR) 0.01 (Flk-1) ^c	0.004 (KDR)
VEGFR3	0.017	ND	ND
PDGFR α	ND	ND	0.069
PDGFR β	0.008	0.004, 0.01 ^c	0.039
KIT	ND	0.001-0.01 ^c , 0.013	0.002
FLT3-ITD	ND	0.05 ^c	0.001-0.01
RET	ND	0.05 ^c	0.05
CSF-1R	ND	0.05-0.1 ^c	ND

ND = not determined; ITD = internal tandem duplication; KDR = human ortholog of VEGFR2; Flk-1 = mouse ortholog of VEGFR2

^a Values were determined in biochemical kinase assays using recombinant enzymes.

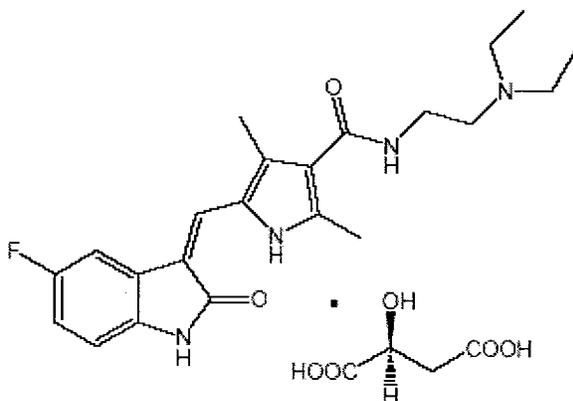
^b Values were determined by measuring intrinsic or ligand-stimulated kinase activity (phosphorylation) in cell lines expressing a given target RTK by immunoblot^c or ELISA assay.

^c Values (or value ranges) were estimated from immunoblot analysis of RTK phosphorylation over a range of concentrations.

^d Values were determined by measuring intrinsic or ligand-stimulated cell proliferation in cell lines expressing a given target RTK.

SU011248 was studied in humans as a free base formulation prior to February 2002. After February 20002, the drug was formulated as an L-malate salt. The structural formula of SUTENT is depicted in Figure 1.

Figure 1: Structural Formula of SU011248 L-Malate Salt



The indication addressed in this review is for treatment of gastrointestinal stromal tumor (GIST) that has progressed on or is intolerant to imatinib. Recommended starting dose is 50 mg orally once daily for four weeks, followed by a two week rest period. Dose adjustments are proposed based on toxicity in 12.5 mg decrements. No dose adjustments are proposed based on age. SUTENT has not been studied in children.

2.2 Currently Available Treatment for Indications

There are no available alternatives to the proposed product for the proposed indication that have been generally recognized as both safe and effective. Cytotoxic chemotherapy and palliative radiotherapy have each been used for this indication. Both suffer from low response rates (< 5%) and a substantial burden of toxicity.

2.3 Availability of Proposed Active Ingredient in the United States

Sutent, a new molecular entity, has not previously been marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

Sorafenib (Nexavar) is an oral tyrosine kinase inhibitor with an activity spectrum similar to that of SUTENT. Nexavar inhibits Raf kinase, VEGF-R2, PDGFR, c-kit, and FLT-3 activity. It was

approved for use in advanced renal cell carcinoma (RCC) on December 20, 2005. In a randomized phase 3 trial comparing sorafenib to placebo in patients with advanced RCC, progression-free survival increased from 84 to 167 days in patients who received sorafenib. The hazard ratio for progression was 0.44 (95% CI 0.35, 0.55). However, response rate was negligible (2% for sorafenib-treated patients vs. 0% for placebo-treated patients).

Common adverse events associated with sorafenib use include rash, hand-foot syndrome, hypertension, diarrhea, sensory neuropathy, neutropenia, increased lipase, hypophosphatemia and hypocalcemia. Incidence of severe hemorrhage was 3% in the sorafenib arm (12/384) vs. 1% (4/385) in the placebo arm. No increase in wound healing complications was noted although few patients were at risk.

Avastin (bevacizumab), a marketed monoclonal antibody inhibitor of VEGF-A, has several unusual and potentially life-threatening toxicities that may be mediated by its inhibition of VEGF. Thus it may be relevant to the safety profile of sunitinib. In studies of patients with advanced colorectal cancer in which bevacizumab was combined with chemotherapy, toxicities included:

- Gastrointestinal Perforations/Wound Healing Complications
- Hemorrhage
- Hypertension/Hypertensive Crises
- Proteinuria and Nephrotic Syndrome
- Congestive Heart Failure
- Arterial Thromboembolic Events

Another unusual toxicity seen with bevacizumab in clinical studies was exfoliative dermatitis, with incidence of 19% in one group of patients receiving bevacizumab in combination with 5-fluorouracil.

2.5 Presubmission Regulatory Activity

4/16/01	IND 62,382 Stamp Date
2/02	Sponsor switched from free-base to L-malate salt form of study drug.
8/22/02	Medical Officer review of submissions #028 (6/6/02) and #036 (7/26/02) <ul style="list-style-type: none">• FDA agreed to schedule of 4 weeks treatment followed by 2 weeks rest.• Based on observed adrenal toxicity in 2 animal species, presence of homologous receptors in human adrenal, and 2 patients with abnormal cortisol responses to ACTH stimulation, FDA advised as follows.<ul style="list-style-type: none">○ Investigators should perform ACTH stimulation tests to screen for adrenal functional reserve; and

- Patients should be informed that SU011248 may cause changes in adrenal functional reserve in humans.

- 5/13/03 Type A Meeting on GIST Phase 3 randomized trial.
 - FDA responses to sponsor queries included the following.
 - TTP was accepted as an endpoint supporting regular approval of Sutent for treatment of malignant GIST following progression on imatinib, dependent on magnitude of benefit and conduct of the study.
 - Response rate and duration would be considered in addition to TTP.
 - TTP was recommended as the sole primary endpoint.
 - Definition of TTP should be standard; deaths without progression should be censored at the last progression-free assessment date.
 - Primary analyses should be performed on intent-to-treat populations.
 - Log rank analysis of the primary endpoint should be based on a pre-specified number of events rather than calendar time.

- 6/24/03 Fast Track Designation granted for imatinib-resistant malignant GIST.

- 8/13/03 SPA requested for imatinib-resistant or intolerant malignant GIST.
 - FDA responded as follows.
 - Imaging review should be used to confirm both eligibility and response.
 - Patients should be stratified on progression vs. imatinib intolerance.
 - Secondary endpoints will be considered only if primary analysis of the primary endpoint shows persuasive evidence for study drug efficacy.
 - Secondary endpoints for claims should be pre-specified, hypothesis-based, and agreed to prospectively by FDA.
 - A positive control was urged for evaluation of QTc prolongation.

- 10/16/03 Teleconference to discuss adrenal toxicity cancelled by sponsor.
 - FDA responded to pre-meeting queries as follows.
 - The sponsor's ACTH stimulation test method was adequate.
 - FDA concurred with sponsor's proposal to conduct ACTH stimulation testing in the GIST Phase 3 protocol (357 patients randomized 2:1 to placebo) at baseline, end of Cycles 2, 4, 6, and end of study.

- 11/10/03 End-of-Phase 2 meeting for metastatic renal cell carcinoma indication.

- 1/12/04 Teleconference to discuss evaluation of potential for QTc prolongation.
 - FDA advised sponsor to conduct a positive control study powered to detect QTc interval prolongation of at least 5 msec by moxifloxacin on Day 1, followed by rest on Day 2 and initiation of SU011248 on Day 3.

- 3/9/04 Sponsor submits Statistical Analysis Plan, Independent Review Charter for confirmation of radiology finding, and changes in GIST trial design.

- FDA responded as follows.
 - Interim analysis at 25% information time risks erroneous conclusions.
 - Adding interim analysis at 75%, however, would be acceptable.
 - Primary analysis employs the log rank test, so O'Brien-Fleming stopping boundaries should be p-values rather than hazard ratios.
 - Given multiple interim analyses, the final analysis stopping boundary should be adjusted using the Lan-DeMets procedure.
 - Primary efficacy analysis should be on the intent-to-treat population.
 - Secondary claim(s), *e.g.* based on time to pain progression, will be unsupported by secondary endpoint(s) if
 - Missing data, particularly if unbalanced, precludes interpretation or
 - Difference(s) between arms don't appear to be clinically meaningful.
- 4/13/04 SPA requested for first-line treatment of metastatic renal cell carcinoma.
- 5/27/04 Teleconference to discuss MRCC SPA and patient-reported outcomes.
- 5/28/04 Treatment protocol A6181036 was submitted ("A Treatment Protocol for Patients with Gastrointestinal Stromal Tumor who are Ineligible for Participation in Other SU011248 Protocols and are Refractory to or Intolerant of Imatinib Mesylate").
- FDA asked that response criteria be defined precisely.
 - FDA asked that information be added to the protocol to apprise investigators of the risk of adrenal gland dysfunction.
- 9/23/04 Pre-NDA meeting for GIST or cytokine-refractory MRCC.
- Sponsor will include CRFs from all GIST responders, as well as SAEs and discontinuations due to death or AEs, in the NDA.
 - Sponsor will pool GIST patient data from Phase 2 (RTKC-0511-013) & Phase 3 (A6181004) studies in Summaries of Clinical Efficacy & Safety. Individual full datasets will be provided.
 - For the supportive Phase 1/2 study (RTKC-0511-013), only films for investigator-reported, RECIST-defined responses will be read by independent third-party reviewers.
 - Safety data from GIST Treatment Protocol A6181036 would be provided in the NDA Summary of Clinical Safety, separately from integrated data collected from other studies. Final data will be submitted to the IND on study conclusion.
 - For Study A6181005 ("A Phase 1 Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors"), Sponsor will submit a full study report when completed, potentially not at the time of NDA submission. A summary of categorical analysis of outliers in QTc duration and changes from baseline will be provided in the NDA.
 - Independent reports in Module 2 will provide cardiac & adrenal data.

- Sponsor will provide patient narratives for all SAEs, discontinuations due to AEs, & deaths during the safety collection period for all patients treated with SU011248 either as single agent or combination therapy.
- 1/21/05 FDA responds to sponsor queries in advance of second pre-NDA meeting. Sponsor cancelled meeting that was scheduled for February 10, 2005.
- FDA concurred with sponsor's plans for submission logistics, clinical pharmacology analysis, clinical efficacy, and nonclinical data.
- 1/26/05 Teleconference to discuss unblinded interim data from GIST Phase 3 trial.
- Sponsor reported that the Data Safety Monitoring Board (DSMB) met on January 24, 2005 and found the following.
 - For ITT analysis, there were 181 patients on the SU011248 arm and 91 patients on placebo.
 - Median TTP was 21.9 weeks on SU011248 & 6 weeks on placebo.
 - Median PFS was 16 weeks on SU011248 & 6.1 weeks on placebo.
 - The progression hazard ratio was 0.353, and the p-value was < 0.0001.
 - There were 19 deaths on SU011248 and 20 deaths on placebo.
 - The survival hazard ratio was 0.461, and the p-value was = 0.0133.
 - Frequent AEs included fatigue (45%), diarrhea (45%), anorexia (40%), nausea (36%), abdominal pain (35%), vomiting (27%), & asthenia (24%).
 - Grade 3/4 toxicities on SU011248 included neutropenia/leucopenia (6.3%), thrombocytopenia (3.8%), diarrhea (5.1%), asthenia (5.7%), fatigue (7.6%), infections (2.5%), elevated amylase (1.9%), hypoglycemia (2.5%), pulmonary embolism (1.9%), rash (1.9%), hypertension (3.8%), and thrombosis (1.9%).
 - 33.8% of patients on SU011248 had systolic blood pressure > 150 mm Hg versus 22.1% of placebo patients.
 - ACTH stimulation testing/analysis on 12 patients revealed normal results.
 - Based on consistency of compelling analyses, the DSMB recommended trial unblinding and placebo cross-over to study drug.
 - Sponsor stated concern that placebo was no longer an appropriate control given 1) Phase 2 data, 2) interim results exceeding the stopping boundary, and 3) consistency of results over multiple endpoints, including survival.
 - FDA concurred with this reasoning but referred any trial termination decision(s) back to sponsor.
 - FDA inquired about availability of expanded access.
 - Sponsor stated treatment protocol ready, but not yet in place.
 - FDA recommended modification of treatment protocol to allow patient enrollment if the GIST Phase 3 trial had stopped.
- 2/10/05 Guidance meeting regarding unblinding of GIST Phase 3 data.
- Sponsor agreed
 - 1) to continue ACTH stimulation testing at baseline and follow-up;

- 2) to submit ACTH testing results on ~90 patients prior to NDA submission; and
- 3) to request a meeting to discuss these data.
- The primary efficacy population will be changed from MITT to ITT.
- FDA inquired regarding expanded access to patients with GIST.
 - Sponsor stated that a Treatment Protocol had opened.

4/19/05

Pre-NDA/Guidance meeting regarding auditing of digitized images.

- FDA requested that sponsor provide a laptop with searchable database containing lesion measurements by each reviewer for each patient at each time point, sites of disease evaluated, calculations for response and progression, cycle by cycle evaluation of response by each reviewer and adjudicator, and overall response by each reviewer and adjudicator.
- Sponsor proposed adoption of the RECIST Working Group's interpretation of overall objective response of PR that includes observation of either stable or unevaluable disease between observations of PR, as long as time elapsed between observations of PR is at least four weeks.
 - FDA agreed.
- Sponsor confirmed that Reviewers 1 and 2 were each to perform an independent assessment of all images. Reviewer 3 was to assess whether their findings were in agreement. If their findings didn't match, then Reviewer 3 was to read the results/images and adjudicate findings with rationale.
- FDA requested financial disclosure on independent primary reviewers.
- FDA requested that sponsor submit files attached to images with the same information that sponsor provided to independent reviewer on each patient, *i.e.* related events, radiation therapy history, procedures, and pathology or cytology reports.

8/1/05

Meeting held to discuss ACTH stimulation test results.

- Dr. Perlstein, a DMEDP consultant, observed the following.
 - Lack of new radiographic changes in adrenals of patients treated with SU011248 is reassuring.
 - SU011248 trials to date in 1400 patients yielded 6 patients with adrenal insufficiency coded as an AE. None of these events appeared to be drug-related.
 - 1 patient from the GIST Phase 3 trial and 3 patients from other SU011248 trials appeared to develop subclinical adrenal insufficiency with unequivocally low baseline (< 1 mcg/dL) or peak post-stimulation cortisol (6-11 mcg/dL).
 - Such patients may be susceptible to adrenal crisis in the setting of a superimposed physiologic stress such as infection, trauma, or surgery.
 - Additional data, including substantial placebo-controlled ACTH stimulation testing, would be of value to delineate more precisely the

incidence of drug-related adrenal insufficiency following use of SU011248.

- Dr. Perlstein concluded that the SU011248 label should clearly indicate that physicians prescribing SU011248 should maintain a high index of suspicion for the presence of adrenal insufficiency preceding and/or following from use of SU011248.

2.6 Other Relevant Background Information

SUTENT is not currently approved for marketing either within or outside the United States.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with *N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (1:1). The molecular formula is C₂₂H₂₇FN₄O₂ • C₄H₆O₅. SUTENT's structural formula can be seen in Figure 1 of Section 2.1 above, and the molecular weight is 532.6 Daltons. The drug substance is a fine, yellowish crystalline powder, soluble in water and ethanol.

Three orally administered immediate release hard gelatin capsules have been developed representing doses of 12.5 mg, 25 mg, and 50 mg of SU011248 free base as sunitinib malate. These contain 12.5 mg, 25 mg, and 50 mg of SU011248 L-malate salt, respectively. The 12.5 mg capsule uses a blend formula containing 12.5 mg w/w sunitinib malate, whereas the 25 mg and 50 mg capsules use a blend formula containing 25 mg w/w sunitinib malate. SU011248 may be light sensitive, and the oral drug formulation is supplied in 10, 20, and 30 capsules bottles. Bottles containing SU011248 capsules are to be stored at controlled room temperature (15 to 30 °C).

SUTENT (sunitinib) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib free base together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

3.2 Animal Pharmacology/Toxicology

Safety Pharmacology

- SU011248 and its active metabolite SU011262 blocked hERG currents with an IC₅₀ of 266 nM and 4.1 μM, respectively.

- In monkeys, corrected QT intervals were increased by 20-50 msec.

Toxicology

- In rats and monkeys, major target organs of SU010398 toxicity are hematopoietic organs (thymus, marrow, spleen, lymph nodes), liver, gastrointestinal tract, glands (pancreas, adrenals, salivary), skeletal, and female reproductive organs (ovaries, uterus).
- GI toxicity included abnormal feces in both species and emesis in the monkey. These findings were corroborated by histological findings of inflammation, mucosal erosion, epithelial depletion, necrosis and hemorrhage in the gastrointestinal tract. These findings were reversible by the end of each recovery period.
- In both rat and monkey repeat dose studies, hematological changes included decreases in red blood cells, with concomitant decrease in red cell mass. Reductions in white blood cells were observed with histological evidence of lymphoid depletion in the spleen, thymus, and lymph nodes and atrophy in the bone marrow.
- In adrenals, toxicity was noted in studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Toxicity was routinely characterized by hemorrhage in both species, but necrosis, congestion, hypertrophy and inflammation were also noted. These findings were reversible within the recovery period.
- Increases in serum hepatic enzymes (AST, ALT and occasionally GGT and total bilirubin) were accompanied by histological changes of peribiliary inflammation, bile duct hyperplasia and degeneration of the portal hepatocytes.
- In the three and nine month oral toxicity studies in the monkey, changes in cardiovascular function were observed. Reductions in heart rate were noted in both studies at doses of ≥ 120 mg/m². Changes in echocardiogram parameters included reductions in the ratio of left atrial diameter to aortic diameter, the left atrial diameter, left ventricular ejection time and left ventricular area.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary data source for this review is the sponsor's Study A6181004, a randomized, double-blind, placebo-controlled Phase 3 clinical trial evaluating the efficacy and safety of single-agent SUTENT in patients with gastrointestinal stromal tumor (GIST) that had progressed on or was intolerant to imatinib mesylate. 312 patients were randomized 2:1 to SUTENT vs. placebo. The sponsor's Study RTKC-0511-013 is considered briefly. This was an open-label, multi-center, dose-escalation, Phase 1/2 clinical trial in patients with GIST after progression on or intolerance to imatinib. Anecdotal safety reports from other trials were considered as needed to complement specific safety issues.

No third party clinical trials have been conducted. No foreign postmarketing safety data is available as the drug has not to date been marketed outside the U.S. No other INDs provided supportive data.

4.2 Tables of Clinical Studies

Clinical studies submitted by the sponsor are divided below into GIST efficacy studies (Table 2), MRCC efficacy studies (Table 3), dose finding studies (Table 4), and pharmacokinetic studies (Table 5). Note that some studies are listed in more than one table. For example, study 013 was a phase 1/2 study in GIST patients that incorporated a dose-finding component as well as an efficacy component. Efficacy claims from studies in advanced renal cell carcinoma are considered in the separate review by Dr. Vicki Goodman for NDA 021968.

Table 2: GIST Efficacy Studies

Study ID	Phase	# Patients	Primary Efficacy Endpoint	Status
013	1/2	55 (at 50 mg 4/2 dose/schedule)	ORR (CR+PR)	Completed
1004	3	312 (207 sunitinb, 105 placebo)	TTP	Ongoing; data cutoff 1/1/05

Table 3: MRCC Efficacy Studies

Study ID	Phase	# Patients	Primary Efficacy Endpoint	Status
014	2	63	ORR (CR+PR)	Completed 8/04
1006	2	106	ORR (CR+PR)	Ongoing; data cutoff 1/28/05

(N.B. Advanced renal cell carcinoma studies are separately reviewed by Dr. Vicki Goodman.)

Table 4: Dose Finding Studies

Study ID	Phase	Population	# Patients	Doses	Schedule
002	1	Solid tumors	28	25-150 mg QD or QOD	4 weeks on/2 weeks off
005	1	Solid tumors	42	25-75 mg QD or QOD	4 weeks on/2 weeks off or 2 weeks on/2 weeks off
013	1/2	GIST	97	25-75 mg QD	4 weeks on/2 weeks off or 2 weeks on/2 weeks off or 2 weeks on/1 week off

Table 5: Pharmacokinetic Studies

Protocol	Design	Type	Population	Sampling	SU011248 Formulation	Dosing	N enrolled
248-ONC-0511-001	Randomized, double-blind, placebo-controlled, single-dose study	SD1	Healthy volunteers	Full PK	free base powder in bottle	50 mg Oral Single dose	9
248-ONC-0511-002 (Study 002)	Open-label, non-randomized, dose-escalation study	MD2	Solid tumor	Full PK and Trough	free base and L-malate salt capsule	25, 50, 75, or 100 mg Oral Repeat doses QD or QOD on Schedule 4/2 ³	28
248-ONC-0511-004	Randomized, open-label, 3-way crossover study of SU011248 free base and L-malate salt and the effect of food,	SD	Healthy volunteers	Full PK	free base and L-malate salt capsule	50 mg, 3 single Oral doses free base fasted L-malate salt, L-malate salt fed	15
RTKC-0511-005 (Study 005)	Open-label, non-randomized, dose-escalation study	MD	Solid tumor	Full PK and Trough	free base and L-malate salt capsule	50, 75 QD or QOD Oral Repeat doses on Schedule 4/2 or 2/2 ⁴	41
248-ONC-0511-006	Open-label, single-treatment, escalating-dose study	SD	AML	Full PK	free base and L-malate salt capsule	Single dose of 50-350 mg	29
RTKC-0511-009	Randomized, open label, 2-way crossover study of SU011248 with and without concomitant administration of Ketoconazole	SD	Healthy volunteers	Full PK	L-malate salt powder in bottle	10 mg + ketoconazole: 400mg po QD x 7 days	27
A6181001	Open-label, crossover study of SU011248 with and without concomitant administration of Rifampin	SD	Healthy volunteers	Full PK	L-malate salt capsule	50 mg + rifampin: 400mg po QD x 7 days	28
RTKC-0511-013 (Study 013)	Open-label, single arm, non-randomized, dose-escalating study of 3 treatment schedules	MD	GIST	Trough and Full PK (18 Full PK)	L-malate salt capsule	25, 50, or 75 mg Oral Repeat doses QD on Schedule 2/2, 4/2, or 4/15	97 (18 with full PK)
RTKC-0511-016	Open-label, non-randomized study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50 mg Oral Repeat doses QD on schedule 2/16	12
RTKC-0511-018	Open-label, dose escalation study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50-175 mg loading dose on day 1 50 mg Oral Repeat doses QD on schedule 2/1	27

1: Single Dose 2: Multiple Dose 3: 4 weeks of dosing followed by 2 weeks off drug 4: 2 weeks of dosing followed by 2 weeks off drug 5: 4 weeks of dosing followed by 1 week off drug 6: 2 weeks of dosing followed by 1 week off drug

Table adapted from clinical pharmacology review (Dr. Roshni Ramchandani)

4.3 Review Strategy

Sources for this review included the following five elements:

- Datasets from Study A6181004, the sponsor's randomized, double-blind, placebo-controlled clinical trial of SUTENT in GIST;
- The sponsor's interim clinical study report on Study A6181004;
- The sponsor's presentation to FDA on September 22, 2005;
- An audit of independent core radiology results by Dr. Barbara Stinson of FDA's Division of Medical Imaging and Hematology Products (DMIHP); and
- The sponsor's additional NDA submissions in response to FDA questions.

For the efficacy analysis, Study A6181004 is pivotal because its design addresses several potentially significant sources of bias. First, the study was randomized with a placebo-control group, which allows unambiguous assessment of both the time-to-event primary endpoint and safety. This particular placebo-controlled design also isolates effectively a potential effect of the study drug. Second, blinding of the independent core radiology laboratory reduced bias in measurement of both response rate and time to progression. Study A6181004 was also used in isolation to examine safety claims. Because the two study groups were well balanced at study entry, randomization allows elucidation of treatment-emergent adverse event rates for both groups. This in turn allows comparison of adverse events following from use of SUTENT vs. those following from GIST's natural history.

A complementary efficacy review by Dr. Vicki Goodman examines the sponsor's efficacy and safety claims in NDA 029168 for use of SUTENT in the treatment of advanced renal cell carcinoma (RCC). This latter NDA is based on partial response rates and response duration in two single-arm trials of SUTENT in 169 patients with cytokine-refractory metastatic RCC.

4.4 Data Quality and Integrity

An audit of Study A6181004 clinical trial sites was requested of and performed by the Division of Scientific Investigations (DSI). DSI audited the two trial sites within the continental U.S. enrolling the greatest number of patients. These two sites enrolled a total of 42 patients, representing 13% of the intent-to-treat population of 312 patients. In addition, DSI also audited the Clinical Research Organization (CRO), [] which supported Study A6181004 with both clinical monitoring and data management. The Bioresearch Monitoring Program conducted inspections of both clinical investigators (CP 7348.811) and the CRO (CP 7348.810).

Summarized findings of these audits are contained in Table 6. Documentation at each of these sites was sufficient to assure that study subjects audited at those sites did exist; study eligibility criteria were fulfilled; participants received assigned study medications; and adverse events were adequately reported. At Site 1031 (Dr. Manisha Shah), three observations were made. A) Two SAEs reported by the site did not appear in the sponsor's data listings; B) Documentation of protocol required ECGs and evaluation of abnormal ECGs was incomplete in at least 3 subjects;

and C) Discrepancies were found involving pain medication entries in subject diaries vs. case report form entries in 2 subjects (Subject # 000190 and Subject # 000300). DSI concluded that data from each of these three sites was acceptable.

Table 6. Summary of DSI inspection findings for Study A6181004

Site	Location	Patients	Form 483 Findings	DSI conclusion
[redacted]	Charlottesville, VA	312	Undocumented CRA training	Data acceptable
George Demetri, M.D. (Site 1006)	Boston, MA	30	No Form 483 issued	Data acceptable
Manisha Shah, M.D. (Site 1031)	Columbus, OH	16	1) 2 SAE's not in data listings 2) Incomplete ecg documentation 3) Medication discrepancies between CRFs & source forms	Data acceptable

The sponsor submitted all case report forms. These were used to confirm and supplement safety findings made from sponsor-provided datasets.

Reviewer's Comment: There is evidence of data integrity from the DSI audit of Study A6181004.

4.5 Compliance with Good Clinical Practices (GCPs)

The sponsor states the following in the A6181004 Interim Clinical Study Report submitted as part of NDA 21938 (p. 57 of 41,894).

- 1) "Study A6181004 final protocol, amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each investigational center participating in the study.
- 2) "The study was conducted in compliance with ethical principles originating in or derived from the Declaration of Helsinki (Revised Edinburgh, 2000) and in compliance with IRB/IEC, informed consent regulations, and International Congress of Harmonization (ICH) Good Clinical Practices (GCP) Guidelines.
- 3) "All local regulatory requirements were followed, including those affording greater protection to trial participant safety.
- 4) "The study was conducted in accordance with FDA Regulations (Title 21 Code of Federal Regulations [21 CFR], Parts 50, 56, and 312).
- 5) "Written informed consent was obtained prior to initiation of protocol-specified procedures. The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent form."

Protocol violations are discussed under Section 6.1.4.2, Deviations.

Reviewer's Comment: There is no evidence of GCP violations in Study A6181004.

4.6 Financial Disclosures

The sponsor disclosed financial arrangements with investigators as recommended in FDA guidance on *Financial Disclosure by Clinical Investigators*. Twenty-five investigators at [] the third party imaging reading center, were included in these disclosures.

In brief, contents of required submissions were:

- Form 3454 certifying that 390 of 396 investigators on Pfizer Protocols A6181004, A6181005, and A6181006 had no Financial Arrangements as defined in 21 CFR 54.2;
- Form 3455 listing financial information for six investigators with disclosable Financial Arrangements.

In addition, the sponsor states:

- Covered studies were not funded via variable compensation.
- None of the investigators in the studies hold any form of proprietary interest in SUTENT.

Reviewer's Comment: None of the required disclosures raise questions about data integrity in Study 6181004.

5 CLINICAL PHARMACOLOGY

Pharmacokinetics, Pharmacodynamics, and Exposure-Response Relationships were evaluated by a Clinical Pharmacology team from the Division of Clinical Pharmacology and Biopharmaceutics V, including Drs. Roshni Ramchandani, Sophia Abraham, Carol Noory, and Brian Booth. The figures in sections 5.1-5.3 were taken from the Clinical Pharmacology Review written by Dr. Roshni Ramchandani.

5.1 Pharmacokinetics

Following oral administration, SU011248 is slowly absorbed from the gastrointestinal tract with maximum concentrations observed from 6 to 12 hours after dosing. The pharmacokinetic profile is comparable for sunitinib when administered as a capsule or as an oral solution. Administration of sunitinib in the presence or absence of food has no effect on the PK profile of sunitinib. Therefore, sunitinib can be administered without regard to meals. Plasma protein binding of sunitinib is high (93.5% to 96.4%).

Fecal excretion is the major route of elimination of sunitinib. Over a 21-day collection period, total recovery of radioactivity averaged $77\pm 8.8\%$, with $61\pm 7.2\%$ in the feces and $16\pm 2.5\%$ in urine. Sunitinib is the primary species identified in feces and urine, followed by SU012662.

Dose proportionality of sunitinib, its active metabolite SU012662, and total drug (sunitinib + SU012662) has been evaluated in oncology patients following single dosing with sunitinib doses ranging from 50 to 350 mg, as well as multiple daily dosing with doses of 25 to 100 mg (for four weeks, followed by two weeks of rest, Schedule 4/2). Comparison of dose-normalized C_{max} and dose-normalized AUCs indicated that PK of sunitinib and its primary metabolite SU012662 were dose-proportional in the range of doses evaluated. Log-log plots of C_{max} vs. dose and AUC vs. dose had slopes close to 1 also indicating that the PK of sunitinib and SU012662 are dose-proportional.

Sunitinib is metabolized via CYP3A4 mediated de-ethylation to the active equipotent metabolite SU012662. AUC of the active metabolite is approximately 20-30% of the parent. The terminal half-lives of sunitinib and SU012662 are approximately 40 to 60 hours and 80 to 110 hours, respectively. Steady-state conditions of SU011248 are reached in approximately 1 to 2 weeks.

Concurrent administration of sunitinib with the CYP3A4 inhibitor, ketoconazole, resulted in a 51% increase in combined (sunitinib plus active metabolite) AUC after a single dose of sunitinib in healthy volunteers. Concurrent administration of sunitinib with the CYP3A4 inducer rifampin resulted in a 46% reduction in combined (sunitinib plus active metabolite) AUC after a single dose of sunitinib in healthy volunteers. In vitro studies in human liver microsomes and hepatocytes indicated that neither sunitinib nor SU012662 is likely to inhibit or induce metabolic clearance of drugs that are substrates for CYP3A4 or other major CYP450 enzymes at clinically relevant concentrations.

A population PK model was developed to describe the SU011248 (parent) and SU012662 pharmacokinetics (PK) following single and multiple dose administration of SU011248. PK data was combined from 13 studies in healthy subjects and patients with GIST, MRCC, solid tumors and AML. Gender, body weight and tumor type were found to have significant effects on the clearance of sunitinib and SU012662. Age, tumor type, weight and gender had significant effects on Vd/F . However, inclusion of the covariates did not result in an appreciable reduction in inter-individual variability in clearance or volume of distribution, indicating that the covariates did not improve the predictability of the model.

5.2 Pharmacodynamics

The sponsor has an ongoing QT prolongation study to address definitively the potential for QT prolongation caused by SUTENT. See section 5.3 for additional pharmacodynamic data.

5.3 Exposure-Response Relationships

A population PK-PD analysis was performed to characterize the exposure-response relationships for measures of effectiveness and tolerability in the GIST and MRCC patient populations. The endpoints modeled were time to tumor progression (TTP) and partial responses, as these were the primary endpoints in the GIST and MRCC patients respectively. The exposure measure was the combined AUC (sunitinib+SU012662) which was estimated from the average dose for each patient and the individual clearance estimates from the base model for sunitinib and SU012662.

In GIST patients but not RCC patients, exploratory analysis suggests a significant relationship between TTP and exposure. A significant relationship was also seen for partial response rates and exposure in GIST patients. Increased AUC was associated with longer time to tumor progression and higher rates of partial responses. The analysis indicated a significant gender effect on the steepness of the exposure-TTP relationship. Females showed lower risk of progression compared to males across studies A6181004 and RTKC-0511-013. In MRCC patients, there was no apparent relationship between TTP and exposure or between partial response rates and exposure in the MRCC patients. Additional analyses examined influence of baseline tumor size on response as well as effect of exposure on changes in tumor size. These analyses also showed that while increased exposure was associated with larger changes in tumor size for GIST patients, no relationship was apparent in the MRCC patients.

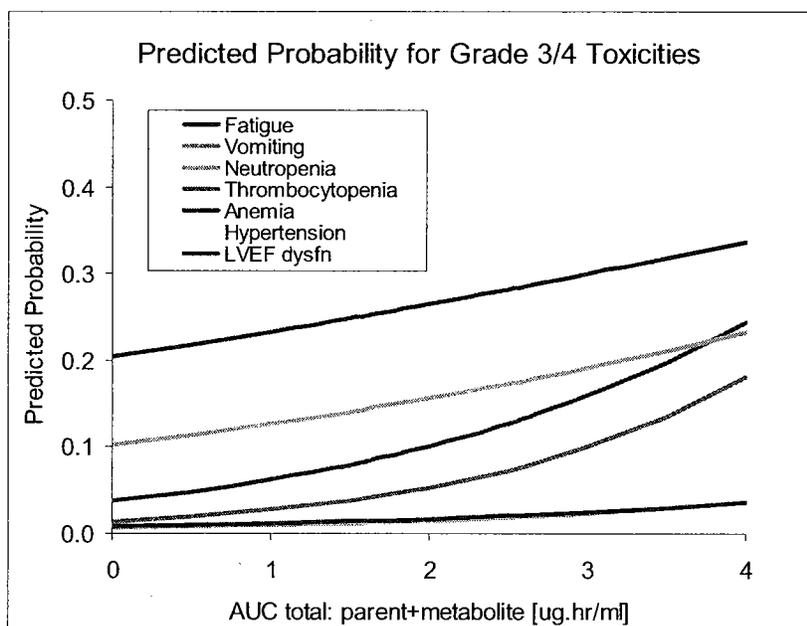
Exposure-response relationships were also assessed for frequency of severe grade 3/4 adverse events seen across the GIST, MRCC and solid tumor studies. Major toxicities included severe fatigue, diarrhea, neutropenia, thrombocytopenia, anemia, vomiting, hypertension and left ventricular ejection fraction (LVEF) dysfunction. Toxicity data was evaluated using logistic regression for all the above adverse events for all patients who received sunitinib throughout the clinical development program. Frequency of severe grade 3/4 toxicity for all the above measures (except nausea and vomiting where all grades were included and hypertension where grade 2/3 toxicity was used) was modeled as a function of AUC_{total} (parent + metabolite). Table 7 summarizes results of this evaluation.

Table 7: Common Toxicities as a Function of AUC

Toxicity	Frequency	Odds ratio for AUC _{tot} (p-value)
Grade 3/4 fatigue	46/516	1.70 (p=0.0038)
Grade 3/4 vomiting	8/544	1.57 (p=0.04)
Grade 3/4 neutropenia	81/544	1.28 (p=0.02)
Grade 3/4 thrombocytopenia	29/544	1.99 (p=0.0001)
Grade 3/4 anemia	139/544	1.19 (p=0.06)
Grade 3/4 pancreatic dysfunction	58/544	NS
Grade 2/3 hypertension	113/544	1.22 (p=0.04)
Grade 2/3/4 LVEF dysfunction	9/544	1.48 (p=0.08)

Figure 2 shows a composite of predicted probabilities for various toxicities as a function of exposure.

Figure 2: Predicted probability of severe grade 3/4 toxicities vs. total AUC (parent + metabolite) in GIST and MRCC patients



As measured by AUC, significant exposure-response safety relationships were obtained for incidence of severe fatigue, neutropenia, thrombocytopenia, anemia, vomiting, hypertension and left ventricular ejection fraction dysfunction. There was no additional effect of gender on exposure-toxicity relationships.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Treatment of gastrointestinal stromal tumor (GIST) following progression on or intolerance to imatinib mesylate (Gleevec)

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors of the digestive tract.^{1,2} Annual incidence is not known with precision in the United States but may be as high as 12.7 per million or approximately 3800.³ GIST is a lethal disease with five year survival estimates ranging from 35-65%, depending on tumor size, mitotic index, and location.⁴ Historically, limited treatment options were available for patients with malignant GIST since conventional cytotoxic

chemotherapy and palliative radiation generated both low response rates and a significant burden of toxicity.

Treatment of GIST changed after CD-117, a transmembrane receptor protein encoded by the *c-kit* gene was recognized.⁵ Imatinib mesylate (Gleevec) targets this receptor tyrosine kinase and has been reported in peer-reviewed literature to produce objective responses and prolongation of progression-free survival in GIST.^{6,7} Gleevec received accelerated approval on 2/1/02 for “treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).” Efficacy of Gleevec in GIST is based on durable objective radiographic responses in a Phase 2 trial. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.⁸

6.1.1 Methods

The primary data source supporting the sponsor’s application for second-line treatment of GIST is Study A6181004, a randomized, double-blind, Phase 3 clinical trial evaluating the efficacy and safety of single-agent SUTENT in patients with gastrointestinal stromal tumor (GIST) that had progressed on or was intolerant to imatinib mesylate. 312 patients were randomized 2:1 to SUTENT vs. placebo.

Sponsor Study RTKC-0511-013 was an open-label, multi-center, dose-escalation, Phase 1/2 clinical trial in patients with GIST after progression on or intolerance to imatinib. This latter single-arm trial is considered supportive.

6.1.2 General Discussion of Endpoints

The primary endpoint of Study A6181004, was time to progression (TTP). This endpoint was acceptable to FDA because in this disease setting absence of progressive disease may by itself be considered clinically beneficial. One drawback of TTP as an endpoint is censoring of deaths presumed not due to cancer. Even with (now infrequent) post-mortem examination, cause of death may not be known with certainty. Without post-mortem examination, presuming a specific cause of death is generally speculative.

Study A6181004’s design incorporated several elements to reduce potential systematic sources of bias that could confound the trial’s results. First, treatment randomization with inclusion of a placebo control group and double blinding enables objective assessment of study agent effect on the TTP endpoint. A placebo control arm is ethical in this trial because a) there is no standard therapy for patients with GIST that has progressed on imatinib mesylate; and b) patients on both treatment arms received best supportive care in addition to study treatment. Furthermore, 2:1 randomization was used to minimize the number of patients treated with placebo. Second, pre-specification of scheduled radiologic assessment for progression every six weeks minimized the likelihood that undetected progression in the SU011248 arm might account for an observed beneficial effect of treatment. Finally, independent, blinded radiologic review was done to

eliminate potential bias in the interpretation of progression; only radiographic assessment of disease progression by the blinded core radiology was considered for evaluation of the primary endpoint, TTP.

Study A6181004's secondary endpoints include progression free survival (PFS) and overall survival (OS). PFS complements TTP in that the former includes any deaths in the outcome measure, rather than simply those that are presumed to be associated with the malignant disease. In oncology it is sometimes difficult to distinguish death due to progressive disease from death due to other causes. Thus a positive PFS finding strengthens clinical relevance of any TTP finding in Study A6181004. Finally, OS in a randomized placebo-controlled trial is particularly compelling as a secondary endpoint because it avoids measurement bias.

Reviewer's Comment: The time to progression endpoint definition used to assess Study A6181004 censored deaths that occurred prior to documented disease progression at time of the last radiographic disease assessment. Thus the primary drawback of TTP, difficulty in ascertaining cause of death, was obviated by the TTP definition used.

6.1.3 Design of Pivotal Study A6181004

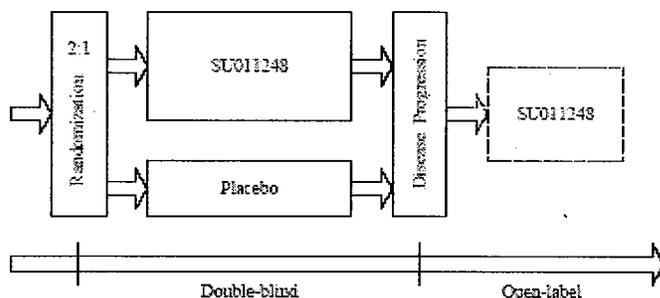
Protocol 6181004-A4 (including Amendment 4, 29 November 2004) is included in the Interim Clinical Study Report of 6 July 2005, pages 2630-2747 of 41,894, submitted as part of the NDA.

This was a randomized, double-blind, multi-center, Phase 3 clinical trial with 2:1 randomization to evaluate the efficacy and safety of single-agent SU011248 as compared to placebo in patients with imatinib mesylate-resistant or intolerant GIST. Treatment was administered in repeated 6-week cycles, consisting of 4 weeks of daily SU011248 or placebo followed by 2 weeks of rest (Schedule 4/2). Patients on both treatment arms received best supportive care in addition to study treatment. Following RECIST-defined disease progression, patients on the placebo arm who met crossover eligibility criteria were offered the opportunity to receive open-label SU011248. Following disease progression, patients receiving SU011248 could continue to do so after unblinding if, in the opinion of the investigator, there was sufficient evidence of clinical benefit.

Reviewer's Comment: This is a well designed study that effectively addresses several prominent potential sources of bias, as discussed above.

Figure 3 depicts the study design (Source: Interim Clinical Study Report: SU011248, RTKC-0511, A618, Section 5.1 (Overall Study Design and Plan), p. 60 of 41,894).

Figure 3: Design of Study A6181004



6.1.3.1 Objectives

Primary Objective

- To compare 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 treatment of patients with imatinib mesylate-resistant or intolerant malignant GIST.

Secondary objectives

- To compare other measures of antitumor efficacy in both treatment arms.
- To compare pain control, analgesic usage, tumor-related signs and symptoms, health status, and performance status in both treatment arms.
- To evaluate 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 correlations of potential biomarkers with clinical outcomes.

Reviewer's Comment: Patient reported outcome and biomarker data are neither included nor considered in this submission.

6.1.3.2 Amendments

Table 8 presents a summary of amendments to Study A6181004 (Source: Interim Clinical Study Report, pages 91-97 of 41,894).

Table 8: Summary of Amendments to Study A6181004

(Source: Interim Clinical Study Report, pages 91-97 of 41,894)

Number	Date	Comments / Major Components
1	8/10/03	<ul style="list-style-type: none"> Incorporated into protocol prior to patient enrollment Imatinib intolerance was clarified. Ineligibility based on low normal LVEF was eliminated. RECIST or WHO progression criteria to determine eligibility. Sponsor to determine eligibility; third-party core lab to confirm. Primary efficacy analysis will be on modified intent to treat population following from core lab review of eligibility. All radiographs were to be reviewed by third party core lab. Clinical benefit pain assessment endpoint was revised. Guidance was added for dose reduction following a cardiac event. Scheduling parameters were liberalized modestly. Crossover to SU011248 following progression was simplified. ACTH stimulation testing of all patients was added.
	12/10/03	<ul style="list-style-type: none"> First subject visit
2	3/8/04	<ul style="list-style-type: none"> Screening limits on amylase, lipase, troponin, and ACTH stimulation were eliminated. Prohibited cardiac events prior to study entry were abbreviated. MUGA scans were reduced from every 6 to every 12 weeks. Exemption from ACTH-stimulation testing was expanded from those receiving hydrocortisone to all those on chronic steroids. Pre-cycle ACTH-stimulation testing was limited to those having normal ACTH-stimulation results at baseline; others would have ACTH-stimulation testing at Day 28 of Cycles 2, 4, and 6. Cycle 1, Day 28 ecg tracings were increased from 1 to 3 at 2 minute intervals with time-matching within 1 hour from baseline. Lymphopenia was excluded from dose reduction criteria. Cycle duration was clarified to be ≥ 6 weeks, including ≤ 28 days of treatment & ≥ 14 days of rest. Unblinding and crossover were allowed based on investigator rather than core radiology lab judgment of progression. Protocol A6181030 allowed patients with declining performance status otherwise ineligible for crossover to receive SU011248. Cancer-related AE's were specified not to be reported as adverse events unless the outcome was death. Hyperlipasemia was added to the list of frequently observed AE's.
3	7/1/04	<ul style="list-style-type: none"> TTP endpoint: a) cancer-related deaths were to be within 28 days of last Sutent; b) TTP data was to be censored at randomization for patients with no on-study tumor assessment. PFS was added as a secondary endpoint. Expedited unblinding was clarified to require RECIST-defined progression that was observed by investigator. Analysis: a) Efficacy interim analysis at 70 events was deleted; b) O'Brien-Fleming stopping boundaries were to be by p-values rather than hazard ratios; p-values were explicitly defined. Minimum time since last imatinib was reduced to 1 week. ACTH-stimulation testing was removed from the study. AE reporting: a) SAE's were to be from consent through 28 days following last study drug; b) SAE's if fatal or life threatening were to be reported immediately and otherwise within 24 hours.
4	11/29/04	<ul style="list-style-type: none"> Guidance on patient management following unblinding was added as Appendix 14 with open-label treatment as appropriate, reduced lab assessments with local labs, and no further core radiology.
	1/1/05	<ul style="list-style-type: none"> Data cutoff date
5	3/18/05	<ul style="list-style-type: none"> Effective only in France with no effect on data submitted herein. Informed consent form modified to include unblinding, as well as cardiac assessments for cross-over patients to SU011248. Analysis plan amended to reflect censoring of all deaths for assessment of TTP endpoint and primary analysis to be performed on intent to treat rather than modified intent to treat population.

(Source: Interim Clinical Study Report, pages 91-97 of 41,894)

6.1.3.3 Eligibility

Inclusion

1. Histopathologically-proven malignant GIST, not amenable to therapy with curative intent.
2. Unidimensionally measurable disease (≥ 1 malignant tumor mass measured in at least 1 dimension ≥ 20 mm with conventional radiographic techniques or MRI, or if spiral CT scan, twice the reconstruction interval used [lesion size ≥ 10 -16 mm depending on interval]).
 - PET scan or ultrasound could not substitute for CT or MRI scans.
 - Bone lesions, ascites, peritoneal carcinomatosis or miliary lesions, pleural or pericardial effusions, lymphangitis of skin or lung, cystic or irradiated lesions, and indirect documentation of disease (e.g., alkaline phosphatase) were not considered measurable.
3. Failure of prior treatment with imatinib mesylate defined either by progression of disease according to RECIST or World Health Organization (WHO) criteria during treatment, or by significant toxicity during treatment with imatinib mesylate that precluded further treatment.
 - Radiographic progression on imatinib had to be confirmed by investigator prior to enrollment and retrospectively by the independent third-party imaging core laboratory.
 - Intolerance to prior imatinib mesylate therapy was defined as:
 - Life-threatening adverse events (i.e., NCI CTCAE Grade 4) at any dose, or
 - Unacceptable toxicity induced by a moderate dose (e.g., 400 mg/day), i.e. Grade 2 or 3 toxicity, unacceptable to patient, that persisted despite standard countermeasures.
 - Type and severity of imatinib intolerance were to be documented prior to entry. If both progression and intolerance were observed, then progression was the entry criterion.
4. Administration of the last dose of imatinib mesylate ≥ 1 week prior to randomization.
5. Male or female, 18 years of age or older.
6. ECOG performance status 0 or 1.
7. Resolution of all toxic effects of any prior imatinib, surgery, radiotherapy, or cryotherapy to NCI CTCAE (Version 3.0) grade ≤ 1 and to baseline laboratory values defined below.
8. Adequate organ function, defined by the following:
 - Serum AST and ALT ≤ 2.5 x upper limit of normal (ULN)
 - If abnormalities were due to malignancy, then AST and ALT could be ≤ 5 x ULN
 - Total serum bilirubin ≤ 1.5 x ULN
 - Prothrombin time (PT) and partial thromboplastin time (PTT) ≤ 1.5 x ULN
 - Serum albumin ≥ 3.0 g/dL
 - Absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$
 - Platelets $\geq 100,000/\mu\text{L}$
 - Hemoglobin ≥ 9.0 g/dL
 - Serum creatinine ≤ 1.5 x ULN
 - Left ventricular ejection fraction (LVEF) $>$ lower limit of normal (LLN) by MUGA scan
9. Signed and dated informed consent document indicating that the patient had been informed of all pertinent aspects of the trial prior to enrollment.
10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

Exclusion

1. Treatment with any chemotherapy, chemoembolization therapy, immunotherapy, or investigational anticancer agent after the last dose of imatinib mesylate.
2. Treatment of patients with imatinib mesylate-resistant disease with surgery, radiotherapy, and/or cryotherapy that affected all areas of measurable disease where progression on imatinib mesylate therapy had been demonstrated.
3. Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or *in situ* carcinoma of the cervix uteri.
4. Within the 12 months prior to study drug administration:
 - severe/unstable angina,
 - symptomatic congestive heart failure, or
 - cerebrovascular accident.
5. Ongoing cardiac dysrhythmias:
 - NCI CTCAE grade ≥ 2 ,
 - atrial fibrillation of any grade, or
 - QTc interval prolongation to > 450 msec for males or > 470 msec for females.
6. Known HIV positivity or acquired immunodeficiency syndrome (AIDS)-related illness.
7. Pregnancy or breastfeeding.
 - Patients were required to be surgically sterile or be postmenopausal or to agree to use effective contraception during the period of therapy.
 - All female patients of childbearing potential were required to have a negative pregnancy test (serum or urine) within 21 days before enrollment.
 - Effective contraception was based on judgment of investigator or designated associate.
8. Other severe, acute, or chronic medical/psychiatric condition or laboratory abnormality that could have increased the risk associated with study participation, study drug administration, or interpretation of study results, in the judgment of the investigator.

Reviewer's Comments: Notable features of eligibility criteria include the following.

1. *There was no requirement for tumoral expression of c-kit, the ostensible tumor-specific target of the study drug. However, it is generally accepted that overexpression of the c-kit gene product occurs in $>95\%$ of GISTs and that this protein drives malignant behavior.*
2. *There was no requirement for a minimum dose of imatinib, only documentation of progression or toxicity.*
3. *On 3/8/04, three months following the first subject visit, the sponsor abbreviated the exclusion criterion concerning prior cardiac history. This is unlikely to have had a substantial effect on results.*

6.1.3.4 Screening and Randomization

Screening included medical history, demographics, ECOG performance status assessment, physical examination, clinical laboratory tests (hematology, cardiac enzymes, serum chemistry, urinalysis, coagulation, and a pregnancy test for women of childbearing potential), 12-lead electrocardiograms (performed 3 times at least 2 minutes apart), multi-gated acquisition (MUGA) scan of left ventricular function, baseline radiographic tumor assessment, tumor biopsy

(for patients who agreed and signed a separate consent); and McGill Pain Questionnaire's Present Pain Intensity scale (MPQ-PPI) and analgesic usage, recorded daily for 7 days before randomization. These are listed below in Table 1 (Schedule of Patient Assessments).

Concomitant medications from 30 days before the start of treatment were recorded and updated at each study visit. After screening and recording of pain symptoms for 7 days, patients were randomly assigned to receive either SU011248, 50 mg (Arm A), or matching placebo (Arm B).

Randomization featured:

- Stratification on
 - Progressive disease within or beyond 6 months from start of imatinib treatment; and
 - Baseline pain score based on the median value of worst daily pain (Baseline MPQ-PPI score 0 vs ≥ 1) over the prior 7 days.
- Central assignment of unique patient and Clinical Trial Material bottle numbers;
- Randomization was weighted 2:1 for SU011248:placebo (Arm A:Arm B).
- Completion of baseline case report forms for all randomized patients, even if not treated;

6.1.3.5 Treatment Plan

Within 7 days after randomization, patients were to begin treatment. Neither investigators nor patients were apprised of treatment assignment until RECIST-defined disease progression or study conclusion. SU011248 and placebo were dispensed as hard gelatin capsules of 12.5 mg, 25 mg, or 50 mg. Patients were to take capsules orally in the morning with a glass of water without regard to meals on Day 1.

Treatment was administered in cycles of 6 weeks with 4 weeks on study drug followed by 2 weeks of rest. Patients without disease progression were eligible for additional cycles of treatment. Patients were instructed to bring their medication bottle(s) to each clinic visit. Compliance was assessed at Day 28 of each treatment cycle. A new supply of medication was dispensed for each cycle.

Adverse events and concomitant medications and treatments were to be recorded throughout each cycle. Following adverse events the dosing period could be interrupted or shortened but was not to be extended. Lengthening of the rest period was allowed as needed to compensate for dosing interruption or to allow additional time to recover from adverse events.

Table 9 provides a schedule of patient assessment activities for Study A6181004. This is a reviewer modified version of the Schedule of Events from Protocol Section 7, 29 November 2004, p. 52-54 of 118 (Interim Clinical Study Report p. 2681-83 of 41,894).

Table 1: Schedule of Patient Assessments

	Screening (Day)		Treatment with Study Agent, 6 week cycles (SU011248 or Placebo) [1]					Post-Treatment		
	≤21	≤7	Cycle 1			Cycle 2 →		End of Tx or Withdrawal [3]	30 Days Post-Treatment	Follow-Up Period
			Day 1 -1/+0 [2]	Day 14 -1/+1	Day 28 -3/+3	Day 1 -1/+0	Day 28 -3/+3			
Baseline Documentation										
Informed Consent	X									
History and Demographics [4]	X									
Baseline Signs and Symptoms [5]	X									
Physical Examination [6]	X			X			X		(X)	
Laboratory Studies [7*]										
Hematology, Cardiac Enzymes [8*]	X			X			X		(X)	
Blood Chemistry [9*]	X			X			X		(X)	
Coagulation [10*]	X									
Pregnancy Test [11]	X									
Urinalysis [12]	X									
ECG [13]	X			X						
MUGA Scan [14]	X							X	(X)	
Study Randomization [15]										
Study Medication [16]										
Tumor Assessments										
Tumor Imaging [17]	X							X		
Other Clinical Assessments										
Adverse Events and Tumor-Related Signs and Symptoms [18]				X			X		X	
EQ-5D Questionnaire [19]				X			X		X	
McGill Pain Questionnaire [20]	X			X			X		X	
Study Drug Compliance [21]				X			X		X	
Concomitant Treatments [22]				X			X		X	
Survival / Treatment [23]										X
Special Lab Studies										
Soluble Protein Assessments [24]				X			X		X	
Trough Drug Level [25]				X			X		X	
Tumor Biopsy [26]	(X)					(X)			(X)	

(Source: modified from Study Protocol Section 1.6, 29-November 2004 (amendment 4), p. 21 of 118; interim study report p. 2650)

Footnotes for Patient Assessments

1. During Treatment, all assessments prior to study agent dosing unless otherwise indicated. Acceptable time windows for each assessment are below each scheduled treatment day. Cycle lengths may be extended by longer rest periods.
2. Cycle 1 Day 1: Not required if assessed during screening within 7 days prior to the start of treatment with study medication.
3. End of Study Treatment/Withdrawal: Obtain if not completed during the last week on study treatment (last 6 weeks for radiological tumor assessments).
4. Medical Oncological History and Demographics: To include prior imatinib mesylate dosing and duration plus tumor assessment data showing disease progression according to RECIST or WHO criteria or type and severity of intolerance.
5. Baseline Signs and Symptoms: Any signs or symptoms within the past 21 days.
6. Physical Examination: During Screening and on Day 1 of each cycle: examination of major body systems, height (at screening only), ECOG performance status, body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate). On Day 28 of each cycle: ECOG performance status, body weight, and vital signs only. During the 30-day post-treatment visit: examination of major body systems, body weight, and vital signs only.
7. *Laboratory Studies: Samples indicated with "*" to be evaluated by central laboratory, but investigators may have portions additionally analyzed locally for planning treatment, dose modification, or following adverse events.
8. Hematology: WBC with differential, RBC, hemoglobin, hematocrit, MCV, and platelets.
9. Cardiac Enzymes: Cardiac troponin T or I.
10. Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, pancreatic amylase and lipase, creatine kinase (CK), total protein, albumin, globulin, sodium, potassium, chloride, CO₂, calcium, phosphorus, BUN, creatinine, uric acid, and glucose.
11. Day 1 only of each cycle beyond Cycle 4.
12. Coagulation: PT/INR and PTT at baseline, then as clinically indicated thereafter.
13. Pregnancy Test (Serum or Urine): Women of reproductive potential within 21 days of first study medication treatment.
14. Urinalysis: Dipstick pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then as clinically indicated thereafter.
15. ECG: Three 12-lead ECGs at least 2 minutes apart during screening and again at Cycle 1 Day 28 to determine mean QTc interval. Allowable scheduling at Day 28 of +3 days does not apply. ECGs should be performed time matched (± 1 hour) in the AM. The Cycle 1 Day 28 PK blood sample (footnote 26) must be obtained together with the Cycle 1 Day 28 ECG. If the mean QTc interval is prolonged (>500 msec), then ECGs should be overlaid by a Cardiologist at clinical site for confirmation. Additional ECGs as clinically indicated.
16. MUGA Scan: At baseline, on Day 28 of even number cycles (ie, Cycle 2, 4, 6 etc.), and at the end of study treatment.
17. Study Randomization: Patient number, randomization and study medication bottle number assignments are via central randomization. Required information: site and patient identifiers, demographic information, and stratification variables (prior imatinib 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 and level of pre-study pain assessment]). Study treatment must begin within 7 days of randomization.
18. Study Medication: Treatment will start on Cycle 1 Day 1 within 7 days of randomization.
17. Tumor Imaging: Chest, abdomen, pelvis CT or MRI at baseline. Subsequent imaging was to include all disease sites identified at baseline or later suspected. Imaging was to occur on Cycle 1, Day 28 and then at 6-week intervals, or sooner if disease progression was suspected, to confirm partial or complete response (at least 4 weeks after initial response documentation), and at time of withdrawal. All imaging studies were to be submitted to independent third-party imaging core laboratory for retrospective verification of entry criteria and disease response, and prospective verification of progression. Tumor assessments were to be repeated at 6-week intervals regardless of alterations in cycle length (ie, fixed by calendar rather than by cycle duration). The allowable window was ± 7 days.
18. Adverse Events: Patients were to be followed for AEs from Cycle 1, Day 1 until at least 30 days after last on-study treatment administration. Baseline tumor-related signs and symptoms were to be recorded as AEs if worsened in severity or increased in frequency. At each clinic visit, severity of all baseline tumor-related signs and symptoms that remain stable or improve were to be recorded, except for stable or improved tumor-related pain, recorded elsewhere.
19. EQ-5D Questionnaire: Self-administered by patient in clinic on Days 1 and 28 of each cycle, and at end of study.
20. McGill Pain Questionnaire: Self-administered by patient daily and recorded for 7 days prior to randomization, then daily throughout therapy. Diaries collected at baseline, start of each new cycle, and completion of therapy.
21. Study Drug Compliance: At end of each treatment cycle and completion of therapy, study drug medication bottles including unused capsules returned to clinic for drug accountability. Concomitant Medications and Treatments: Concomitant medications and treatments recorded from 30 days prior to start of study treatment, at study entry, and during study. Once patient has withdrawn, concomitant medications and treatments were to be recorded if used to treat new or unresolved study treatment-related adverse events.
22. Post-Study Survival Status and Treatment: After discontinuation of study treatment, post-study survival status and treatment were to be collected by clinic visit or telephone every 2 months for up to 3 years from last dose of study medication.
23. Soluble Protein Assessments: One 10-mL blood sample at specified time points for analysis of markers associated with SU011248 mechanism of action, angiogenesis, or tumor proliferation (eg, sKIT, sVEGFR2).
24. Trough Drug Level: A single 5-mL blood sample pre-dose on specified days and at end of study. During Cycle 1, the Day 28 sample must coincide with the ECG. Additionally, a single blood sample should be obtained if clinically feasible for plasma drug level determination at a time coincident with any serious cardiac event or other serious and/or unusual adverse event that is causally related to study medication administration.
25. Tumor Biopsy: Pre-study biopsy of tumor tissue (or previously collected paraffin tumor block) is optional for correlative laboratory analysis. Repeat tumor biopsies on study are also optional.
27. Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, MCV=mean corpuscular volume, MPO=McGill pain questionnaire, MRI=magnetic resonance imaging, MUGA=multiple gated acquisition scan, PDGF=platelet-derived growth factor, PT/INR=prothrombin time/international normalized ratio, PK=pharmacokinetic, PTT=partial thromboplastin time, RBC=red blood cell, sKIT=soluble KIT, sVEGFR2=soluble VEGF receptor 2, VEGF=vascular endothelial growth factor, VS=vital signs, WBC=white blood cell.

6.1.3.6 Unblinding, Crossover Eligibility, and Open Label Treatment

Patients whose disease met the Response Evaluation Criteria in Solid Tumors (RECIST) definition for disease progression according to the independent third-party imaging core laboratory could have their treatment assignment unblinded. If patients experienced clinical deterioration, treatment could be unblinded based on the Principal Investigator's determination of RECIST-defined progression.

Eligibility criteria for placebo patients to receive crossover SU011248 treatment using the Arm A dosing regimen were as follows:

- RECIST-defined disease progression
- ECOG performance status 0, 1, or 2 and
- No severe, acute, or chronic medical/psychiatric condition or laboratory abnormality that could increase the risk associated with study participation, study drug administration, or interpretation of study results, in the judgment of the investigator.

Patients found to be receiving SU011248 treatment could continue study treatment after unblinding at the investigator's discretion after discussion with the sponsor, provided that they did not meet study treatment withdrawal criteria. Patients ineligible for crossover due to deteriorating performance status were eligible for a separate SU011248 access protocol, Study A6181030, at the discretion of the investigator.

Reviewer's Comment: Amendment 2 on March 8, 2004 allowed unblinding and crossover based on investigator rather than core radiology lab judgment of progression. Amendment 3 on July 1, 2004 further clarified that expedited unblinding required RECIST-defined progression that was observed by the investigator. Both these amendments concern patient safety and are not expected to have a significant impact on efficacy results due to independent assessment of progression by the core radiology lab for assessment of the primary endpoint.

6.1.3.7 Dose Modifications, Supportive Care, and Treatment Withdrawal

Inpatient dose reduction by 1, and if needed 2, dose level(s) (to 37.5 then 25 mg/day) were required depending on the type and severity of toxicity encountered (detailed in Table 10) (Source: Protocol A6181004, 29 November 2004, Section 9.2.3.1, p. 58 of 118, Interim Clinical Study Report p. 2687 of 41,894), provided that criteria for patient withdrawal from study medication had not been met. Subsequent dose reductions below 25 mg daily could be made at the investigator's discretion. All inpatient dose reductions were relative to the lowest dose of the current cycle.

Although the dosing period was not to be extended to compensate for interruptions in study treatment, the next cycle could be delayed if additional time was required for a patient to recover from study treatment-associated toxicity experienced during any given cycle.

Patients who developed grade 3 hyperlipasemia without clinical, radiological, or other evidence of pancreatitis could be permitted to continue with study therapy. However, frequency of monitoring was increased until resolution. Grade 4 hyperlipasemia or grade 3 hyperlipasemia with clinical or radiological evidence of pancreatitis were considered unacceptable and were to be managed as described in Table 3 below.

Doses reduced for drug-related toxicity were generally not to be re-escalated. However, inpatient re-escalation to a prior level was allowed at investigator discretion.

Table 10: Dose Modifications for Study Medication-Associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic ^a	Continue same dose level.	Continue same dose level except for: • asymptomatic LVEF decrease by 20% in absolute terms to below LLN, • non-urgent ventricular paroxysmal dysrhythmia requiring intervention withhold dose until toxicity is grade ≤ 1, then either: 1. reduce dose by 1 level and resume treatment OR 2. continue same dose level at the discretion of the investigator, after discussion with the sponsor if toxicity resolved within 1 week.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then either: 1. resume treatment OR 2. continue at the same dose level at the discretion of the investigator after discussion with the sponsor if toxicity resolved within 1 week.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then either: 1. reduce dose by 1 level and resume treatment after discussion with the sponsor, OR 2. discontinue at the discretion of the investigator.
Hematologic (excluding lymphopenia)	Continue same dose level.	Continue same dose level.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then continue same dose level after discussion with sponsor.	Withhold dose until toxicity is grade ≤2, then reduce dose by 1 level and resume treatment after discussion with sponsor.

^a Non-serious non-hematologic toxicities may be exempt at investigator's discretion.

(Source: Protocol A6181004, 29 November 2004, Section 9.2.3.1, p. 58 of 118, Interim Clinical Study Report p. 2687 of 41,894)

Reviewer's Comment: Dose reductions were mandated for Grade 4 adverse events, as well as for the sponsor's modified Grade 2 definition of reduction in LVEF (See Section 7.1.7.4, Additional Analyses and Explorations – LVEF Reduction).

Supportive care instructions included the following:

- Premedication was allowed with antiemetics to limit potential nausea and vomiting.
- Loperamide was allowed for treatment or prophylaxis of potential diarrhea.
- Prophylactic hematopoietic factors were allowed.
- Prophylactic neutropoietic factors were to be discussed with Sponsor's monitor.
- Palliative radiotherapy was allowed if medically indicated; irradiated lesions would subsequently not be accounted for in evaluation of response.

- Patients developing adrenal insufficiency could continue to receive study medication, provided that the patient was medically manageable with appropriate replacement therapy.
- Agents known to inhibit CYP3A4 or prolong the QT interval were to be avoided as feasible.

Patients were to be withdrawn from study treatment if any of the following occurred:

- Cessation of study treatment was medically necessary in the opinion of the investigator.
- The patient withdrew consent; no further evaluations or data collection were to occur.
- RECIST-defined disease progression was observed, unless there was reasonable evidence of clinical benefit to justify continuation of dosing with SU011248 on protocol.
- There was need for surgery or irradiation to only measurable site(s) of disease (with subsequent option to receive crossover or open-label treatment at Investigator's discretion).
- There was need for other anticancer therapy not specified in the protocol.
- Development of symptoms of congestive heart failure.
- The patient was lost to follow-up; efforts would be made to contact the patient and to document outcome.
- The patient no longer required treatment.

Data to be collected at the end of study treatment/withdrawal visit are described in the Schedule of Patient Assessments, Section. 6.1.3.5. Patients were to be followed for 30 days after the last dose of study medication for adverse events. Survival was to be followed every 2 months for up to 3 years from the last dose of study medication.

6.1.3.8 End of Study

At end of study procedures listed in Table 1 (Schedule of Patient Assessments) were performed. These assessments could be omitted if they had been completed within the previous 7 days. Tumor assessments could be omitted if completed within the previous 6 weeks.

AEs were recorded for 28 days after the last dose of study medication. Any SAEs or drug-related AEs ongoing at that time were followed until resolution or stabilization. Any known untoward event subsequent to the AE reporting period that the investigator assessed as possibly related to study drug was reported as an adverse event.

6.1.3.9 Quality Assurance

- The sponsor monitored the study through routine center visits.
- At these visits, study procedures were reviewed, CRF/DCT data compared to original clinical records, data queries resolved, and protocol deviations discussed with the investigator.
- After resolving data issues detected at the site, data on the CRFs were to be entered into a computer data base.

- Data management standard operating procedures were to include double entry of data from each CRF and a quality control check to ensure a match between data reported on the CRF and data entered into the clinical data base.
- Data were checked for completeness, consistency, and reasonableness by a series of computer and manual procedures based on a study-specific data clarification policies document prepared before beginning data processing for the study.
- Any missing or questionable items detected were recorded on a data query form for resolution at the study site and return with appropriate documentation.
- If a change was required, it was to be documented on the CRF, and the data base was to be updated to reflect the change.
- After data queries were resolved, a data quality control check was to be performed before the data base was frozen for analysis.

6.1.3.10 Efficacy Evaluations

Assessments

Determination of antitumor efficacy was to be based on objective tumor assessments made according to the RECIST system of unidimensional evaluation. To accommodate use of spiral CT scan (ie, reconstruction interval up to 8 mm), minimum lesion size qualifying as measurable was to be twice the reconstruction interval used (lesion size at least 10-16 mm depending on interval). The same method and technique was to be used to characterize each identified and reported lesion at baseline, during treatment, and at follow-up.

Imaging-based evaluation was to be preferred over clinical examination when either could be used. CT or MRI scan was to be preferred over chest X-ray when either could be used. Whenever possible, clinical evaluation of superficial lesions was not to be used as the sole form of measurement although color photograph with metric caliper was acceptable when necessary. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound were not to be substituted for CT or MRI scans.

Radiological tumor assessments were to be performed at baseline, at the end of the dosing period (Day 28) of every 6-week cycle during study treatment with SU011248, and whenever disease progression was suspected. Tumor assessments were to be repeated at 6-week intervals regardless of the impact of early or prolonged treatment rest periods on cycle lengths (*i.e.*, assessments fixed by calendar rather than by cycle duration). After withdrawal from study treatment, another tumor assessment was to be performed if an assessment has not been performed within the prior 6 weeks. All patients with an objective response of PR or CR were to have the response confirmed at least 4 weeks after the initial documentation of response.

All patients' files and radiological images were to be available for source verification of CRFs. Copies of all imaging studies were to be made available for review by the independent third party imaging core laboratory, including images demonstrating study eligibility, baseline assessments, and disease response and progression.

Primary Endpoint

- Time to progression (TTP) was 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 was to be censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who a) did not have objective tumor progression and were still on study at time of an analysis, b) were given antitumor treatment other than the study treatment, c) were removed from treatment prior to documentation of objective tumor progression, or d) died of any cause in the absence of documented disease progression. Patients without tumor assessments after randomization were to have TTP censored at randomization. Imaging studies documenting progression were to be reviewed for verification by an independent, third party imaging core laboratory.

Secondary Endpoints

- Overall survival (OS) was 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 was to be censored at the last date the patient was known to be alive. Patients lacking data beyond randomization were to have survival censored at randomization.
- Progression-free survival (PFS) was 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). PFS data were censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who a) did not have objective tumor progression and were still on study at time of analysis, b) were given antitumor treatment other than the study treatment, or c) were removed from treatment prior to documentation of objective tumor progression. Patients without tumor assessments after randomization were to have PFS censored at randomization.
- Overall confirmed objective response rate (ORR) was 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 were those that persisted on repeat imaging study ≥ 4 weeks after initial documentation of response. Imaging studies of responders (PR or CR) were to be reviewed by an independent third party imaging core laboratory for verification.
- Time to tumor response (TTR) was defined as the time from date of randomization to first documentation of objective tumor response. TTR was to be calculated only for the subgroup of patients with objective tumor response.
- Duration of response (DR) was the time from first documentation of objective tumor response to first documentation of objective tumor progression or to death due to cancer. DR data were to be censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and a) were still on study at the time of an analysis, b) were given antitumor treatment other than the study treatment, c) were removed from study follow-up prior to documentation of objective tumor progression, or d) died of non-cancer-related causes

including death due to an unknown cause in the absence of documented disease progression. DR was to be calculated only for the subgroup of patients with a confirmed objective tumor response.

- Duration of performance status maintenance (DPSM) was defined as the time from randomization until the last time the performance status (PS) was no worse than at baseline or to death due to cancer in the absence of prior documentation of worsening PS. Performance status maintenance was to be censored on the day following the date of last performance status assessment for patients who a) did not have performance status worsening, b) were removed from study, c) were given antitumor treatment other than study treatment, or d) died of non-cancer-related symptoms including death due to an unknown cause in the absence of documented disease progression.
- Clinical benefit-related parameters included a) pain relief response rate and time to pain progression; b) investigator-rated changes in severity of other baseline tumor-related signs and symptoms; and c) other patient reported outcomes as measured by the EQ-5D questionnaire.
- Adverse events (AEs) recording included type, incidence, severity (graded by the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0), timing seriousness, and relatedness to study drug, as well as laboratory abnormalities.
- C_{min} values of SU011248 and SU012662 were to be determined from plasma trough samples.
- Plasma protein levels, e.g. sKIT and sVEGFR2, that might be associated with tumor proliferation or angiogenesis, were to be assessed.

Reviewer's Comments:

1. *On 7/1/04, seven months after the first subject enrollment, the sponsor submitted an amendment specifying that in the TTP endpoint, deaths occurring prior to the first on-study assessment were to be censored at the time of randomization.*
2. *In a pre-NDA guidance meeting on 2/10/05, FDA stipulated that deaths prior to documented progression due to any cause should be censored at the time of last tumor evaluation prior to death and not be included as progression events.*
3. *Clinical benefit-related parameters including patient and investigator reported outcomes were prospectively identified by FDA as exploratory and unlikely to be supportive of any labeling claim(s). No such outcomes were submitted with this application.*

Study Populations for Analysis

- Intent-to-Treat Population
 - All patients randomized, with study drug assignment designated according to initial randomization, regardless of whether patients received any study drug or receive a different drug from that to which they were randomized.
- Modified Intent-to-Treat
 - 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.

- As-Treated Population
 - All patients who received at least 1 capsule of study medication with treatment assignments designated according to actual study treatment received. This population is the primary population for evaluating treatment administration/compliance and safety.

6.1.3.11 Statistical Analysis

Sample Size Calculations

- In a survey of investigators who regularly use imatinib mesylate to treat advanced malignant GIST, the reported TTP following imatinib failure was generally < 4 months.
- A 50% improvement (hazard ratio 0.67 [SU011248:placebo]) in median TTP from 4 to 6 months in patients randomized to receive SU011248 was considered to be clinically relevant.
- Adopting a sequential monitoring procedure with 2 interim and one final analyses, a total of 281 patients with disease progression is required for a 2-sided, unstratified log-rank test with an overall significance level of 0.05 and power of 0.90.
- Applying 2:1 randomization, planned accrual period of 18 months, and minimum follow-up period of 6 months, it was estimated that 357 patients (238 on SU011248 and 119 on placebo) would need to be enrolled in order to observe 281 patients with progressive disease by the end of the minimum follow-up period.
- The nominal significance level for interim and final efficacy analyses was determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule.
- Assuming that the trial was not stopped early based on the criteria stated below, final analysis was planned to take place when the 281st patient had documented progressive disease.
- The nominal significance level for final analysis would be 0.044 (if exactly 141 and 211 expected number of events have occurred at the time of the interim analyses).

Statistical Decision Rules

- This study was to be considered a positive trial if the unstratified log-rank test for TTP was significant at the level determined at the time of interim or final analysis in favor of SU011248 using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule.
- Secondary and supportive analyses were to be tested at a significance level of 0.05. No adjustments were planned for multiple testings/comparisons in secondary and supportive hypothesis tests.

Analyses of Time-to-Event Endpoints

- Time-to-event endpoints between the 2 treatment arms were to be compared with a 2-sided unstratified log-rank test at the $\alpha = 0.05$ overall significance level.

- Stratified log-rank tests and Cox proportional hazard models were to be used to adjust for potential influences of baseline stratification factors on time-to-event endpoints.
 - Potential influences of baseline patient age, sex, ethnic origin, performance status, and time from initial diagnosis on the endpoints were to be evaluated.
 - Each prognostic factor was preliminarily to be evaluated by including treatment effect and that individual baseline factor in the Cox proportional hazard model.
 - Variables significant at a 10% level were to be used in building a multivariate model.
 - Backward selection was to be applied to identify the final relevant factors.
- Once a model was established, treatment was to be added to study its effect.
- Treatment-by-factor interactions were to be included in follow-up analyses of each factor.
- Estimated hazard ratios and 2-sided 95% confidence intervals (CI) were to be provided.
- The method was to generate median event time with CI for each treatment arm.
- The CI was 2-sided, had stated coverage probability of 95%, and was calculated using normal approximation methods.

Data Management and Analysis

- Data management and analysis were to be blinded.
 - No study team member had access to the unblinded assignments.
- Analyses for the Data Safety Monitoring Board (DSMB) were prepared by an unblinded statistician at [redacted] who was not otherwise involved in study conduct.

Interim Analyses

Objectives of interim analyses were:

- To allow for early stopping in case of extreme differences in efficacy while maintaining the overall type I error rate at the 0.05 level. If the results of the interim analyses demonstrate statistically significant differences between the 2 treatment arms for TTP (at the appropriate nominal significance that have occurred at the time of that interim analyses), the Sponsor was to consult with health regulatory authorities (HRAs) regarding stopping the clinical trial.
- To adjust sample size if indicated by the data.
- To assess safety, including any unexpected toxicity. If results of interim analyses indicated serious safety concerns, the Sponsor was to consult with HRAs regarding stopping the clinical trial.
- To perform conditional power calculations. If conditional power were very low, then the trial was to be stopped due to futility of continuing the study any further.

One interim assessment of safety was to be conducted after the first 70 patients were observed to have documented progressive disease (~25% of total expected events). There was to be no adjustment for the overall type I error rate because of this safety assessment. Two interim analyses of efficacy and safety were to be performed after the first 141 and 211 patients have documented progressive disease (~50%, and 75% of the total expected events, respectively). The nominal levels of significance for interim analyses were to be determined at time of the interim

analysis (if exactly 141 and 211 expected number of events have occurred at the time of the interim analysis, then nominal significance levels would be 0.0031 and 0.0183, respectively).

The sponsor designated a biostatistician not affiliated with the project to evaluate interim results. If no action was warranted, then no other sponsor staff were to be aware of the interim result. If action or consultation with the US FDA and other Health Regulatory Authorities was indicated, then other sponsor staff would become involved. Clinical sites were to be restricted from access to study results until study conclusion. An independent third-party Data Safety Monitoring Board (DSMB) monitored patient safety on a periodic basis and evaluated results of interim analyses. The DSMB recommended any changes to the patient informed consent form and determined whether the trial should be terminated.

Changes in Planned Analyses

The following changes were made in the final analysis:

- The primary analysis population was changed from MITT to ITT at FDA request.
- TTP definition was revised. Death due to cancer was considered tumor progression in protocol. However, in analysis for deaths prior to documented progression, TTP was censored at the time of last tumor evaluation prior to death.
- The study analysis plan called for results of local laboratory assessments be listed but not included in the summaries. However, the sponsor included local laboratory results in the summaries, reportedly to keep Study A6181004 safety assessment consistent with that used in other studies and in integrated analyses.

Reviewer's Comment: Study A6181004 was well designed with appropriate safeguards to address potential sources of bias that could affect assessment of the primary endpoint. Randomization, double-blinding, regular assessment for progression in all patients, and blinded radiographic reading for determination of disease progression are essential elements of a credible trial with the primary objective of showing an advantage in time to tumor progression in GIST. Phase 2 dose finding was adequate to support the dose and regimen employed. Sample size calculations and the statistical analysis plan were thorough and appropriate. Interim analyses were well planned with appropriate objectives, procedures, and decision rules.

Safety was similarly well addressed in the protocol. The placebo control was appropriate in second-line GIST after imatinib given absence of any known active therapy for this disease. Appropriate safeguards were in place to ensure patient safety.

Entry criteria precluded assessment of safety in patients with significant history and/or evidence of cardiac, liver, or renal disease. Safety of SUTENT in these populations cannot be estimated based on the data submitted.

In summary, the design provides a reasonable assessment of benefit. This is an adequate and well controlled study in the sense of 21 CFR 314.126.

6.1.4 Efficacy Findings

The Data Safety Monitoring Board met on 1/24/05 and recommended early closure of the trial based on achievement of the primary objective. A data cut-off date of 1/1/05 was set for this report, the same cut-off date as was available to the DSMB. The date was prior to study unblinding except for individual patients who had experienced disease progression and were unblinded for purposes of cross-over treatment. Data management and analysis activities after 1/27/05 were unblinded. Hence the sponsor submitted datasets in two forms, one exclusively containing blinded data and the other supplementing that data with additional information added in an unblinded fashion after 1/27/05.

Reviewer's Comment: This review focuses primarily on blinded data.

6.1.4.1 Demographics

The ITT population of pivotal GIST Phase 3 Study A6181004 consisted of 312 patients who were randomized as of the data cutoff date of January 1, 2005.

Table 11 summarizes demographic characteristics of these patients. This information was provided in the study report and confirmed by reviewer analysis of dataset demo.xpt. Study groups were well balanced with respect to age, gender, and self-identified race. More male than female patients enrolled with a ratio of about 2:1.

Table 11: Baseline Demographics

	SU011248 (N=207)	PLACEBO (N=105)
Age (Years) [Median (Range)]	58 (23-84)	55 (23-81)
Gender [N (%)]		
• Female	75 (36)	41 (39)
• Male	132 (64)	64 (61)
Self-identified Race [N (%)]		
• Asian	10 (5)	5 (5)
• Black	8 (4)	4 (4)
• White	183 (88)	92 (88)
• Not allowed to ask / Not listed	6 (3)	4 (4)

(Source: reviewer analysis of dataset demo.xpt)

Table 12 summarizes prior surgery and radiotherapy of enrolled patients. This information is from reviewer analysis of datasets surghx.xpt and rtherhx.xpt. Virtually all patients in both arms had surgical treatment of GIST in addition to biopsy. More patients in the placebo than the treatment group received adjuvant radiotherapy. One patient in the placebo group and none in

the treatment group received both adjuvant and palliative radiotherapy. Patients receiving palliative radiotherapy had best reported prior responses as follows. On the Sutent arm, one patient had PD, and one patient had SD. On the placebo arm, three patients had stable disease.

Table 12: Prior Surgery and Radiotherapy

[N (%)]	SU011248 (N=207)	PLACEBO (N=105)
Surgery other than biopsy	194 (94)	98 (93)
Radiotherapy	16 (8)	16 (15)
• Adjuvant	7 (3)	12 (11)
• Palliative	9 (4)	5 (5)

(Sources: reviewer analysis of datasets surghx.xpt and rtherhx.xpt)

Table 13 summarizes responses to systemic therapy of enrolled patients. This information was generated from reviewer analysis of dataset stherhx.xpt. For patients receiving systemic chemotherapy, a variety of single agent and multi-agent cytotoxic regimens were used. A majority of patients in both arms received systemic chemotherapy prior to study entry. More patients in the Sutent study arm progressed on prior systemic therapy. 29 of 223 patients (13%) receiving prior chemotherapy had an uncharacterized response. The two study arms appear to be reasonably well balanced for surgery, radiotherapy, and systemic therapy of malignant GIST prior to enrollment on Study A6181004.

Table 13: Responses to Prior Systemic Therapy

[N (%)]	SU011248 (N=207)	PLACEBO (N=105)
Systemic Therapy	152 (73)	71 (68)
• Complete Response	2 (1)	0 (0)
• Partial or "Minor Response"	3 (1)	11 (10)
• Stable Disease	33 (16)	12 (11)
• Progressive Disease	98 (47)	36 (34)
• "Not Applicable" or blank	16 (8)	12 (11)

(Sources: reviewer analysis of dataset stherhx.xpt)

Reviewer's Comments:

- Baseline demographic results from dataset demo.xpt match those provided by the sponsor.
- More patients in the placebo arm had adjuvant radiotherapy. This could introduce bias that would enhance the reported treatment effect if these patients were either sicker prior to adjuvant therapy or sicker as a result of having received more radiotherapy.
- Best response to radiotherapy and prior radiotherapy dose were incompletely documented for patients that reportedly received prior radiotherapy. Although the limited data obtained cannot be interpreted, there's no reason to presume that they would affect efficacy analysis.

- *Dataset stherhx.xpt lists prior systemic therapy information for 298 of the 312 patients enrolled on the trial. It is not clear why this information is not included for the other patients. In addition, the meaning of “Minor Response” and “Not Applicable” are not described.*

Table 14 summarizes ECOG performance status reported from the baseline visit just prior to commencement of study treatment. This information was provided in the study report and confirmed by reviewer analysis of dataset popgen.xpt. Performance status was well balanced between study arms.

Table 14: Baseline Performance Status

[N (%)]	SU011248 (N=207)	PLACEBO (N=105)
• 0	92 (44)	48 (46)
• 1	113 (55)	55 (52)
• 2	2 (1)	2 (2)

(Sources: reviewer analysis of dataset popgen.xpt)

Table 15 summarizes prior imatinib exposure. Median duration of prior imatinib was ~2 years. Average prior imatinib dose was at least 400 mg in the top three quartiles of both the SUTENT and placebo arms and was above 600 mg in the top quartile of both study arms.

Table 15: Prior Imatinib Exposure

[Median (Range)]	SU011248 (N=207)	PLACEBO (N=105)
Duration, Dose [Median (Range)]		
• Weeks on imatinib	105 (0-205)	107 (11-187)
• Average daily imatinib dose	503 (204-1600)	485 (235-1394)
• Total dose of imatinib (grams)	367.4 (1.0-1,667.2)	376.4 (32.0-1,312.8)
Best response to imatinib [N (%)]		
• Complete Response	6 (3)	1 (1)
• Partial Response	51 (25)	36 (34)
• Stable Disease	87 (42)	36 (34)
• Progressive Disease	58 (28)	30 (29)
• “Not Applicable” or Blank	5 (2)	2 (2)
Imatinib outcome [N (%)]		
• Intolerance	9 (4)	4 (4)
• Progression within 6 months	36 (17)	17 (16)
• Progression beyond 6 months	162 (78)	84 (80)

(Sources: dataset popgen.xpt)

Reviewer's Comment: Study groups were adequately balanced with respect to prior imatinib. Most patients had an average prior imatinib dose that was at or greater than that approved in the product label for Gleevec (imatinib mesylate).

6.1.4.2 Deviations

Protocol deviations were collected from two locations in the sponsor's "Interim Clinical Study Report, 06-July-2005." These include Section 6.2, "Protocol Deviations" on pp. 100-102 of 41,894 and Section A13, "Errata" on p. 6507 of 41,894. Such protocol deviations could have an impact on either efficacy or safety results of the sponsor's pivotal trial.

Table 16 lists the reviewer's collation of protocol deviations that might affect efficacy results.

Table 16: Protocol Deviations That Might Affect Efficacy Results

Patient ID	Study Arm	Pt #	Nature of Deviation
A6181004-101149-00019	SU011248	19	Found to have had surgery after imatinib failure
A6181004-067665-00086	SU011248	86	History of adenocarcinoma of unknown origin; disease free since radiotherapy in 2000
A6181004-088097-00132	SU011248	132	Found not to have progressed on imatinib on core lab review
A6181004-129926-00058	Placebo	58	History of pulmonary embolism, ♂ ♀
A6181004-113649-00070	Placebo	70	Received ifosfamide following failure of imatinib/capecitabine
A6181004-130706-00072	Placebo	72	History of pulmonary embolism
A6181004-130036-00082	Placebo	82	History of prostate cancer; disease free since 2000

(Source: Section 6.2, "Protocol Deviations" on pp. 100-102 of 41,894)

Circumstances surrounding the protocol deviations in Table 1 are as follows.

Sutent arm

Patient 19 This 72 year old female randomized to the Sutent arm was diagnosed with GIST in ♂ ♀ at which time a partial resection was performed. She received imatinib from February 2002 until July 2003 when disease progression was reported in the liver and left upper quadrant; this was recorded by the investigator as evidence of progression. In ♂ ♀ patient underwent hepatic segmentectomy and gastrocolic mass resection. Surgery following imatinib to all areas of measurable disease where progression on imatinib mesylate therapy had been demonstrated was a violation of exclusion criterion 2. However, core radiology assessment of images from July and October 2003 indicated disease progression following surgery via development of a new splenic lesion. The patient was randomized into Study A6181004 in February 2004 based on the investigator's assessment of prestudy progression. The sponsor allowed the patient to remain on protocol.

Patient 86 No additional information was provided in the treatment-related SAE narrative about violation of exclusion criterion 3 (antecedent malignancy) in this 60 year old female who was randomized to the Sutent arm. The patient was diagnosed with GIST on [REDACTED] following exploratory laparotomy and colostomy. She received adjunctive radiotherapy in January 2001, followed by imatinib 600 mg twice daily from May 2001 through March 2003 and 800 mg twice daily from March 2003 to April 1, 2004. On Study Day 253; Cycle 6, Day 43, the patient was hospitalized with Grade 3 nausea and vomiting, as well as anuric renal failure thought to be due to hypovolemia. The subject declined further therapy or unblinding, and she died on [REDACTED] reportedly due to progressive disease. Protocol deviation does not appear to have affected efficacy in this patient.

Patient 132 This 23 year old female randomized to the Sutent arm was diagnosed with GIST [REDACTED] and received imatinib between February 2002 and June 2004. Based on scans from May 2003 she enrolled to Study A6181004 in June 2004. However, retrospective review of patient records and additional imaging studies indicated that she had shown recent evidence of benefit from imatinib treatment. She then withdrew from the study and went on to receive further treatment with imatinib. Thus she was in violation of inclusion criterion 3, which required demonstration of imatinib failure or intolerance. She was also noted to be in violation of inclusion criterion 2, which concerns documentation of measurable disease.

Placebo arm

Patient 58 No additional information was provided in a treatment-related SAE narrative about violation of exclusion criterion 4 (pulmonary embolus within 12 months of study entry) in this 63 year old female who was initially randomized to the placebo arm. She subsequently crossed over to complete five cycles of open label Sutent with two dose reductions prior to being found dead in bed of unknown cause one day after starting Cycle 6. The pulmonary embolus exclusion criterion was deleted in Amendment 2 on March 8, 2004, prior to this patient's Day 1 treatment March 23, 2004. Protocol deviation does not appear to have affected efficacy in this patient.

Patient 70 A treatment-related SAE narrative clarifies the recorded deviation from exclusion criterion 1 (antecedent chemotherapy following imatinib). Although the patient did receive ifosfamide (from September to November 2003) after imatinib (from July to September 2003), he subsequently received additional imatinib from March 15 to April 1, 2004, prior to starting (placebo) study drug on May 4, 2004. Protocol deviation does not appear to have affected efficacy in this patient.

Patient 72 No additional information was provided in a treatment-related SAE narrative about violation of exclusion criterion 4 (pulmonary embolus within 12 months of

study entry) in this 51 year old male who was initially randomized to the placebo arm. On [redacted] (Cycle 1, Day 9) the patient experienced paralysis. Blinded therapy was withdrawn. Crossover did not occur, and the patient died on July 10, 2004. The pulmonary embolus exclusion criterion was deleted in Amendment 2 on March 8, 2004, prior to this patient's Day 1 treatment May 6, 2004. Protocol deviation does not appear to have affected efficacy in this patient.

Patient 82 This 72 year old male randomized to the placebo arm was allowed to enroll in Study A6181004 despite violation of exclusion criterion 3. This excludes patients carrying diagnosis of a second malignancy within five years prior to study entry, except for adequately treated basal cell or squamous cell skin cancer, or *in situ* carcinoma of the cervix uteri. The patient was diagnosed with prostate cancer in 2000, following which he did not receive systemic therapy. In [redacted] he was diagnosed with GIST and underwent resection. Between September 2003 and October 2004 he received imatinib. From May through October 2004 nausea and weight loss become treatment limiting. He enrolled on Study A6181004 on the basis of imatinib intolerance although subsequent core radiology laboratory imaging assessment revealed disease progression that was presumed due to GIST rather than prostate cancer based on the prostate malignancy's low grade and ~four year disease free interval.

Reviewer's Comment: Reported protocol deviations are unlikely to have influenced efficacy results overall.

Table 17 provides the reviewer's collation of patients who reportedly deviated from protocol inclusion criterion 4, which stipulated that randomization was to occur at least one week following the last dose of imatinib. The washout period following imatinib was defined as at least two weeks in the original protocol and reduced to at least one week following Amendment 3 on July 1, 2004.

Table 17: Deviations in Minimal Interval From Last Imatinib to Randomization

Patient ID	Treatment	#	Nature of Deviation
A6181004-029293-00198	SU011248	198	Began treatment 8 days post-imatinib mesylate
A6181004-130482-00173	SU011248	173	Began treatment 13 days post-imatinib mesylate
A6181004-130704-00247	SU011248	247	Began treatment 5 days post-imatinib mesylate
A6181004-113649-00039	Placebo	39	Began treatment < 2 weeks post-imatinib mesylate
A6181004-086022-00164	Placebo	164	Began treatment 13 days post-imatinib mesylate

(Source: Section 6.2, "Protocol Deviations" on pp. 100-102 of 41,894 and Section A13, "Errata" on p. 6507 of 41,894)

Reviewer's Comment: Based on documented progression or intolerance to imatinib, the observed deviations in minimal interval from last imatinib to randomization are unlikely to influence efficacy results in a meaningful way. However, these protocol deviations could have led to toxicity that was caused by imatinib to be attributed to Sutent.

Table 18 provides a list of patients who were observed to have deviations from protocol exclusion 5 concerning prolongation of the QTc interval to > 450 msec for males or > 470 msec for females.

Table 18: Deviations in QTc interval prolongation at baseline

Patient ID	Treatment	#	Nature of Deviation
A6181004-127449-00018	SU011248	18	QTc = 460 in 1 of 3 ECGs
A6181004-127449-00090	SU011248	90	QTc = 460 in 1 of 3 ECGs
A6181004-127449-00122	SU011248	122	QTc = 480 in 1 of 3 ECGs
A6181004-011526-00009	Placebo	9	Deviation not specified
A6181004-086022-00012	Placebo	12	QTc = 458 by 3 ECGs on 3/22/04 & elevated lipase/amylase
A6181004-127449-00031	Placebo	31	QTc = 460 in 1 of 3 ECGs

(Source: Section 6.2, "Protocol Deviations" on pp. 100-102 of 41,894 and Section A13, "Errata" on p. 6507 of 41,894)

Reviewer's Comment: The observed baseline asymptomatic deviations in baseline QTc interval are unlikely to influence efficacy results in a meaningful way. The potential safety effect will be addressed in Section 7.

Table 19 provides a list of patients who were observed to have deviations from protocol exclusion criterion 8 concerning adequate organ function as defined by clinical laboratory values.

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Table 19: Deviations in baseline organ function

Patient ID	Treatment	#	Nature of Deviation
A6181004-091532-00005	SU011248	5	Elevated lipase (63 U/L)c
A6181004-029293-00030	SU011248	30	Elevated amylase and lipase **
A6181004-103556-00037	SU011248	37	Elevated creatinine (2.0 mg/dL)
A6181004-103556-00040	SU011248	40	Low hemoglobin (8.4 g/dL)
A6181004-086022-00048	SU011248	48	ACTH stimulation testing not done **
A6181004-103556-00057	SU011248	57	Low albumin
A6181004-129926-00060	SU011248	60	Abnormal ACTH-stimulation resultc
A6181004-103556-00062	SU011248	62	Low hemoglobin (8.7 g/dL) Elevated amylase and lipase **
A6181004-131182-00068	SU011248	68	Elevated amylase and lipase **
A6181004-086022-00069	SU011248	69	Low hemoglobin (8.8 g/dL)
A6181004-127449-00090	SU011248	90	Low albumin
A6181004-103556-00101	SU011248	101	Low hemoglobin (7.8 -8.8 g/dL) Elevated amylase and lipase **
A6181004-086022-00109	SU011248	109	Elevated amylase **
A6181004-133140-00115	SU011248	115	Elevated bilirubin (34 µmol/L)
A6181004-014405-00137	SU011248	137	ACTH stimulation testing not done **
A6181004-086022-00141	SU011248	141	ACTH stimulation testing not done **
A6181004-127449-00150	SU011248	150	Low hemoglobin
A6181004-110129-00181	SU011248	181	ACTH stimulation testing not done **
A6181004-086022-00254	SU011248	254	baseline left ventricular ejection fraction 50%
A6181004-113649-00259	SU011248	259	Elevated amylase and lipase ** Low albumin (2.8 g/dL)
A6181004-133253-00302	SU011248	302	Low hemoglobin (8.2 g/dL) Elevated PT (24.8 seconds)
A6181004-011526-00026	Placebo	26	Abnormal lab values, not specified
A6181004-011526-00028	Placebo	28	Low hemoglobin
A6181004-011526-00035	Placebo	35	Abnormal lab values, not specified
A6181004-130706-00072	Placebo	72	Prolonged PT
A6181004-131182-00077	Placebo	77	Coagulation/troponin results not available from central lab
A6181004-103556-00092	Placebo	92	Abnormal ACTH-stimulation result **
A6181004-014405-00102	Placebo	102	Elevated amylase **
A6181004-026823-00126	Placebo	126	Elevated lipase **
A6181004-026823-00139	Placebo	139	Elevated amylase **
A6181004-086022-00164	Placebo	164	ACTH stimulation testing not done **

(Source: Section 6.2, "Protocol Deviations" on pp. 100-102 of 41,894 and Section A13, "Errata" on p. 6507 of 41,894)

21 violations were observed in the Sutent study arm; 10 were observed in the placebo arm. Deviations marked "****" under Nature of Deviation would not have been characterized as violations following Amendment 2 on March 8, 2004; 9 such violations occurred in the Sutent study arm, and 5 were observed in the placebo arm.

Reviewer's Comment: The observed deviations in baseline organ function are balanced and unlikely to influence efficacy results in a meaningful way. Potential safety effect(s) are addressed in Section 7.

6.1.5 Primary Efficacy Endpoint: Time to Tumor Progression (TTP)

Section 6.1.3.10 of this review contains Protocol A6181004's definition of TTP. For review purposes Table 20 groups patients into protocol-defined categories based on the date at which either progression was documented or censoring was to occur.

Table 20: Patient Groups for Evaluation of Time to Progression (TTP)

Patient Group(s)	Progression Date for TTP Analysis
Patients without tumor assessment after randomization	Date of Randomization
Progression date assessed by independent core lab	Date of Documented Progression
<ul style="list-style-type: none"> ○ Deaths before documented progression ○ Off study before documented progression ○ Still on study without documented progression 	Censor at Last Recorded Assessment

Reviewers' Assessment of Patients to be Censored at Randomization

Patients without radiographic assessment following randomization were to be censored at date of randomization. To identify such patients we examined BDERRADT.XPT, the file containing central radiology laboratory-provided radiographic progression dates. BDERRADT.XPT contains 271 patients with central radiology lab derived dates of progression and time to response. These 41 patients had progression censored at Day 1.

Reviewers' Assessment of Patients with Documented Progression

Patients having a radiographic progression event observed by the independent core radiology laboratory or who went off study without a recorded progression event were included in sponsor dataset BRADLES1.XPT. This file was checked to verify progression dates or last documented assessment without progression. Fifteen trial subjects had divergent progression dates recorded by different readers with adjudicated progression occurring after one reader had established a different progression date. These patients, listed in Table 21, are the basis of a sensitivity analysis of the primary endpoint described subsequently in Table 25.

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Table 21. Patients with Equivocal Progression Dates by Core Radiology Reading

Patient ID	Treatment Arm	Sponsor Progression Date	FDA Progression Date	Discrepancy in BRADLESI.XPT
A618X1004-038733-00002	SUTENT	08/17/2004	1/13/2004	cycle 1 new liver lesions 1/13/04
A618X1004-127449-00018	SUTENT	12/04/2004	10/25/2004	non-target PD on 10/25/04
A618X1004-129926-00060	SUTENT	12/06/2004	4/27/2004	cycle 1 new liver lesions 4/27/04
A618X1004-127449-00063	SUTENT	12/31/2004	11/29/2004	target lesion PD, unscheduled exam 11/29/04
A618X1004-133140-00100	SUTENT	07/16/2004	6/7/2004	cycle 1 target lesion progression
A618X1004-133140-00116	SUTENT	09/08/2004	7/28/2004	non-target and target lesion PD
A618X1004-086022-00123	SUTENT	08/10/2004	6/29/2004	non-target and target lesion PD
A618X1004-127984-00147	SUTENT	12/16/2004	11/5/2004	Cycle 3 new lesions
A618X1004-133140-00174	SUTENT	12/14/2004	10/11/2004	target and non-target lesion PD
A618X1004-086022-00180	SUTENT	12/21/2004	10/25/2004	target lesion PD, unscheduled exam 10/25/04
A618X1004-029293-00198	SUTENT	11/10/2004	9/27/2004	cycle 1 new lesions on 9/27/04
A618X1004-113649-00039	Placebo	05/20/2004	4/8/2004	cycle 1 target lesion progression
A618X1004-130703-00131	Placebo	10/14/2004	9/3/2004	cycle 2 non-target and target lesion PD
A618X1004-011526-00160	Placebo	09/21/2004	8/10/2004	cycle 1 non-target PD
A618X1004-101149-00183	Placebo	09/29/2004	8/31/2004	non-target and target lesion PD

(Source: dataset BRADLESI.XPT)

Image Integrity Audit

Dr. Barbara Stinson of FDA's Division of Medical Imaging and Hematology Products (DMIHP) conducted a review of imaging data from Study A6181004 submitted by the sponsor's independent core radiology laboratory. J

Sixty randomly chosen subjects (22% of 271 randomized subjects with evaluable radiographic data) were selected for image review. Dr. Stinson and DMIHP colleagues were able to verify measurement of target lesions and description of non-target lesions for each of these 60 subjects. Sixteen of the 60 reviewed cases had been adjudicated. The most common discrepancies requiring adjudication were attributed to the choice of which lesion(s) to measure and the time point(s) at which lesions were called "new". Full studies were reviewed for all adjudicated cases, and some lesions were measured for each adjudicated case. There was no significant difference in lesion sizes measured by C J and FDA readers.

In summary, the sponsor's submitted radiographic database from Study A6181004 supports integrity of their independent core radiology assessments.

Primary Efficacy Analysis

Efficacy analyses were performed jointly with Dr. Janet Jiang of the Division of Biometrics I.

This NDA submission summarized results of the second interim analysis (first efficacy analysis) with 312 randomized patients and 149 TTP events based on the central radiologist assessment. Results of TTP analysis on both ITT and MITT populations show that SUTENT prolonged time to progression in GIST patients following progression on or intolerance to imatinib.

Table 22 displays the sponsor's and FDA's results on the ITT population. There was a clinically relevant and statistically significant difference between SUTENT and placebo groups in favor of SUTENT with respect to time to progression. Results from analysis of the MITT population were similar and are presented in Table 23.

Table 22: Sponsor's & FDA's TTP Results (ITT Population)

Treatment	Number of TTP Events (%)	Median Survival Time (weeks, 95% CI)	Hazard Ratio (Su0011248/Placebo) (95% CI)	p-value (log-rank test)
<i>Sponsor's analysis (Based on Central Radiologist Assessment)</i>				
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)		
<i>FDA sensitivity Analysis (Based on Central Radiologist Assessment)</i>				
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)		

(Source: NDA 01938 Statistical Review and Evaluation by Dr. Xiaoping (Janet) Jiang)

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Figure 4. Kaplan-Meier Curve of TTP in Study A (Intent-to-Treat Population)

(Source: Sponsor's Figure from product label following based on FDA analysis results)

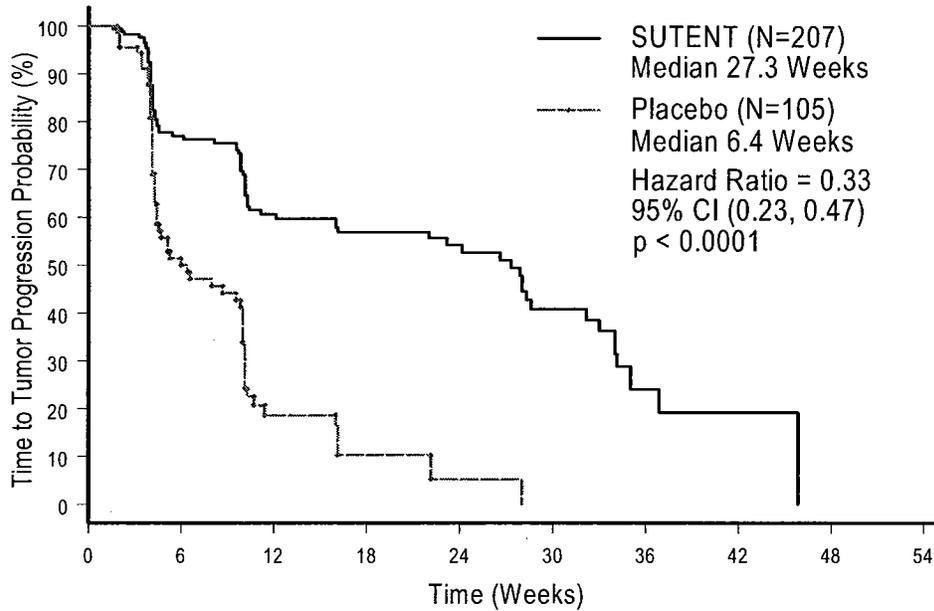


Table 23: Sponsor's and FDA's TTP Results (MITT Population)

Treatment	Number of TTP Events (%)	Median Survival Time (weeks, 95% CI)	Hazard Ratio (Su0011248/Placebo) (95% CI)	p-value (log-rank test)
<i>Sponsor's analysis (Based on Central Radiologist Assessment)</i>				
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)		
<i>FDA sensitivity Analysis (Based on Central Radiologist Assessment)</i>				
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)		

(Source: NDA 01938 Statistical Review and Evaluation by Dr. Xiaoping (Janet) Jiang)

Secondary Endpoints

Table 24 displays interim results of secondary endpoints. Nominal α -level for the primary endpoint, TTP, is 0.0031. Therefore p-values for secondary endpoints should be compared with 0.0031, not 0.05. No multiplicity adjustment was performed for the number of secondary endpoints. Forty-one patients (~13% of the ITT population) did not have independent radiographic assessments available, and the sponsor's PFS results were based on data without inclusion of those 41 entries. However, among those 41 patients, seven patients died, of whom five should have resulted in a PFS event based on the protocol definition. Following a request by Dr. Jiang, the sponsor resubmitted PFS results. Included in the sponsor's reanalysis were five extra PFS events, as well as censoring at date of randomization for the other 36 patients without independent radiographic assessment. Resubmitted PFS results were confirmed by Dr. Jiang and showed that patients on SUTENT in Study A6181004 had a statistically significant improvement in progression free survival in comparison to patients on placebo.

The trial was stopped based on results of the first interim analysis for efficacy. At this time there were 56 deaths among 312 ITT patients. With about 1 year of maximum treatment duration and follow-up, the data were not mature enough to determine any survival benefit offered by SUTENT.

Table 24: Sponsor's Results of Secondary Endpoints * (ITT Population)

(Source: NDA 01938 Statistical Review and Evaluation by Dr. Xiaoping (Janet) Jiang)

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

Sensitivity Analyses

We performed 3 sensitivity analyses on the primary endpoint, TTP, based on the following changes.

1. Alternative progression dates observed by one of three independent core radiology reviewers for fifteen patients;
2. The above modification in the MITT population; and
3. Exclusion of three patients based on protocol deviations that may have influenced efficacy. See Table 16 in Section 6.1.4.2 (Deviations) concerning details of patients 19, 82, and 86.

None of the TTP sensitivity analyses resulted in a substantial change of the results of efficacy analysis. Results are shown in Table 25.

Table 25: Results of FDA’s TTP Sensitivity Analysis

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

(Source: NDA 01938 Statistical Review and Evaluation by Dr. Xiaoping (Janet) Jiang)

Subgroup Analyses

Subgroup exploratory analyses were conducted on the primary endpoint, TTP, based on age, gender, race (Caucasian patients, 88% of subjects), and trial site (U.S. vs. foreign). Table 26 summarizes results. In each case subgroups yielded TTP efficacy results that were similar to that of the entire ITT population.

Table 26: 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 Countries	111	58	0.293 (0.176,0.489)	<0.0001

(Source: NDA 01938 Statistical Review and Evaluation by Dr. Xiaoping (Janet) Jiang)

Effectiveness data for men versus women are addressed in Section 5.3 (Exposure-Response Relationships). Most patients in Study A6181004 were white (88%). Racial subgroups were not separately examined. Age as a covariate did not improve productivity of the population PK model described in Section 5.1 (Pharmacokinetics).

Reviewer’s Comment: Primary efficacy results of Study A6181004 are statistically robust with no significant diminution of the observed SUTENT effect following either sensitivity or subgroup analyses.

6.1.5.1 Supportive Single-Arm-Trial: Study RTKC-0511-013

RTKC-0511-013, “A Phase I/II Study of SU011248 in the Treatment of Patients with Malignant Gastrointestinal Stromal Tumor (GIST) who are Intolerant of, or with Disease Progressing on Imatinib Mesylate (Gleevec), was a sponsor-conducted, open-label, multi-center, single-arm, dose-escalation study in patients with GIST after imatinib. Following identification of the recommended Phase 2 regimen (50 mg once daily on Schedule 4/2), fifty-five patients in this study received the 50 mg dose of SUTENT on treatment Schedule 4/2. Partial responses were observed in 5 of 55 patients [9.1% PR rate, 95% CI (3.0, 20.0)]. Overall median TTP was 34 weeks [95% CI (22.0 – 38.6)]. Median overall survival for the 55 patients was 85.1 weeks [95% CI (58.9, 108.1)].

Reviewer’s Comment: This single-arm trial yielded a similar response rate result to Study A6181004.

6.1.6 Clinical Microbiology

Based on the proposed indication and SUTENT's presumed mechanism of action, no Clinical Microbiology review was conducted of this application.

6.1.7 Efficacy Conclusions

In Study A6181004, SUTENT showed a convincing, statistically robust advantage over placebo in prolongation of the primary endpoint, TTP, as well as PFS. Conclusions from the consultative review by Dr. Barbara Stinson (of DMIHP) on image data integrity strengthen credence of the sponsor's claims. Results were consistent for identified subgroups based on age, gender, race, and trial site location. The response rate was 7% in the patients on SUTENT and 0% in those on placebo. Survival results are not mature; only 56 (18%) of the patients died at the time of interim analysis. The sponsor should update survival results when the data become available. This will be a post-marketing commitment.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The analysis that follows is focused primarily on Study A6181004, the blinded, randomized, placebo-controlled trial of sunitinib in patients who either progressed on or were intolerant to imatinib.

Of 207 patients randomized to sunitinib treatment in Study A6181004, 202 patients were considered in the sponsor's safety analysis. One patient (PTNO 132) was found not to have progressed on imatinib following randomization to sunitinib; she received no study drug. Four patients (292, 304, 307, and 308) were excluded from safety analysis, reportedly because there was no study drug dosing information available for them. PTNO 292 was randomized on 12/10/04; PTNO's 304, 307, and 308 were randomized on 12/17/04. Thus these patients would all have completed less than one cycle of therapy at the time of database lock on 1/1/05. None of these patients had any recorded adverse events on study. The sponsor's exclusion of these patients from its safety analysis is legitimate.

7.1.1.1 Safety Evaluations

The investigator was to obtain and record on the case report form all observed or volunteered adverse events, event severity, and their opinion of relationship to study treatment. AEs included adverse drug reactions, any illnesses with onset during study, and exacerbation of previous illnesses. Additionally, the investigator was to record as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (e.g., ECG, x-ray,

laboratory). For all AEs, the investigator was to pursue and obtain information adequate to determine both outcome and whether the event met criteria for classification as a SAE. If the AE or its sequelae persisted, follow-up was required until resolution or stabilization at a level acceptable to investigator and sponsor.

7.1.2 Deaths

Twenty-three patients on SUTENT (11%) versus 11 on placebo (11%) died during the blinded phase or after discontinuing the blinded phase without crossing over to open-label treatment. Thirteen patients on SUTENT (6%) vs 8 on placebo (8%) died within 28 days of their last dose of study medication. Patients who died within 28 days of receiving their last on-study treatment are listed in Table 27. No increase in deaths following from use of SUTENT was observed relative to the placebo control group in Study A6181004.

Table 27. Deaths within 28 Days of Treatment

Treatment	Patient Number	Days Since Last Dose
SU011248	A6181004-038733-00007	0
	A6181004-088097-00134	4
	A6181004-094103-00169	25
	A6181004-103556-00037	26
	A6181004-103556-00057	2
	A6181004-118908-00179	21
	A6181004-127449-00033	11
	A6181004-127449-00073	17
	A6181004-127449-00122	14
	A6181004-127449-00150	15
	A6181004-131182-00068	9
	A6181004-133140-00116	11
	A6181004-133140-00195	2
Placebo	A6181004-011526-00028	0
	A6181004-038733-00003	10
	A6181004-086022-00012	9
	A6181004-088097-00149	8
	A6181004-103556-00092	13
	A6181004-118908-00074	22
	A6181004-127449-00105	9
	A6181004-132401-00211	6

Source: Section 9.3.1, Interim Clinical Study Report, p. 136 of 41,894

7.1.3 Other Serious Adverse Events

Grade 3 or 4 adverse events were observed in 115 patients (57%) on SUTENT and 53 (52%) on placebo. Grade 4 adverse events were observed in 31 patients (15%) on SUTENT and 15 (15%) on placebo.

7.1.4 Dropouts and Other Significant Adverse Events

7.1.4.1 Overall profile of dropouts

Nineteen of 202 patients (9%) on SUTENT versus eight of 102 patients (8%) on placebo discontinued treatment due to an adverse event.

7.1.4.2 Adverse events associated with dropouts

In general the adverse events that led to discontinuation were balanced between treatment arms, as indicated by sponsor Table 13.6.6.1 (p. 1028 of 41,894 of the interim study report). Exceptions include study drug discontinuation due to anemia (4 SUTENT and 0 placebo patients), liver failure (2 SUTENT and 0 placebo patients), and metabolic disorders (3 SUTENT and 0 placebo patients). Overall the pattern of AEs leading to dropouts in patients taking SUTENT is difficult to differentiate from the natural history of GIST.

7.1.4.3 Other significant adverse events

There were no other significant adverse events observed during Study A6181004 in the sense intended by the International Conference on Harmonisation. See Section 7.1.5 for other search strategies used to evaluate the safety database of Study A6181004.

7.1.5 Other Search Strategies

7.1.5.1 Reductions in left ventricular ejection fraction

Prior collective clinical data suggested the possibility of drug-related ventricular dysfunction with SU011248. These findings were most notable in patients with AML, several of whom had histories of prior anthracycline exposure or prior cardiac risk factors, experienced serious disease complications, and were receiving higher doses of study drug than were administered in Study A6181004. While this pattern may have been primarily a consequence of complications of AML in an elderly population, the possibility of SU011248-mediated cardiac injury in other patients at lower doses of study drug continues to undergo systematic evaluation. Thus all patients in Study

A6181004 were to undergo cardiac troponin level monitoring and MUGA scanning during the study.

The sponsor employed a modified criterion of CTCAE version 2.0 for evaluation of left ventricular systolic dysfunction in Study A6181004. In CTCAE version 2.0, resting ejection fraction below the lower limit of normal (LLN) *or* a $\geq 20\%$ absolute decrease in LVEF is considered a Grade 2 event. Grade 3 events include treatment-responsive CHF, and Grade 4 events comprise severe or refractory CHF. For comparison CTCAE version 3 does not differentiate relative differences within the normal range and instead assesses absolute ranges of left ventricular ejection fraction (LVEF). Grade 1 systolic dysfunction comprises an ejection fraction from the LLN downward to 50%. Grade 2 events represent LVEF below 50% downward to 40%. Grade 3 includes symptomatic CHF and/or LVEF below 40% downward to 20%. By contrast, the sponsor defined Grade 2 left ventricular systolic dysfunction as an ejection fraction below 50% *and* a 20% absolute decrement in ejection fraction from the baseline value. When these conditions were met, trial subjects were to have dose reduction of study drug by one level. The sponsor's lower limit of normal for ejection fraction was 50%.

Twenty-two patients (11%) on SUTENT and 3 patients (3%) on placebo had treatment-emergent LVEF values below 50%. Of 22 patients on SUTENT with treatment-emergent Grade 2 or greater declines in LVEF, 9 (41%) had documented LVEF recovery to the normal range without any intervention.¹ 5 patients (23%) had documented LVEF recovery following intervention (dose reduction or change in concomitant medications).² 6 patients (27%) had no documented recovery of LVEF to the normal range prior to going off study.³ 2 patients (9%) with Grade 2 or greater decreased LVEF died.⁴

Three of 202 patients (1.5%) on Sutent had Grade 3 reductions (CTCAE version 3.0) to LVEF < 40%. One of these patients recovered without intervention. The two other died without receiving any additional study drug.

Of three GIST patients on placebo with LVEF < 50%, none had documented Grade 3 left ventricular systolic dysfunction. A single patient on placebo whose death was attributed to "heart failure" had baseline abnormal ecg, cycle 2 serum albumin/protein of 3.5/6.2 mg/dL, multiple blood transfusions for recurrent lower GI bleeding in the two weeks prior to death, and no documentation of abnormal LVEF at any time.

We queried the database for CTCAE defined Grade 2 or greater left ventricular systolic dysfunction, *i.e.* for patients with any recorded ejection fraction less than 50%. The 24 patients identified are listed in Table 28, as well as an additional patient identified by death narrative. In order to place these results into context, we assessed recorded symptoms suggestive of

¹ Recovery without intervention: Patients 1, 34, 42, 64, 71, 79, 101, 146, 218.

² Recovery following intervention: Patients 6, 19, 23, 30, 46.

³ No documented recovery of LVEF prior to going off study: Patients 41, 60, 118, 128, 175, 180.

⁴ Deaths following Grade 3 decreased left ventricular systolic function: Patients 68, 73.

congestive heart failure (fatigue, dyspnea, edema), elevations of blood pressure, elevations in cardiac troponin or creatine kinase, and changes in concomitant cardiac medications.

In dataset BAE.XPT, systemic hypertension of any grade was observed in 31 patients (15.3%) on Sutent and 11 patients (10.8%) on placebo. Grade 2 or 3 hypertension was observed in 23 patients (11.4%) on Sutent and 8 patients (7.8%) on placebo. Grade 3 hypertension was observed in 9 patients (4.4%) on Sutent and none on placebo. In patients with at least one treatment-emergent LVEF value below 50%, Grade 2 or 3 hypertension was reported in 4 of 22 patients (18.0%) on Sutent and none of 3 patients on placebo. In patients with at least one treatment-emergent LVEF value below 50%, Grade 3 hypertension was noted in 2 of 22 patients (9.1%) on Sutent and none of 3 patients on placebo, respectively.

Routine cardiac troponin I (cTnI) and creatine kinase (CK) laboratory monitoring was performed. In dataset BCLCHEM.XPT, treatment-emergent, detectable cTnI levels were observed in 50 of 202 patients (24.8%) on Sutent and 13 of 102 patients (12.7%) on placebo. Treatment-emergent Grade 3 cTnI elevations of ≥ 0.3 ng/ml were observed in 8 patients (4.0%) on Sutent and 3 patients (2.9%) on placebo. In patients with at least one treatment-emergent LVEF value below 50%, treatment-emergent cTnI was detectable in 7 of 22 patients (31.8%) on Sutent and none of 3 patients on placebo, respectively.

In dataset BCLCHEM.XPT, treatment-emergent, elevated creatine kinase levels were observed in 31 of 202 patients (15.3%) on Sutent and 9 of 102 patients (8.8%) on placebo. Treatment-emergent Grade 3 CK elevations were observed in 3 patients (1.5%) on Sutent and none on placebo. In patients with at least one treatment-emergent LVEF value below 50%, treatment-emergent CK was detectable in 6 of 22 patients (27%) on Sutent and none of 3 patients on placebo, respectively.

Summary: Of 22 patients on SUTENT with treatment-emergent Grade 2 or greater declines in LVEF, Patients 68 and 73 *may* have had CHF due to SUTENT. No other patients had congestive heart failure attributable to SUTENT. However, in 11 patients (50%) observed decreases in ejection fraction were followed either by medical intervention prior to LVEF recovery or by no subsequent LVEF measurements that would confirm reversibility.

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Table 28. Patients with Grade 2 or greater left ventricular systolic dysfunction in GIST Phase 3 randomized, placebo-controlled trial

Rx	Pt	Age Sex	Baseline LVEF ¹	CYCLE #: 1 st low EF ¹ / # blinded ²	Low LVEF ¹	More drug / Dose Reduction ²	Htn ³ / AE ³ / cTnI ⁴ / CK ⁴	Concomitant meds ⁵ / Outcome
S	1	48 M	59	6 / 7	45	Yes, No	Fatigue Grade 2, cycles 6-9. CK Grade 1, cycles 1, 3, 4.	LVEF recovered in cycle 7.
S	6	74 M	60	2 / 8	49	Yes / No	Dizziness Grade 1 or 2, cycles 1-3. Fatigue Grade 3 cycle 1, Grade 2 cycles 2-5, Grade 1 cycles 6, 7. CK elevation Grade 1 cycle 3. cTnI detectable cycles 1, 2, 6.	Metoprolol started cycle 3. LVEF recovered cycle 3.
S	19	72 F	58	5 / 6	45	Yes / No	Fatigue, Edema, NOS, Grade 1 in cycles 2-6. cTnI detectable cycles 1 & 2.	Lasix started cycle 1 (edema), HCTZ cycle 5 (Htn). LVEF recovered cycle 6.
S	23	58 F	53	1 / 7	49.2	Yes / No	Grade 1 or 2 AST/ALT in cycle 2.	Started diuretics in cycle 1. LVEF recovered cycle 2.
S	30	55 F	68	2 / 2	49	No / --	Fatigue Grade 3, cycles 5, 6. Ankle edema Grade 1, PND Grade 3, & pulmonary Htn Grade 4 in cycle 6. Angina cycle 7, Grade 2 Htn cycles 2-7. cTnI detectable cycles 1-7, Grade 3 cycles 5, 6.	Started diuretics cycle 1 & beta blocker after cycle 2. Patient went off study after cycle 2 due to PD. LVEF recovered in cycle 4. Cardiac cath for chest pain in cycle 6. Dose reduced at cycles 6 & 7.
S	34	67 F	72.2	3 / 7	35	Yes / No	Fatigue Grade 3, cycles 5, 6. Ankle edema Grade 1, PND Grade 3, & pulmonary Htn Grade 4 in cycle 6. Angina cycle 7, Grade 2 Htn cycles 2-7. cTnI detectable cycles 1-7, Grade 3 cycles 5, 6.	Patient off study after cycle 1 due to PD. LVEF recovered to normal range in cycle 3.
S	41	50 M	55	1 / 1	40.6	No / --	Grade 1 CK elevations in cycles 1-7.	Dose reduced at cycle 6.
S	42	44 M	68	1 / 7	48.9	Yes / No	Htn Grade 2 cycles 1, 2. cTnI detectable on pre-study screening.	Started Procardia XL cycle 1. Lisinopril cycle 2 for Htn. LVEF >55% in cycle 2.
S	46	64 M	52	1 / 2	46	Yes / No	Cardiac cath between cycles 1 & 2.	Dose reduced at cycles 2 & 5. No LVEF at cycle 7 evaluation.
S	60	60 F	51	6 / 6	49	No / --	Fatigue Grade 1-3 in cycles 3-6. Edema Grade 1 cycles 2-6. Grade 2 cycles 6, 7.	LVEF recovered cycle 4.
S	64	44 M	58	2 / 7	44	Yes / No	Fatigue Grade 2 in cycles 1-4. Grade 1 in cycle 5. Grade 3 cycle 6. Edema Grade 1, cycles 2-6. Grade 2 cycles 6, 7. Ascites Grade 3, cycles 2-4, Grade 2 cycles 6, 7. CK elevation Grade 3, cycle 2.	Started Lasix one week after cycle 1. Died 9 days after MUGA of "brainstem ischemia". LVEF recovered in cycle 2.
S	68	65 M	50	1 / 1	36	No / --	Fatigue Grade 3 & Edema Grade 4 in cycle 1.	Started Ramipril in cycle 4 and Dyazide in cycle 6.
S	71	73 M	64	1 / 6	49	Yes / No	Fatigue Grade 1 or 2 in cycles 1, 2, 4, 5. Hypertension Grade 2 in cycles 4 & 5. CK elevation Grade 1 in cycles 1, 3.	Started Lasix 8 days & dabutamine 9 days after last SUTENT. Died 16 days after last SUTENT.
S	73	65 F	58	3 / 3	29	No / --	cTnI elevated cycle 2, Grade 3 in cycle 3.	Dose reduced at cycles 2 & 6. LVEF recovered cycle 3.
S	79	61 F	57.8	2 / 6	41	Yes / No	cTnI detectable in cycles 5-7.	Started Amilor cycle 1, Empiconcor cycle 4 for Htn. LVEF recovered cycle 3.
S	101	70 M	78	2 / 6	48	Yes / No	Fatigue Grade 1 or 2 in cycles 3-6. Edema Grade 1 in cycles 1-6. Hypertension Grade 1 cycle 1, Anorexia Grade 1 cycles 1-4.	Dose reduced at cycle 2. LVEF 45% in cycle 2, 48% at last MUGA in cycle 3.
S	118	44 F	66	1 / 4	47	Yes / Yes	Leighargy Grade 1 cycles 3-4.	No cycle 5 LVEF. Cycle 6 LVEF 48%.
S	128	41 M	53	4 / 5	45	Yes / No	cTnI detectable cycle 3.	LVEF recovered cycle 2.
S	146	67 M	51.7	1 / 4	48	Yes / No	Edema Grade 1, cycles 1, 2. Fatigue Grade 1 in cycle 2.	No additional LVEF after cycle 4.
S	175	55 M	58.7	4 / 4	45.6	No / --	CK elevation Grade 3 in cycle 1, Grade 1 in cycle 2.	PD on cycle 2 images. No known follow-up MUGA.
S	180	28 M	53	2 / 2	48	No / --	Grade 2 fatigue, Grade 1 irregular heartbeat in cycle 3.	LVEF recovered cycle 4.
S	218	52 M	58	1 / 3	40	Yes / No	Grade 2 or 3 fatigue, Grade 1-6. Grade 1 edema cycles 5, 6.	Cycle 2 LVEF 47%. LVEF recovered cycle 3.
P	26	47 M	68	3 / 6	40	Yes / No	Grade 2 hypoxanthinemia & peripheral edema in cycle 2.	Cycle 2 LVEF 59%.
P	77	63 M	65	1 / 6	40	Yes / No		
P	189	72 M	57	1 / 7	44	Yes / No		

¹ From dataset BEM5.XPT (except Pt 73 -- death narrative). ² From dataset BDRUGDT.XPT or DRUG.XPT. ³ From dataset BAE.XPT. ⁴ From dataset BCLCHEM.XPT. ⁵ From CRF's.

7.1.5.2 Adrenal suppression

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation.

In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Laboratory testing of patients on Study A6181004 did not raise significant concerns for overt adrenal insufficiency caused by SUTENT. However, testing was limited. Also subclinical adrenal insufficiency may become overt in the setting of significant physiological stress, e.g. infection, surgery, or trauma. If unnoticed, such unmasking of subclinical adrenal suppression by SUTENT could be life threatening. Thus we recommend that a Precaution be included in the product label to indicate that physicians prescribing SUTENT should monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

7.1.5.3 Genitourinary complaints

Effects of SUTENT on the female reproductive system were identified in a 3-month repeat dose monkey study, where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (~5.1 times AUC in patients administered the recommended daily dose (RDD)). Uterine changes (endometrial atrophy) were noted at ≥ 2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6-mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

In order to evaluate these preclinical findings further, non-specific genitourinary complaints were sought in the study database. Table 29 shows results of this investigation. Treatment-emergent genitourinary complaints were increased in the SUTENT relative to placebo arm. However, such complaints in patients receiving SUTENT were all Grade 1 or 2 in severity with the exception of a single placebo patient that experienced a Grade 3 vaginal hemorrhage. It is

feasible that cystitis and dysuria may be ameliorated by supportive care measures such as phenazopyridine.

Table 29. Genitourinary Complaints in Patients Taking SUTENT versus Placebo

[N (%)]	SU011248 (N=202)	PLACEBO (N=102)
Cystitis	4 (2%)	1 (1%)
Chromaturia	11 (5%)	3 (3%)
Dysuria	7 (3%)	0
Hematuria	6 (3%)	2 (2%)
Vaginal bleeding/erythema/pain	3 (1%)	2 (2%)
TOTAL	27 (14%)	7 (7%)

(Source: dataset BAE.XPT)

7.1.6 Common Adverse Events

7.1.6.1 Eliciting adverse events data in the development program

The investigator was to obtain and record on the case report form all observed or volunteered adverse events, event severity, and their opinion of relationship to study treatment. AEs included adverse drug reactions, any illnesses with onset during study, and exacerbation of previous illnesses. Additionally, the investigator was to record as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (e.g., ECG, x-ray, laboratory). For all AEs, the investigator was to pursue and obtain information adequate to determine both outcome and whether it the event met criteria for classification as a SAE. If the AE or its sequelae persisted, follow-up was required until resolution or stabilization at a level acceptable to investigator and sponsor.

7.1.6.2 Appropriateness of adverse event categorization and preferred terms

Formal comparison of literal terms used by investigators to preferred dictionary terms used by the sponsor was not performed. Rather, adverse events in dataset BAE.XPT were summarized for all dictionary terms with subgrouping by treatment group. By reviewing all such terms, differences in event rates were sought between treatment groups. In some cases related terms were grouped.

7.1.6.3 Incidence of common adverse events

Common adverse events were explored in Study A6181004 only. Although this placebo-controlled trial represents only a portion of the overall SUTENT safety database, the ability to

compare adverse event rates between SUTENT and placebo groups outweighs the disadvantage of basing estimates on a relatively smaller number of subjects.

7.1.6.4 Common adverse event tables

Table 30 presents treatment-emergent adverse events from dataset BAE.XPT that occurred at a frequency of at least 10% in either SUTENT or placebo patients on Study A6181004.

Treatment-emergent adverse events were derived by censoring on-study adverse events from dataset BAE.XPT for any baseline adverse events of the same Grade in the same patients from dataset BPSS.XPT.

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Table 30. FDA Analysis of Treatment-Emergent Adverse Events Reported in at Least 10% of GIST Patients Who Received SUTENT or Placebo in Study A6181004*

(Source: datasets BAE.XPT and BPSS.XPT)

Adverse Event, n (%)	GIST			
	SUTENT (n=202)		Placebo (n=102)	
	All Grades	Grade 3/4 ^a	All Grades	Grade 3/4 ^b
Any		114 (56)		52 (51)
Constitutional				
Fatigue	84 (42)	17 (8)	48 (47)	8 (8)
Fever	36 (18)	3 (2)	17 (17)	1 (1)
Gastrointestinal				
Diarrhea	81 (40)	9 (4)	27 (27)	0 (0)
Nausea	63 (31)	3 (2)	33 (32)	5 (5)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Vomiting	49 (24)	4 (2)	24 (24)	3 (3)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Abdominal pain ^c	67 (33)	22 (11)	39 (38)	12 (12)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Skin Discoloration	61 (30)	0 (0)	23 (23)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Headache	26 (13)	3 (2)	23 (23)	0 (0)
Musculoskeletal				
Arthralgia	24 (12)	2 (1)	16 (16)	0 (0)
Back pain	23 (11)	2 (1)	16 (16)	4 (4)
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Respiratory				
Dyspnea	20 (10)	0 (0)	19 (19)	3 (3)
Cough	17 (8)	0 (0)	13 (13)	0 (0)
Metabolism/Nutrition				
Anorexia ^d	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)
Hemorrhage/bleeding				
Bleeding, all sites	37 (18)	14 (7)	17 (17)	9 (9)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

^a Grade 4 AEs in patient on SUTENT included abdominal pain (2%) and bleeding (2%).

^b Grade 4 AEs in patients on placebo included fatigue (3%), mucositis (1%), vomiting (1%), abdominal pain (3%), back pain (1%), and bone pain (1%).

^c Includes abdominal quadrant, gastric, hypochondrial, abdominal, flank, and cancer-related pain

^d Includes decreased appetite

Other common adverse events (>1%) are as follows. Oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUTENT versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo.

7.1.6.5 Identifying common and drug-related adverse events

We based our assessment of drug-related adverse events on SUTENT's established mechanism of action and observed AEs following use of other drugs in the same pharmacologic class (tyrosine kinase inhibitors and vascular endothelial growth factor inhibitors).

Common (>10%) adverse events following from use of SUTENT include increased blood pressure, gastrointestinal disturbances, skin abnormalities, altered sense of taste, asthenia, and laboratory abnormalities. Common laboratory abnormalities include elevated pancreatic enzymes, electrolyte disturbances, lowered neutrophils and platelets, and decreased left ventricular ejection fraction (LVEF). Uncommon (<10%) laboratory abnormalities following from use of SUTENT include hypophosphatemia and acquired hypothyroidism.

7.1.6.6 Additional analyses and explorations

Please see Section 5.3 (Exposure-Response Relationships) for additional assessment of relationships between AE categories and drug exposure.

7.1.7 Less Common Adverse Events

See Sections 7.1.5.1 (Reductions in left ventricular ejection fraction) and 7.1.5.2 (Adrenal suppression) for discussion of the potential for SUTENT to cause clinically significant congestive heart failure and/or adrenal suppression.

7.1.8 Laboratory Findings

7.1.8.1 Overview of laboratory testing in the development program

The following clinical laboratory tests were to be conducted before dosing on the schedule in Table 9 of Section 6.1.3.5 (Treatment Plan). Most tests were performed at least once each cycle and additionally as medically indicated to preserve patient safety and to confirm timing of resolution.

- Serum Chemistry: sodium, potassium, calcium, chloride, phosphorus, carbon dioxide, creatinine, total bilirubin, indirect bilirubin, total protein, albumin, globulin, alkaline phosphatase, creatine kinase (CK), AST, ALT, glucose, blood urea nitrogen (BUN), uric acid, amylase, and lipase;
- Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, platelets, hematocrit, mean corpuscular volume (MCV), and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils);
- Cardiac enzymes: cardiac-specific troponin I (cTnI) and/or troponin T (cTnT);
- Urinalysis: specific gravity, pH, protein, glucose, ketones, blood, leukocyte esterase, nitrite;

- Coagulation: activated partial thromboplastin time (aPTT) and PT or PT expressed as the international normalized ratio (INR);
- LVEF was assessed by MUGA scan at screening, on the last day of dosing of even-numbered cycles (Cycles 2, 4, 6, etc.), and at the time of study withdrawal.

Laboratory analyses were assessed using the grading scale from Common Toxicity Criteria for Adverse Events, version 3.0 (CTCAE). See Section 6.1.4.2 for patients who displayed baseline laboratory abnormalities.

7.1.8.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Study A6181004, a randomized, double-blind, placebo-controlled trial, was the source of data for drug-control comparisons of laboratory values.

7.1.8.3 Standard analyses and explorations of laboratory data

Table 31 provides common ($\geq 10\%$) treatment-emergent laboratory abnormalities from datasets BCLCHEM.XPT and BCLHEMA.XPT. Treatment-emergent rates were derived by verification that observed laboratory abnormalities of any given Grade on-study were not present at baseline.

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Table 31. Treatment-Emergent Laboratory Abnormalities (≥10%) from Study A*
(Source: datasets BCLCHEM.XPT and BCLHEMA.XPT)

Adverse Event, n (%)	SUTENT (n=202)		Placebo (n=102)	
	All Grades	Grade 3/4 ^a	All Grades	Grade 3/4 ^b
Any		68 (34)		22 (22)
Gastrointestinal				
AST / ALT	78 (39)	3 (2)	23 (23)	1 (1)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Total Bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect Bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Cardiac				
Decreased LVEF	21 (10)	2 (1)	3 (3)	0 (0)
Renal / Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Hypokalemia	24 (12)	1 (1)	4 (4)	0 (0)
Hypernatremia	20 (10)	0 (0)	4 (4)	1 (1)
Uric acid	31 (15)	16 (8)	16 (16)	8 (8)
Hematology				
Neutropenia	107 (53)	20 (10)	4 (4)	0 (0)
Lymphopenia	76 (38)	0 (0)	16 (16)	0 (0)
Anemia	52 (26)	6 (3)	22 (22)	2 (2)
Thrombocytopenia	76 (38)	10 (5)	4 (4)	0 (0)

*Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

^a Grade 4 AEs in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), hypokalemia (1%), neutropenia (2%), anemia (2%), and thrombocytopenia (1%).

^b Grade 4 AEs in patients on placebo included amylase (1%), lipase (1%), anemia (2%), and thrombocytopenia (1%).

Grade 3 or 4 treatment-emergent laboratory abnormalities were observed in 68 (34%) versus 22 (22%) patients on SUTENT and placebo, respectively. Elevated liver function tests, pancreatic enzymes, and creatinine were more common in patients treated with SUTENT than placebo. Decreased LVEF and myelosuppression were also more common with SUTENT treatment. Treatment-emergent electrolyte disturbances of all types were more common in patients on SUTENT than on placebo, including hyperkalemia (6% vs. 4%), hypokalemia (12% vs. 4%), hypernatremia (10% vs. 4%), hyponatremia (6% vs. 1%), and hypophosphatemia (9% vs. 0%). Three SUTENT patients (1.5%) had Grade 3 hypophosphatemia. Acquired hypothyroidism was noted in 8 patients (4%) on SUTENT versus 1 (1%) on placebo.

Hematologic abnormalities

Grade 3 and 4 neutropenia were reported in 19 patients (9%) and 3 patients (2%) patients on SUTENT and none on placebo. One patient each in the SUTENT and placebo groups had febrile neutropenia. Grade 3 and 4 thrombocytopenia was reported in 7 patients (4%) and 1 patient (1%) on SUTENT and none on placebo. The rates of dose reductions and delays for hematologic abnormalities were 2% for neutropenia, 0% for anemia, and 1% for thrombocytopenia.

We recommend that product labeling include language indicating that patients receiving SUTENT should be monitored regularly for myelosuppression.

Hypothyroidism

Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT versus 1 (1%) on placebo.

We recommend that product labeling include language indicating that patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated by standard medical practice.

7.1.8.4 Additional analyses and explorations

For additional analyses of dose or time dependency, as well as drug-demographic, drug-disease, and drug-drug interactions, see Section 5.3 (Exposure-Response Relationships).

7.1.8.5 Special assessments - Hepatotoxicity

Two patients on the SUTENT arm and none on the placebo arm died of hepatic failure.

Patient A6181004-127449-00033, a patient with documented liver involvement with GIST (dataset BRADLESI.XPT), received SUTENT for 15 days before stopping of his own volition. Four days later he was hospitalized for acute liver failure. He died 11 days after his last dose of SUTENT. Death was attributed to disease progression. His liver function tests at baseline were all normal. On Day 15 when he stopped SUTENT, he was observed to have Grade 1 elevation of AST, ALT, and alkaline phosphatase (dataset BCLCHEM.XPT). Other liver function tests remained normal at that time.

Patient A6181004-133140-00195, a patient with documented liver involvement with GIST, died two days after his last dose of SUTENT in Cycle 2. No death or SAE narrative was provided. This patient's liver tests remained in the normal range at the conclusion of Cycle 2 treatment with SUTENT. Thus there is no evidence that SUTENT was responsible for this patient's reported liver failure.

At screening, mean AST was 27.6 IU/L (standard error of mean (SEM) 1.0) in the SUTENT arm and 28.4 IU/L (SEM 1.3) in the placebo arm. On treatment, mean AST was 30.3 (SEM 0.53) in the SUTENT group and 28.3 IU/L (SEM 1.0) in the placebo group. AST rose slightly on treatment in the SUTENT arm, whereas in the placebo arm AST was unchanged.

At screening, mean ALT was 24.1 IU/L in the SUTENT arm (SEM 1.3) and 24.2 IU/L in the placebo arm (SEM 1.4). On treatment, ALT was 26.4 IU/L in the SUTENT arm (SEM 0.7) and 27.0 IU/L in the placebo arm (SEM 1.2). ALT rose slightly slightly on both the SUTENT and placebo arms.

One patient on SUTENT and none on placebo had a Grade 3 elevation in AST. Two patients on SUTENT and one patient on placebo had Grade 3 elevations of ALT. No patients on study were observed to have a Grade 4 elevation of any liver function test with the exception of those whose deaths were attributed to liver failure.

In summary, there is an equivocal suggestion of hepatotoxicity caused by SUTENT. Two patients on SUTENT died of liver failure in either the first or second cycle of treatment, and mean AST rose slightly on treatment in the group receiving SUTENT, whereas it remained unchanged in those receiving placebo. However, both patients who died had known liver involvement with tumor at baseline, and transaminases were normal or near normal after SUTENT was stopped and before development of liver failure. Whereas mean AST rose slightly on treatment in patients receiving SUTENT, mean ALT rose in both SUTENT and placebo arms. Finally, only three patients on SUTENT had an observed Grade 3 elevation in transaminases. In all three cases, resolution of this abnormality to Grade 1 or below was noted at the next observed lab draw.

Juxtaposed against the indication and described effect on the primary endpoint of Study A6181004, the potential for hepatotoxicity resulting from use of SUTENT is relatively modest. Routine postmarketing surveillance will be adequate to address this issue.

7.1.9 Vital Signs

7.1.9.1 Overview of vital signs testing in the development program

During screening and on Day 1 of each cycle, patients received a physical exam including ECOG performance status and vital signs (temperature, heart rate, blood pressure, and respiratory rate).

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Vital sign data was assessed from Study A6181004 only.

7.1.9.3 Standard analyses and explorations of vital signs data

Hypertension was explored through evaluation of datasets BAE.XPT and BPSS.XPT, which contain all recorded adverse events on treatment and at baseline, respectively, and BDERVIT.XPT, which contains vital signs data summarized by cycle for each enrolled patient.

Comparison of datasets BAE.XPT and BPSS.XPT reveal that treatment-emergent systemic hypertension was observed in 25 patients (12%) on SUTENT and 8 patients (8%) on placebo. Grade 3 treatment-emergent hypertension was observed in nine patients (4%) on SUTENT and none on placebo.

Dataset BDERVIT.XPT was examined to clarify and expand on the above indirect observations. Treatment-emergent systolic blood pressure > 160 mm Hg was observed in 31 patients (15%) on SUTENT and 2 (2%) on placebo. Treatment-emergent systolic blood pressure > 200 mm Hg was observed in two patients (1%) on SUTENT and none on placebo. Treatment-emergent diastolic blood pressure > 100 mm Hg was observed in 20 patients (10%) on SUTENT and one patient (1%) on placebo. Treatment-emergent diastolic blood pressure > 110 mm Hg was observed in six patients (3%) on SUTENT and none on placebo.

In summary, SUTENT causes systemic hypertension of mild to moderate intensity. We recommend that the label incorporate language indicating patients receiving SUTENT should have blood pressure monitored and appropriate medical treatment of hypertension.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations of vital signs data were performed.

7.1.10 Electrocardiograms (ECGs)

7.1.10.1 Overview of ECG testing in the development program, including brief review of preclinical results

SU011248 and its active metabolite SU011262 blocked hERG currents with an IC_{50} of 266 nM and 4.1 μ M, respectively.

Triplicate standard 12-lead ECGs were performed at least 2 minutes apart at screening and on Day 28. The investigator evaluated the ECG results and noted any abnormalities. The primary interest was in the mean corrected QT interval (QTc), based on all 3 measurements at each time point.

7.1.10.2 Selection of studies and analyses for overall drug-control comparisons

The sponsor has an ongoing QT prolongation study to address definitively the potential for QT prolongation caused by SUTENT.

7.1.10.3 Standard analyses and explorations of ECG data

Patients on Study A6181004 were to have baseline eeg assessment at screening, as well as at Cycle 1 Day 28. Table 32 presents our analysis of mean QT intervals at baseline and on treatment from the sponsor's submitted eeg data from dataset BECG.XPT. Cycle 1 eeg collection was incomplete but balanced between SUTENT and placebo groups. No evidence of clinically significant mean QT prolongation by SUTENT was observed.

Table 32. Mean QT intervals in patients from Study A6181004

[msec, (SEM)]	SUTENT		Placebo	
	Patients (%)	Mean QT (SEM)	Patients	Mean QT (SEM)
At Screening	207 (100%)	0.412 +/- 0.002	104 (100%)	0.415 +/- 0.001
Cycle 1 Day 28	157 (76%)	0.414 +/- 0.002	80 (77%)	0.414 +/- 0.003

(Source: dataset BECG.XPT)

7.1.10.4 Additional analyses and explorations

No additional analyses of ecg data were performed.

7.1.11 Immunogenicity

Immunogenicity studies of sunitinib, a small molecule of molecular weight 532.6 Daltons, have not been performed.

7.1.12 Human Carcinogenicity

Carcinogenicity studies with sunitinib have not been performed. SUTENT did not cause genetic damage in the bacterial reverse mutagenesis (Ames) test, the rat bone marrow micronucleus test, or the the human lymphocyte chromosome assay.

7.1.13 Special Safety Studies

Please see Sections 7.1.5 (Other Search Strategies).

7.1.14 Withdrawal Phenomena and/or Abuse Potential

There is no history of abuse potential in the therapeutic class of tyrosine kinase inhibitors. No studies were performed to assess for abuse potential or withdrawal phenomena. SUTENT does not fulfill any criteria for scheduling under the Controlled Substances Act.

7.1.15 Human Reproduction and Pregnancy Data

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study, where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the recommended daily dose (RDD)),

while uterine changes (endometrial atrophy) were noted at ≥ 2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6-mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

In female rats, no fertility effects were observed at doses of ≤ 5.0 mg/kg/day (administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was approximately 5 times the AUC in patients administered the recommended daily dose [RDD]), however significant embryoletality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤ 10 mg/kg/day (the 10-mg/kg/day dose produced a mean AUC that was approximately 25.8 times the AUC in patients administered the RDD).

Reviewer's Comment: Based on data in monkeys and the drug's known mechanism of action, SUTENT[®] may impair fertility in humans. We recommend Pregnancy Category D in the label.

7.1.16 Assessment of Effect on Growth

Safety and efficacy of SUTENT in pediatric patients have not been studied in clinical trials.

Physeal dysplasia was observed in Cynomolgus monkeys with open growth plates treated for ≥ 3 months with sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at > 5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment however findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

7.1.17 Overdose Experience

No overdose of SUTENT was reported in completed clinical studies. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m²) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of

toxicity were observed at lower doses when administered for longer durations. There is no specific antidote for overdosage with SUTENT.

Reviewer's Comment: Treatment of SUTENT overdose should consist of general supportive measures. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage.

7.1.18 Postmarketing Experience

Sutent has yet to be marketed in any country. No postmarketing information is available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources Used to Evaluate Safety

The primary clinical data source used to evaluate safety was Study A6181004. Datasets were supplemented when appropriate by information culled from case report forms, all of which were submitted with NDA 021938. Drug exposure is described in Table 33 by the number of trial subjects starting each cycle of treatment with SUTENT or placebo. More than half the patients randomized to SUTENT received two cycles or less of study treatment. Less than 10% received more than six cycles. This data is derived from dataset BDERDRUG.XPT.

Table 33. Treatment cycles started by subjects in Study A6181004.

[N, (%)]	SUTENT	Placebo
Cycle 1	202 (100%)	102 (100%)
Cycle 2	136 (67%)	47 (46%)
Cycle 3	92 (46%)	17 (17%)
Cycle 4	71 (35%)	10 (10%)
Cycle 5	49 (24%)	5 (5%)
Cycle 6	33 (16%)	2 (2%)
Cycle 7	17 (8%)	0
Cycle 8	3 (1.5%)	0
Cycle 9	1 (0.5%)	0

(Source: dataset BDERDRUG.XPT)

Twenty-three patients (11%) on SUTENT and none on placebo underwent at least one dose reduction of study drug to 37.5 mg. Five SUTENT patients (2%) underwent a second dose reduction to 25 mg. Cycles during which dose reduction occurred are presented in Table 34, which is also derived from dataset BDERDRUG.XPT. In any given cycle of treatment, ~5-10% of patients taking SUTENT required dose reduction.

Table 34. SUTENT dose reductions by cycle in Study A6181004

[N, (%)]	Patients starting cycle	50 mg → 37.5 mg	37.5 mg → 25 mg
Cycle 1	202	0	0
Cycle 2	136	9 (7%)	0
Cycle 3	92	5 (5%)	0
Cycle 4	71	6 (8%)	2 (3%)
Cycle 5	49	1 (2%)	1 (2%)
Cycle 6	33	2 (6%)	1 (3%)
Cycle 7	17	0	1 (6%)
Cycle 8	3	0	0
Cycle 9	1	0	0

(Source: dataset BDERDRUG.XPT)

Reviewer's Comment: Patient exposure for evaluation of safety is adequate for the indication under consideration. Safety data regarding SUTENT should not be extrapolated from this study to use in the adjuvant setting where one year of study drug over nine treatment cycles is to be expected.

7.2.1.1 Study type and design/patient enumeration

Please see Section 4.2 (Tables of Clinical Studies) for a list of trials in the SUTENT development program.

7.2.1.2 Demographics

Demographic subsets were not pooled for all studies due to the focus on analysis of randomized safety data from Study A6181004.

7.2.1.3 Extent of exposure (dose/duration)

Median duration of blinded study treatment was two cycles for patients on SUTENT® (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo. Dose reductions occurred in 23 patients (11%) on SUTENT® and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT® and 31 patients (30%) on placebo.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary data sources were considered in this review.

7.2.2.1 Other studies

No other data was integrated with that from Study A6181004, which was a randomized, double-blind, placebo-controlled clinical trial.

7.2.2.2 Postmarketing experience

Sutent has yet to be marketed in any country. No postmarketing information is available.

7.2.2.3 Literature

The applicant's literature search was adequate. Safety findings in this review are based on Study A6181004.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects was exposed to the drug for evaluation of safety in the indication under consideration. Doses and durations of exposure were adequate to assess safety for the intended use. Study design was adequate to answer important questions. Potential class effects were evaluated.

However, important limitations of the safety database from Study A6181004 must be recognized. Patients excluded from Study A6181004 limit generalizability of safety assessments. Importantly, patients with significant history of cardiac disease or laboratory evidence of cardiac, renal, or hepatic disease were excluded. Also duration of exposure was relatively modest with more than half of the 202 patients in the as treated population receiving at most two cycles of therapy and less than 10% receiving more than six cycles of SUTENT. These data limitations are important in light of the prospect that SUTENT will be studied further and/or used off-label with more prolonged exposure in other diseases.

Additional safety data in randomized population(s) should be collected when SUTENT is studied in populations other than that covered by the indication under consideration here. For example, data from randomized trials of SUTENT for adjuvant treatment of cancer are likely to provide important safety information regarding longer durations of exposure to the drug.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical testing was adequate to explore potential adverse events.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of study subjects were adequate to assess expected and unexpected adverse events in the second-line GIST population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Section 5 (Clinical Pharmacology).

SUTENT is metabolized by CYP450 3A4. Inhibition and induction of this isoenzyme results in increased and decreased drug exposure, respectively.

7.2.7 Adequacy of Evaluation for Potential Adverse Events; Recommendations for Further Study

The applicant's efforts to detect specific adverse events that are potentially problematic and might be expected with a tyrosine kinase inhibitor are adequate for the indication sought.

7.2.8 Assessment of Quality and Completeness of Data

Quality and completeness of the data available for conducting the safety review, as well as quality of the assessment, are adequate for the indication sought.

7.2.9 Additional Submissions, Including Safety Update

On November 11, 2005, the sponsor submitted Amendment 010 to NDA 021938. This update safety information for Study A6181004 with information obtained following the data cut-off date of 1/1/05. We restricted our focus in this review to consideration of safety data collected during the blinded phase of Study A6181004.

Reviewer's Comment: We recommend that the sponsor submit additional safety information on SUTENT with both its Annual Reports to the NDA and with its final report on Study A6181004.

7.3 Summary of Drug-Related Adverse Events, Data Limitations, and Conclusions

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 56% vs. 51% of patients on SUTENT versus placebo, respectively. Grade 3 or 4 AEs increased in incidence in patients receiving SUTENT relative to placebo include diarrhea (4% vs. 0%), hypertension (4% vs. 0%), and decreased platelets (5% vs. 0%).

Common (>10%) adverse events following from use of SUTENT relative to placebo include hypertension (15% vs. 11%), diarrhea (40% vs. 27%), constipation (20% vs. 14%), mucositis/stomatitis (29% vs. 18%), skin abnormalities (63% vs. 54%), altered sense of taste (21% vs. 12%), asthenia (22% vs. 11%), and laboratory abnormalities. Common laboratory abnormalities include elevated pancreatic enzymes (35% vs. 30%), electrolyte disturbances (38% vs. 20%), lowered neutrophils (53% vs. 4%) and platelets (38% vs. 4%), and decreased left ventricular ejection fraction (LVEF) (10% vs. 3%). Uncommon (<10%) laboratory abnormalities following from use of SUTENT include hypophosphatemia (9% vs. 0%) and acquired hypothyroidism (4% vs. 1%). Safety data is limited by the fact that SUTENT has not been studied in patients with liver disease or pre-existing heart disease.

Two important safety questions persist. First, Study A6181004 revealed an increased incidence of decreased LVEF in patients on SUTENT (11%) versus those on placebo (3%). There was no difference in clinical heart failure observed between the two study groups with one death from diagnosed heart failure occurring in both SUTENT and placebo groups. However, patients with baseline cardiac abnormalities were excluded from Study A6181004. It is not clear whether patients with cardiac abnormalities before starting SUTENT will experience increased incidence of clinical heart failure.

Second, adrenal toxicity was seen in rats and monkeys at doses as low as 0.7 times the AUC observed in clinical trials. No overt clinically important adrenal suppression was observed in patients taking SUTENT. However, if SUTENT is even marginally toxic to the adrenals, patients undergoing stress such as infection, trauma, or surgery may be unable to mount an appropriate adrenal response. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma, or severe infection.

In conclusion, there is adequate data to be able to make an appropriate safety assessment of SUTENT, as well as to provide directions for safe use in the approved indication. Given that there is no other therapy known to be effective in treatment of second-line GIST following imatinib, the safety profile of SUTENT on balance is not limiting. Additional information should be collected concerning pharmacokinetics of the drug in hepatic insufficiency, as well as cardiac effects both after longer drug exposures and in patients with pre-existing heart disease.

7.4 General Methodology

There are no general methodologic issues that have not been covered elsewhere in this review.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

A single study was evaluated in this review.

7.4.1.2 Combining data

A single study was evaluated in this review.

7.4.2 Explorations for Predictive Factors

Please see Section 5.3 regarding Exposure-Response Relationships.

7.4.2.1 Explorations for dose dependency for adverse findings

Please see Section 5.3 regarding Exposure-Response Relationships.

7.4.2.2 Explorations for time dependency for adverse findings

Please see Section 5.3 regarding Exposure-Response Relationships.

7.4.2.3 Explorations for drug-demographic interactions

Please see Section 5.3 regarding Exposure-Response Relationships.

7.4.2.4 Explorations for drug-disease interactions

Please see Section 5.3 regarding Exposure-Response Relationships.

7.4.2.5 Explorations for drug-drug interactions

Please see Section 5.3 regarding Exposure-Response Relationships.

7.4.3 Causality Determination

Causality of adverse events in this review was attributed to SUTENT when incidence of the event in patients receiving SUTENT on Study A6181004 exceeded the incidence in patients receiving placebo.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There is reasonable confidence that an appropriate dose/regimen has been selected based on the dose finding study conducted, Study RTKC-0511-013, A Phase 1 / 2 Study of SU011248 in the Treatment of Patients with Malignant Gastrointestinal Stromal Tumor (GIST) who are Intolerant of, or with Disease Progressing on, Imatinib mesylate (Gleevec). Five different regimens were investigated with variations of daily dose and schedule. The dose and regimen chosen for investigation in Study A6181004 achieved an appropriate balance of maximizing drug exposure while limiting toxicity to a reasonable level. In Study RTKC-0511-013, Schedule 4/2 was tested in 22 patients with GIST following progression on or intolerance to imatinib, two of whom (9%) were observed to have partial responses to treatment with SUTENT.

Please see Section 5.3 for discussion of exposure-response relationships. There was a trend in Study A6181004 towards increased radiographic response rates in patients with higher exposure levels. Men on average have lower exposure levels than women. Thus it is uncertain whether men might experience increased response rates and prolonged PFS relative to that observed if their daily dose were increased by 50%. However, at this time there is no prospective clinical data to test this hypothesis, and toxicity also correlated with exposure. Thus this hypothesized exposure-response relationship is at present not addressed in the product label. This issue remains unresolved and under investigation.

SUTENT's bioavailability is unaffected by food.

8.2 Drug-Drug Interactions

The primary pathway of elimination of sunitinib is via CYP3A4. Drug-drug interaction studies have shown a 51% increase in exposure when co-administered with ketoconazole and a 46% reduction in exposure when co-administered with rifampin.

Dosing adjustments for patients on CYP3A4 inhibitors

There was an approximately 50% increase in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with ketoconazole. To adjust for this increase, we recommend that the sunitinib dose be reduced to 66% of the recommended dose in patients who must receive concomitant CYP3A4 inhibitors.

Dosing adjustments for patients on CYP3A4 inducers

There was an approximately 50% decrease in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with rifampin. To adjust for this decrease, we recommended that the sunitinib dose be increased to 200% of the recommended dose in patients who must receive concomitant CYP3A4 inducers.

8.3 Special Populations

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for body weight, creatinine clearance, race, gender or ECOG score.

No differences in safety or effectiveness were observed in adult patients, regardless of age. The pharmacokinetics of sunitinib have not been evaluated in pediatric patients.

Hepatic Insufficiency

No clinical studies were conducted in patients with impaired hepatic function. Studies that were conducted excluded patients with ALT or AST > 2.5 x ULN or, if due to underlying disease, > 5.0 x ULN.

Renal Insufficiency

No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42 –347 mL/min.

8.4 Pediatrics

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] Finally, in nonclinical animal studies relatively high levels of sunitinib were found in brain tissue indicating that it was able to penetrate the blood-brain barrier. Although the sponsor cites []

8.5 Advisory Committee Meeting

This application was not discussed at an advisory committee meeting.

8.6 Literature Review

Please see Section 6.1 (Indication: Second-line Treatment of Gastrointestinal Stromal Tumor).

8.7 Postmarketing Risk Management Plan

Over the course of the safety data review, the following issues were identified, assessed, and determined to be in one of two categories:

- Real risk: hypertension, hemorrhage (including tumor bleeding), and cytopenias.
- Potential risk: thromboembolic events, hypothyroidism, gastrointestinal perforations, and QTc prolongation, alterations in adrenal gland dysfunction, left ventricular dysfunction, and pancreatic dysfunction.

The sponsor proposes that routine pharmacovigilance and package label information will be sufficient to minimize risks and maximize benefits in the indicated patient populations. Their rationale is that safety issues identified that require clinician vigilance are addressed in the product label for treatment of GIST after failure of imatinib mesylate treatment due to resistance or intolerance, and for the treatment of MRCC after failure of cytokine-based therapy.

Clinicians should be aware of SUTENT's potential for blood pressure, gastrointestinal, and hematologic effects. These are included in the proposed label and are likely to be managed effectively through recourse to specific therapies or, when required, a reduction or temporary delay in dosing. None of these effects would be considered unusual or unfamiliar, physicians would be expected to be able to recognize and manage them.

Additional potential risks identified in the safety database include left ventricular dysfunction, adrenal suppression, pancreatitis, hypothyroidism, and QT prolongation. Bevacizumab, an agent having a similar putative mechanism of action, has demonstrated potential to cause

thromboembolism. These risks for the patient populations covered by the indications sought have been adequately identified in the product label.

8.8 Other Relevant Materials

No materials were considered in this review other than those discussed above.

9 OVERALL ASSESSMENT

9.1 Conclusions

We conclude that the sponsor has generated substantial evidence of efficacy with acceptable safety from adequate and well controlled studies to support use of SUTENT for treatment of gastrointestinal stromal tumors (GIST) after progression on or intolerance to imatinib mesylate (Gleevec). Pivotal Study A6181004 was adequate and well-controlled, revealing a clinically and statistically significant four-fold increase in time to tumor progression from 6.4 to 27.3 weeks ($P < 0.0001$). Adverse events were mostly mild or moderate in severity, and risk management issues can be addressed by appropriate labeling of SUTENT. Safety issues for which significant uncertainty persists are identified in the product label.

9.2 Recommendation on Regulatory Action

We recommend regular approval of SUTENT for treatment of patients with GIST following progression on or intolerance to imatinib.

9.3 Recommendation on Postmarketing Actions

The sponsor should submit a completed study report, including mature survival data, for Study A6181004.

9.3.1 Risk Management Activity

No risk management activities other than provided for in the label need be undertaken.

9.3.2 Required Phase 4 Commitments

- 1) Submit the completed report and datasets for study titled “A Phase 1 Study to Evaluate the Effect of SU011248 on Cardiac Repolarization Following Repeat Doses of SU011248 in Patients with Advanced Solid Tumors”.
- 2) Submit the completed report and datasets for study titled “A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function”.
- 3) Submit completed final study report for study titled “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”.

9.3.3 Other Phase 4 Requests

There were no optional Phase 4 requests.

9.4 Labeling Review

Major changes made to the applicant’s proposed labeling include the following.

Clinical Studies –

- We edited the sponsor’s claim that SUTENT has been studied for treatment of patients with GIST that “*has progressed on or is intolerant to*” imatinib. Instead, we substituted “*has progressed on or is intolerant to*” imatinib. We prefer not to allow this inferred claim since there is no convincing data available to support this hypothesis.
- We added a table of baseline demographics of patients in Study A6181004.
- With Drs. Jiang, Yang, and Mahjoob of the Division of Biometrics, we clarified a table of statistics with corrected values, eliminated unwarranted assertions, and provided a corrected Kaplan-Meier curve of time to progression in Study A6181004.
- The sponsor’s description of a supportive study in patients with GIST was edited to eliminate ambiguous or unwarranted claims.

Indications –

- The GIST indication was clarified consistent with the comment above regarding disease resistance versus disease that has progressed on imatinib.

Precautions –

- We added sections on Left Ventricular Ejection Fraction and Adrenal Function.

Adverse Reactions –

- We deleted the applicant's text and table, □
In place of these we added FDA analyses that were organized by body system and articulate more clearly the safety issues identified by evaluation of Study A6181004.
- We added sections on venous thromboembolic events, seizures, hematologic events, hypothyroidism, and pancreatic function.

A trade name review was conducted by the Division of Medication Errors and Technical Support (DMETS).

We do not at this time recommend generation of either a Medication Guide or Product Package Insert.

9.5 Comments to Applicant

Label negotiations with the applicant are ongoing. SUTENT's sponsor has agreed to the list of FDA specified postmarketing commitments described above.

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10 APPENDICES

10.1 Line-by-Line Labeling Review

Please see Section 9.4 for details of labeling modifications.

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- ⁸ Gleevec product label.

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Summary Review of NDA

NDA Numbers : 21938 Gastrointestinal Stromal Tumors (GIST)
21968 Renal Cell Cancer (RCC)

Drug : Sutent (sunitinib malate)

Sponsor : Pfizer

Indications : gastrointestinal stromal tumor after disease progression on or
intolerance to imatinib mesylate

advanced renal cell carcinoma

Authors : Dr. Ramzi Dagher, Acting Deputy Division Director, DDOP

Dr. Robert Justice, Acting Division Director, DDOP

Date : January 25, 2006

Recommendations

The Division of Drug Oncology Products (DDOP), OODP, CDER, USFDA recommends approval of sunitinib (SUTENT® capsules 12.5 mg, 25 mg and 50 mg, Pfizer Corp.), a small molecule receptor tyrosine kinase (RTK) inhibitor, for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. This indication is based on demonstration of improved time to progression in a randomized double-blind placebo controlled study. Approval is also recommended for the treatment of advanced renal cell carcinoma under subpart H (accelerated approval) based on partial response rates and duration of response.

Efficacy in GIST and in RCC

Efficacy and safety in GIST patients were evaluated in a randomized, double-blind placebo-controlled trial in patients who had disease progression during prior imatinib treatment or who were intolerant of imatinib. The primary endpoint was time-to-progression (TTP). Two-hundred seven patients were randomized (2:1) to sunitinib and 105 to placebo. Baseline age, gender, race and performance status (PS) were comparable between the two treatment arms. Most patients enrolled (96% in both arms) had progressed on or within 6 months of completing prior imatinib therapy. Approximately 30% of patients were \geq 65 years of age and more than 98% had an ECOG PS of 0/1.

A planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a significant advantage for sunitinib over placebo in TTP. There was also an advantage for sunitinib in progression-free survival. Survival data were not mature enough for evaluation. Objective responses were observed in patients receiving sunitinib. Efficacy findings are summarized in Table 1

Table 1

Efficacy Parameter	Study A			
	SUTENT (N = 207)	Placebo (N = 105)	P-value (log-rank test)	HR (95% CI)
Time to Tumor Progression ^a [median, weeks (95% CI)]	27.3 (16.0, 32.1)	6.4 (4.4, 10.0)	<0.0001*	0.33 (0.23, 0.47)
Progression Free Survival ^b [median, weeks (95% CI)]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	<0.0001*	0.33 (0.24, 0.47)
Objective Response Rate (PR) [% (95% CI)]	6.8 (3.7, 11.1)	0	0.006 ^c	

CI=Confidence interval, HR=Hazard Ratio, PR=Partial response

* A comparison is considered statistically significant if the p-value is < 0.0042 (O'Brien Fleming stopping boundary)

^a Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation

^b Time from randomization to progression or death due to any cause

^c Pearson chi-square test

A separate single arm phase 1 / 2 study conducted in patients with GIST following progression on or intolerance to imatinib enrolled 55 patients after identification of the recommended phase 2 regimen. Partial responses were observed in 5 patients for a PR rate of 9.1% (95% C.I. 3.0, 20.0)

Efficacy and safety for advanced renal cell carcinoma (RCC) were evaluated in two open-label, single-arm, multicenter trials (study 1 and study 2) enrolling a total of 169 patients with metastatic disease. All patients had experienced disease progression or intolerance to interleukin-2 and/or interferon- α . The median age across the two studies was 57 years (range 24-87). 65% of patients were male, and 86-94% were white. All patients had an ECOG performance score of < 2 at screening.

95% of the treated population had a component of clear cell histology and 97% had undergone prior nephrectomy. Approximately half of the patients had 3 or more sites of disease at study entry; common sites included lung, liver and bone. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

The primary endpoint for both studies was overall response rate (ORR). All responses on both trials were partial responses. Study 1 had a 25.5% (95% CI 17.5, 34.9) partial response rate as assessed by a core radiology laboratory. Duration of response data for study 1 are immature as only 4/27 responders had progressed at the time of the analysis, with a median duration of response of 27 weeks (95% CI 24.4, upper limit could not be estimated). Study 2 had a 36.5% (95% CI 24.7, 49.6) partial response rate as assessed by the investigators. The median duration of response was 54 weeks (95% CI 34.3, 70.1).

Several regulatory issues were discussed as part of the review process for the RCC indication. First, approval under subpart H requires demonstration of an improvement over available therapy or an effect in a population for which no available therapy exists. Clearly, the patients enrolled to the two single arm trials no longer had interleukin-2 and/or interferon- α available as viable options. Even if these options were still considered possible, they would be associated with limited clinical effects, and certainly no expectation of a survival benefit. Although sorafenib has recently been approved for advanced RCC based on a placebo-controlled trial with demonstration of a progression-free survival effect, sorafenib was associated with an objective partial response rate of 2%, compared with approximately 25-35% with sunitinib. Furthermore, sunitinib has also demonstrated a clinical benefit in a separate population of patients with advanced cancer, namely imatinib refractory or intolerant GIST patients. At a regulatory briefing conducted in November 2005, the office and center leadership agreed that the totality of evidence supports the view that sunitinib has demonstrated an improvement over available therapy.

A second issue was the specific wording of the RCC indication. Although patients evaluated in the RCC studies all had metastatic disease and had progressed or were intolerant to cytokine therapy, discussion with the OODP leadership resulted in agreement to grant approval for advanced RCC. It was determined that requiring patients to receive cytokine therapy, whether in the context of advanced or metastatic disease, before considering sunitinib would be overly burdensome, especially given the limited benefits and substantial toxicity associated with cytokine use.

Finally, approval under subpart H requires confirmation of clinical benefit. An ongoing trial comparing sunitinib to interferon- α as first-line therapy for patients with metastatic RCC with progression-free survival as the primary efficacy endpoint will provide evidence of clinical benefit.

Safety

The safety database for this action consists of 450 patients with solid tumors including 257 patients (57%) with GIST and 169 patients (38%) with cytokine-refractory metastatic RCC who were treated in 7 completed non-randomized, open-label, single arm clinical trials and 1 randomized, double-blind, placebo-controlled clinical trial. All patients received sunitinib once daily as a 50-mg oral capsule on Schedule 4/2.

The most common treatment-emergent adverse events occurring more frequently in the sunitinib arm of the placebo-controlled GIST study included (sunitinib versus placebo) diarrhea (40% vs. 27%), skin discoloration (30% vs 23%), mucositis/stomatitis (29% vs 18%), asthenia (22% vs. 11%), and altered taste (21% vs. 12%) . Hypothyroidism was observed in 4% of patients receiving sunitinib; hypothyroidism was not observed on the placebo arm. Grade 3/4 events that were more common with sunitinib included diarrhea (4% vs. 0%), hypertension (4% vs. 0%), and asthenia (5% vs. 3%). Grade 3/4 treatment-emergent laboratory abnormalities occurring more commonly with sunitinib included neutropenia (10% vs. 0%) and thrombocytopenia (5% vs. 0%). The safety profile in the RCC single-arm trials was similar to that in the GIST randomized study.

The following is a summary of adverse events that the DDOP recommends describing in the PRECAUTIONS section of the labeling.

Left Ventricular Dysfunction

Decreases in LVEF were observed in patients receiving sunitinib. In the randomized GIST Study, 22 patients (11%) on sunitinib and 3 patients (3%) on placebo had treatment-emergent LVEF values below the LLN. Nine of twenty-two GIST patients on sunitinib with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction- 1 patient; addition of antihypertensive or diuretic medications- 4 patients). Six patients went off study without documented recovery. Additionally, three patients (1%) on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF < 40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. Congestive heart failure was observed rarely in both arms.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from clinical studies. Patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered during treatment. In patients without cardiac risk factors, a baseline evaluation of ejection fraction may be considered.

In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The dose should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Hemorrhagic Events

Bleeding events have occurred in patients receiving sunitinib. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC or GIST patients included rectal, gingival, upper GI, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In GIST Study A, 14/202 patients (7%) receiving sunitinib and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in Study A taking placebo had a fatal gastrointestinal bleeding event during cycle 2.

Tumor-related hemorrhage has been observed. Fatal pulmonary hemorrhage occurred in 2 patients receiving sunitinib on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving sunitinib on Study A. Tumor hemorrhages were observed as early as cycle 1 and as late

as cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage has not been observed in patients with MRCC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with sunitinib.

Hypertension

Hypertension (all grades) was reported in 48/169 MRCC patients (28%), 31/202 GIST patients on sunitinib (15%), and 11/102 GIST patients on placebo (11%). Grade 3 hypertension was reported in 10 MRCC patients (6%), 9 GIST patients on sunitinib (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. Sunitinib dosing was reduced or temporarily delayed for hypertension in 6/169 MRCC patients (4%) and none of the patients in GIST Study A. No patients were discontinued from treatment due to systemic hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 10/169 MRCC patients (6%), 8/202 GIST patients on SUTENT (4%), and 1/102 GIST patients on placebo (1%).

Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of sunitinib is recommended until hypertension is controlled.

Adrenal Function

Adrenal toxicity was noted in non-clinical repeat dose studies in rats and monkeys. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of therapy demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Physicians are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

The following represent summary findings and recommendations from Clinical Pharmacology/Biopharmaceutics, Statistical/Biometrics, Pharmacology/Toxicology, Chemistry, Division of Drug Marketing and Advertising, Division of Scientific Investigations, and Division of Medication Errors and Technical Support (DMETS).

Clinical Pharmacology / Biopharmaceutics

The clinical pharmacology/biopharmaceutics review team recommends approval of sunitinib for the indications discussed above.

The following summarizes findings and recommended labeling regarding potential drug interactions.

Co-administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase sunitinib plasma concentrations. Co-administration with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving sunitinib should not take St. John's Wort concomitantly. Sunitinib dose modification is recommended in patients who must use CYP3A4 inhibitors or inducers concomitantly.

Statistical / Biometrics

The statistical/biometrics review team recommends approval of sunitinib for the indications discussed above. Efficacy findings from clinical studies as summarized above were confirmed by the statistical reviewers. In addition, multiple sensitivity analyses were conducted based on the results of the randomized trial in GIST patients. Results of these analyses were consistent with the primary efficacy findings.

Pharmacology / Toxicology

The pharmacology / toxicology review team recommends approval of sunitinib for the indications discussed above. Review findings regarding mechanism of action, carcinogenicity, mutagenicity, and impairment of fertility including recommendations for designation as pregnancy category D have been incorporated into the labeling.

Chemistry

The chemistry review team recommends approval of sunitinib for the indications discussed above. A number of deficiencies related to drug product and drug substance identified during the review process have been addressed. In addition, the Office of Compliance has given an overall acceptable recommendation.

Division of Drug Marketing and Advertising (DDMAC)

Recommendations from DDMAC have been considered in the labeling process.

Division of Scientific Investigations

Audits of clinical sites enrolling patients to clinical studies of sunitinib in metastatic renal cell cancer and GIST indicated no violations that would likely influence study outcomes.

Division of Medication Errors and Technical Support, Office of Drug Safety (DMETS)

DMETS has no objections to the proprietary name Sutent. Labeling recommendations have been taken into consideration.

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Subpart H Commitments for NDA 21-968 (RCC)

1. Provide the response rate and duration of response data from the first interim efficacy analysis of study titled “A Phase 3, Randomized Study of SU011248 versus Interferon- α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma”. Also, submit the comparative safety data that are available at the time of data cutoff for the interim analysis. This will include an interim study report as well as raw and derived datasets.
2. Submit efficacy data obtained at the final analysis, including progression-free survival, overall survival, response rate and duration of response; as well as updated safety data for study titled “A Phase 3, Randomized Study of SU011248 versus Interferon- α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma”. This submission will include the final study report as well as raw and derived data sets.
3. Submit updated case report tabulations that include the core imaging facility assessments used to derive the median duration of response on study titled “A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma”.
4. Submit follow-up left ventricular ejection fraction (LVEF) data for patients 16, 46, and 81 on the study titled “A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma”. Case narratives should be submitted and should include additional cardiac evaluations that were performed and treatments that were administered for congestive heart failure. Additionally, submit LVEF data and clinical narratives for any patient who, after the data cutoff for the initial NDA submission, had a documented LVEF of $\leq 40\%$ and/or signs and symptoms of cardiac failure.
5. Submit comparative LVEF and cardiac safety data for patients enrolled on the adjuvant renal cell carcinoma trial, E2805 titled “A Randomized, Double-Blind Phase III Trial of Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected Renal Cell Carcinoma”. The protocol will be revised to include a plan acceptable to the FDA for ejection fraction monitoring at baseline and follow-up.

Post-Marketing Commitments (both NDAs)

6. Provide an analysis of the relationship between exposure and efficacy outcomes from the study titled “A Phase 3, Randomized Study of SU011248 versus Interferon- α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma”.
7. Submit the completed report and datasets for study titled “A Phase 1 Study to Evaluate the Effect of SU011248 on Cardiac Repolarization Following Repeat Doses of SU011248 in Patients with Advanced Solid Tumors”.
8. Submit the completed report and datasets for study titled “A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function”.
9. Submit completed final study report for study titled “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”.

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CLINICAL REVIEW

Application Type NDA
Submission Number 21-968
Submission Code N000

Letter Date 8/10/05
Stamp Date 8/11/05
PDUFA Goal Date 2/11/06

Reviewer Name Vicki L. Goodman, M.D.
Team Leader Ramzi Dagher, M.D.
Review Completion Date January 17, 2006

Established Name sunitinib
(Proposed) Trade Name Sutent
Therapeutic Class Receptor Tyrosine Kinase
Inhibitor
Applicant Pfizer

Priority Designation P

Formulation oral
Dosing Regimen 50 mg PO QD
Indication Advanced renal cell carcinoma
Intended Population same

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The Division of Drug Oncology Products, Office of Oncology Products, Center for Drug Evaluation and Research, Food and Drug Administration recommends **accelerated approval** of this application for sunitinib for the treatment of advanced renal cell carcinoma (RCC). This approval is based upon the demonstration of durable responses, a surrogate endpoint which is considered reasonably likely to predict clinical benefit in this setting. Sunitinib has not demonstrated an effect on an endpoint of known clinical benefit, such as survival or symptom benefit, in advanced RCC.

Two single-arm, phase 2 studies relevant to the advanced RCC indication were submitted with this application. One hundred and sixty nine patients with metastatic renal cell carcinoma (MRCC) who had received prior cytokine therapy (interferon- α [IFN- α] and/or interleukin-2 [IL-2]) were enrolled in the two trials. The studied population differs from the proposed indicated population in two ways. First, all studied patients had metastatic disease; patients with advanced unresectable disease were excluded. In practice, these patients are treated similarly to patients with metastatic disease. Second, all studied patients had received prior cytokine therapy, which is the standard of care in MRCC. Cytokine therapies used to treat RCC are highly toxic and have limited efficacy. As a result, restricting the indication to the second-line following cytokine failure would create an “artificial” clinical scenario (one that is inconsistent with expected clinical practice) in which a patient would be required to complete treatment with a highly toxic regimen of minimal benefit prior to receiving a significantly less toxic regimen with a higher response rate. After discussion between the review team, the DDOP and OODP leadership, and later the sponsor, we therefore propose to expand this indication to include all patients with advanced renal cell carcinoma, without a requirement for prior cytokine therapy.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. Unusual toxicities that are seen with sunitinib, including hypertension, bleeding, changes in left ventricular ejection fraction and dermatologic effects, will be described in the labeling.

1.2.2 Required Phase 4 Commitments

This application was reviewed under subpart H (accelerated approval) regulations. The sponsor will therefore be required to provide confirmation of clinical benefit. The sponsor currently has an ongoing study (A6181034) evaluating sunitinib vs. IFN- in the first-line treatment of MRCC; this is intended to be the study in which clinical benefit (as measured by disease-free survival) will be confirmed. The sponsor will be asked to submit the following:

- The response rate data from the interim efficacy analysis of study A6181034. The sponsor will also submit the comparative safety data that are available at the time of data cutoff for the interim analysis. This will include an interim study report as well as raw and derived datasets.
- Efficacy data obtained at the final analysis, including progression-free survival, overall survival, response rate and duration of response; as well as updated safety data for study A6181034. This submission will include the final study report as well as raw and derived data sets.

The duration of response data for study 1006 provided in this submission were immature, with only 15% of events occurring prior to data cutoff. At that time the median duration of response (DR) was 27.1 weeks. In a slide presentation shortly after NDA submission, the sponsor claimed a median DR of 43.1 weeks. The data tables supporting this result were not provided. The sponsor has since updated the response rate as well based on data obtained since the NDA submission. These data will be requested as a post-marketing commitment so that mature response rate and duration of response can be added to the drug labeling.

- The sponsor will submit updated raw and derived datasets containing the core imaging facility data used to derive the updated response rate and duration of response from study 1006.

Changes in left ventricular ejection fraction occurring in patients receiving sunitinib are an ongoing safety issue which may become an important clinical issue as the development of the drug moves from treatment of advanced cancers to earlier stages of disease. Several patients on both MRCC studies have a markedly abnormal LVEF as the last available measurement. On study 1006, three such patients remained on study at the time of data cutoff; these patients should have had additional assessments of LVEF throughout the study. The sponsor will therefore be asked to submit additional LVEF data for those patients, as well as clinical narratives detailing additional cardiac evaluations performed, and treatments administered for congestive heart failure. In addition, the sponsor will be asked to submit LVEF data and clinical narratives for any patient who, after the data cutoff for this submission, had a documented LVEF of $\leq 40\%$ and/or signs and symptoms of cardiac failure.

- The sponsor will submit follow-up LVEF data for patients 16, 46, and 81 on study 1006. Case narratives should be submitted and should include additional cardiac evaluations that were performed and treatments that were administered for congestive heart failure. Additionally, the sponsor will submit LVEF data and clinical narratives for any patient

who, after the data cutoff for the initial NDA submission, had a documented LVEF of \leq 40% and/or signs and symptoms of cardiac failure.

- The sponsor will submit comparative LVEF data for all patients enrolled on the adjuvant RCC trial, E2805.

1.2.3 Other Phase 4 Requests

The sponsor will be asked to provide an analysis of the relationship between exposure and efficacy outcomes from the randomized trial of sunitinib versus interferon in the first-line treatment of metastatic MRCC.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Sunitinib is a receptor tyrosine kinase (RTK) inhibitor which is administered orally at a starting dose of 50 mg daily for 4 weeks out of 6. The NDA submission includes two proposed indications: the treatment of patients with cytokine-refractory metastatic renal cell carcinoma (MRCC) and the treatment of patients with imatinib-resistant gastrointestinal stromal tumor (GIST). The submission includes two single-arm phase 2 trials to support safety and efficacy in the advanced RCC population; the GIST indication contains a randomized phase 3 trial supported by a single-arm phase 2 trial. The GIST database is reviewed separately by Dr. Edwin Rock under NDA 21-938. This review will focus on the safety and efficacy of sunitinib in the advanced RCC population.

1.3.2 Efficacy

Two single-arm, open-label phase 2 studies were submitted to support the advanced RCC indication. The two studies enrolled a total of 169 patients. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between the two studies. Approximately 86-94% of patients in the 2 studies were Caucasian. Men comprised 65% of the population in a disease which has a 1.6:1 male predominance. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients were required to have metastatic disease, and to have received one prior cytokine-based therapy. The 014 study enrolled patients with MRCC regardless of histology, while the 1006 study required at least some component of clear cell histology, the most common histologic subtype of renal cell carcinoma (approximately 85% of all cases). Most patients had undergone nephrectomy (92% on 014, 100% on 1006). Prior cytokine therapy included IL-2 and/or IFN- α .

Patients in both studies received sunitinib at 50 mg daily on a 4 weeks on/2 weeks off schedule, for a cycle length of 6 weeks. Median duration of treatment was 34 weeks for study 014

(including participation in the continuation studies) and 23.6 weeks in study 1006 at the time of data cutoff.

The primary efficacy endpoint was ORR using RECIST criteria, as measured by the investigator (014) or the [redacted] core imaging laboratory (1006). ORR was measured in the intention-to-treat (ITT) population for both studies, and in a modified ITT (MITT population) consisting of patients with retrospective core imaging laboratory confirmation of prior disease progression in study 1006. Duration of response was assessed in both studies as a secondary endpoint. All responses on both studies were partial responses. The ORR was 25.5% (95% CI 17.5-34.9%) for study 1006, and 37% (95% CI 24.7-49.6%) for study 014. These results were supported by three secondary analyses of ORR in the 1006 trial: the investigator assessed ORR in both the ITT and MITT populations, and the third-party radiology core laboratory assessment of ORR in the MITT population.

Duration of response, measured from the time of first documentation of a response to the first documentation of progression, was a secondary endpoint on both studies. DR data were immature for study 1006: with 4/27 (15%) progression events occurring, the median DR was 27.1 weeks (95% CI 24.4; upper limit could not be calculated). On study 014, 13/23 (57%) events had occurred with a median DR of 54.0 weeks (95% CI: 34.3-70.1).

Tumor responses in the second-line treatment of MRCC are rare, with historical response rates of $\leq 5\%$ with either cytokine or cytotoxic therapies. Response rates of 25-37% have not previously been demonstrated with any agent in MRCC, in either the second-line or first-line setting. While this NDA was under review, sorafenib was given regular approval for the treatment of advanced renal cell carcinoma based on an improvement in progression-free survival (PFS) demonstrated in a randomized trial. Patients receiving sorafenib had a median PFS of 167 days while patients receiving placebo had a median PFS of 84 days; the hazard ratio for progression was 0.44 (95% CI 0.35, 0.55). The response rate in both arms was negligible (2% for sorafenib-treated patients vs. 0% for placebo-treated patients). The substantial response rate of sunitinib may provide a benefit over sorafenib in advanced renal cell carcinoma patients, particularly in those patients with bulky disease in whom cytoreduction may be an important goal of treatment.

The demonstration of an impressive response rate with sunitinib in MRCC is supported by a significant duration of response. While an effect on an endpoint of known clinical benefit such as survival or symptom benefit has not been demonstrated for sunitinib in MRCC, the combination of response rate and response duration demonstrated in this application is reasonably likely to predict a clinical benefit in patients with advanced renal cell carcinoma.

1.3.3 Safety

The safety population includes the 169 patients treated in the 2 single-arm trials. All patients received sunitinib on the 50 mg daily 4 weeks on/2 weeks off schedule. Median duration of exposure was 5.5 months on study 1006 and 7.7 months on study 014. The most common adverse events in the pooled MRCC population included fatigue (74%), diarrhea (55%), nausea

(54%), mucositis/stomatitis (53%), dyspepsia (46%), taste alterations (43%), rash (38%), vomiting (37%), constipation (34%), skin discoloration (yellow skin) (33%), anorexia (31%), hypertension (28%), dyspnea (28%), arthralgia (28%), bleeding (all sites) (26%), headache (25%), and abdominal pain (20%). Other significant events that are likely to be drug-related included peripheral edema (17%), glossodynia (15%), hand-foot syndrome (12%), peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), and periorbital edema (7%).

The most common grade 3/4 events included fatigue (11%), hypertension (6%), diarrhea (5%), dyspnea (5%), mucositis/stomatitis (4%), vomiting (4%), hand-foot syndrome (3%), dehydration (3%) and abdominal pain (3%). All of these events were grade 3.

Common grade 3/4 laboratory abnormalities included lymphopenia (21%), increased lipase (16%), neutropenia (13%), hypophosphatemia (10%), uric acid elevation (10%), leucopenia (7%), anemia (7%), thrombocytopenia (7%), and increased amylase (5%).

Twenty-five patients (15%) experienced declines in left ventricular ejection fraction (LVEF) to below normal during the study. In some cases, these changes are transient and reversible without dose reduction or interruption. However, three patients were discontinued from study 014 due to LVEF changes and four patients with MRCC had declines to below 40% as the last measured LVEF on study. The reversibility of LVEF changes in these patients has not been established.

1.3.4 Dosing Regimen and Administration

The recommended starting dose and schedule for sunitinib in advanced RCC is 50 mg orally once daily for four consecutive weeks, followed by a two week rest period (the 4/2 schedule). Dose reductions to 37.5 mg or 25 mg daily on the 4/2 schedule are appropriate in the setting of intolerable toxicity.

1.3.5 Drug-Drug Interactions

The primary pathway of elimination of sunitinib is via CYP3A4. Drug-drug interaction studies have shown a 51% increase in exposure when co-administered with ketoconazole and a 46% reduction in exposure when co-administered with rifampin.

Dosing adjustments for patients on CYP3A4 inhibitors

There was an approximately 50% increase in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with ketoconazole. To adjust for this increase, the clinical pharmacology reviewers recommend that the sunitinib dose be reduced to 66% of the recommended dose in patients who must receive strong CYP3A4 inhibitors concomitantly.

Dosing adjustments for patients on CYP3A4 inducers

There was an approximately 50% decrease in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with rifampin. To adjust for this decrease, the clinical

pharmacology reviewers recommend that the sunitinib dose be increased to 200% of the recommended dose in patients who must receive strong CYP3A4 inducers concomitantly.

1.3.6 Special Populations

Hepatic Insufficiency

No clinical studies were conducted in patients with impaired hepatic function. Studies that were conducted excluded patients with ALT or AST > 2.5 x ULN or, if due to underlying disease, > 5.0 x ULN.

Renal Insufficiency

No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42 –347 mL/min.

Pediatrics

Sunitinib has not been studied in pediatric patients; a population in whom RCC is rare. []

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Sunitinib (SU011248, Sutent) is a small molecule, receptor tyrosine kinase (RTK) inhibitor that blocks signaling via multiple RTKs including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), KIT and FLT-3.

2.2 Currently Available Treatment for Indication

Advanced renal cell carcinoma (RCC) is resistant to standard cytotoxic chemotherapies, with typical response rates of $\leq 5\%$. Standard therapy for advanced RCC includes the cytokines interferon-alpha (IFN- α) and interleukin 2 (IL-2) either alone or in combination. Although it is not approved by the FDA for this indication, IFN- α is the most commonly used therapy for RCC worldwide. The objective response rate for patients treated with IFN- α is reported to be 10-15%. Patients with non-bulky pulmonary and soft tissue metastases and good performance status are most likely to respond. While durable complete responses are rare, IFN- α has been associated with a modest survival benefit in one report.¹ Reported toxicities include influenza-like symptoms, fever, weight loss, loss of appetite, altered taste, depression, anemia, leucopenia, nausea, fatigue, and elevated liver function tests.²

High dose IL-2 (600,000 IU/kg IV every 8 hours for 14 doses, repeated once after a nine day rest) is approved in the U.S. for MRCC, and has a response rate of approximately 15%, with about a 5% durable complete response rate. Although IL-2 has been associated with durable remissions in a minority of patients, its use is associated with severe toxicities including a sepsis-like capillary leak syndrome which limits its use to the healthiest patients. Combinations of IL-2 and IFN- α have been used in metastatic renal cell carcinoma (MRCC) as well. While the response rate for the combination was higher (18.6% vs. 7.5% for IFN- α and 6.5% for IL-2) and the 1-year event free survival was higher (20% vs. 12% vs. 15%), there was no significant difference in overall survival and toxicity was additive.^{3,4}

After failure of cytokine therapy, treatment options in MRCC are very limited. One cross-over study looked at the response rates using IFN- α and IL-2 in patients who had failed to respond to the other cytokine; less than 5% of patients responded.⁵ There are currently no approved or standard regimens for cytokine-refractory MRCC. Overall survival in cytokine-refractory MRCC is estimated to be approximately 10 months.

2.3 Availability of Proposed Active Ingredient in the United States

This is a new molecular entity.

2.4 Important Issues With Pharmacologically Related Products

One additional tyrosine kinase inhibitor with a similar spectrum of inhibitory activity has received marketing approval. Sorafenib (Nexavar) has inhibitory activity against Raf kinase, VEGF-R2, PDGFR, c-kit, and FLT-3. It was approved for use in advanced (unresectable or metastatic) renal cell carcinoma on December 20, 2005. In a randomized phase 3 trial comparing sorafenib to placebo in patients with advanced renal cell carcinoma, the progression-free survival was doubled in patients who received sorafenib (167 days vs. 84 days); the hazard ratio was 0.44 (95% CI 0.35, 0.55). The response rate was negligible (2% for sorafenib-treated patients vs. 0% for placebo-treated patients).⁶

The most common adverse events associated with sorafenib use included rash, hand-foot syndrome, hypertension, diarrhea, sensory neuropathy, neutropenia, increased lipase, hypophosphatemia and hypocalcemia. The incidence of severe hemorrhage was 3% in the sorafenib arm (12/384) vs. 1% (4/385) in the placebo arm. No increase in wound healing complications was noted, however, few patients were at risk.

Additionally, bevacizumab, a currently marketed monoclonal antibody inhibitor of VEGF-A, has several unusual and potentially life-threatening toxicities which may be mediated by its inhibition of VEGF and therefore may be relevant to the safety profile of sunitinib. In studies of patients with advanced colorectal cancer in which bevacizumab was combined with chemotherapy, these toxicities included:

- Gastrointestinal Perforations/Wound Healing Complications
- Hemorrhage
- Hypertension/Hypertensive Crises
- Proteinuria and Nephrotic Syndrome
- Congestive Heart Failure
- Arterial Thromboembolic Events⁷

Bevacizumab is currently approved for first-line use in metastatic colorectal cancer in combination with 5-fluorouracil. In the phase 3 trial which supported that indication, bevacizumab use was associated with an increased incidence of hypertension (33.9% vs. 14.3% on the IFL control arm, grade 3 18.3% vs. 3.1%), epistaxis (32.1% vs. 10.2%), grade 3-4 bleeding events (6.4% vs. 1%), proteinuria (34.9% vs. 25.1%), grade 3-4 diarrhea (37.6% vs. 25.5%).

The risk of arterial thrombotic events was also increased (4.6% vs. 2.0%).⁸ This toxicity was further explored in a pooled analysis of five randomized controlled trials of bevacizumab in combination with chemotherapy.⁹ The pooled population consisted of 1745 patients with metastatic cancers of the breast, colon and lung and demonstrated an increased risk for arterial thrombotic events in patients receiving bevacizumab compared to chemotherapy alone (3.8% vs. 1.7%). The highest risk patients were those over the age of 65 and those with a prior history of atherosclerosis.

The incidence of gastrointestinal perforation in patients receiving bolus-IFL with bevacizumab was 2%. Impaired wound healing and wound dehiscence following surgery has also been observed.^{7, 10} The incidence of NCI-CTC grade 2-4 congestive heart failure in patients receiving Avastin in Genentech-sponsored studies was 2%, and 14% in those receiving concurrent anthracyclines (APL).

Additionally, in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab, 31% of patients with squamous histology and 4% of patients with non-squamous histology experienced life-threatening or fatal pulmonary hemorrhage compared to 0% of patients receiving chemotherapy alone.

Another unusual toxicity seen with bavacizumab in the clinical studies was exfoliative dermatitis, with an incidence of 19% in one group of patients receiving bevacizumab in combination with 5-fluorouracil.

2.5 Presubmission Regulatory Activity

April 13, 2001

IND filed (# 62,382)

May 14, 2001

FDA requests monitoring study patients for adrenal toxicity based on preclinical evidence of adrenal hemorrhage.

August 22, 2002

Meeting to discuss potential adrenal toxicity

Based on observed adrenal toxicity in 2 animal species, presence of homologous receptors in human adrenal, and 2 patients with abnormal cortisol responses to ACTH stimulation, FDA advised the sponsor of the following.

- Investigators should perform ACTH stimulation tests to screen for adrenal functional reserve.
- Patients should be informed that sunitinib may cause changes in adrenal functional reserve in humans.

October 16, 2003

A meeting was held to discuss monitoring of potential adrenal toxicity with ACTH stimulation testing. The following points were agreed upon:

- The testing method would follow the package insert for cosyntropin.
- If the results were positive, a serum ACTH level would be obtained.
- ACTH stimulation testing would be conducted in the phase 3 GIST study patients at baseline and at the end of cycles 2, 4, and 6 and at the end of study.

November 10, 2003

EOP2 meeting for the renal cell carcinoma indication

The sponsor requested this meeting to discuss the development plan and registration strategy. Two studies were proposed:

- (1) An open-label, single arm, multi-center study of single agent sunitinib (50 mg orally) in patients with metastatic renal cell carcinoma who had failed one cytokine therapy. Eligible patients were those who had progressive disease during or within 9 months of completing cytokine-based therapy with IL-2 and/or IFN- α . The planned enrollment was 100 patients. The primary endpoint was response rate [complete response (CR) + partial response (PR)], using RECIST criteria, and the response rate of interest was $\geq 15\%$.
- (2) A randomized, placebo controlled trial of sunitinib in cytokine-refractory metastatic renal cell carcinoma. The primary endpoint was time to progression (TTP). FDA agreed that this may be an appropriate endpoint to support clinical benefit given the possibility of cross-over at disease progression but stated that the study should be powered to detect a difference in overall survival.

November 24, 2003

A special protocol assessment was submitted for a single-arm study of sunitinib in cytokine-refractory metastatic renal cell carcinoma (the trial proposed in item 1, November 10, 2003). Efficacy was to be assessed by determination of CR+ PR rates with CT or MRI used to assess disease status by RECIST criteria at defined intervals. The analytic plan assumed a historical ORR $<5\%$ in this setting. A 100 patient study was proposed to detect an ORR of $\geq 15\%$ with 90% power. FDA noted that the sponsor intended this study to support accelerated approval and stated that the adequacy of this study to support accelerated approval was a review issue which would require consideration of ORR, the numbers of complete and partial responses, duration of response, toxicity profile and the adequacy of planned confirmatory trial(s).

April 12, 2004

A special protocol assessment was submitted for a phase III, randomized study of sunitinib versus IFN- α as first line therapy in metastatic renal cell carcinoma. TTP was the primary endpoint, with a secondary endpoint of overall survival. Efficacy evaluation was based on CT/MRI using RECIST criteria and independent third party review was planned. The statistical plan estimated that 690 patients would be needed to demonstrate an improvement in TTP from 20 weeks to 27 weeks (35%) with 90% power. This was also estimated to be an appropriate sample size for demonstrating a 35.7% improvement in overall survival (from 56 to 76 weeks).

March 25, 2004

Summary of sponsor's clinical data regarding ACTH stimulation testing sent to FDA along with a proposal to discontinue routine ACTH stimulation testing.

June 1, 2004

Responding to sponsor's query regarding the proposal to discontinue routine testing, an email is sent stating that the proposal is acceptable. The sponsor subsequently discontinued routine ACTH stimulation testing on all clinical trials including the placebo controlled GIST study.

July 12, 2004

Fast track designation granted for metastatic renal cell carcinoma indication.

September 23, 2004

Pre-NDA meeting for both renal cell carcinoma and GIST indications

FDA and sponsor agreed on:

- eCTD format
- submission of case report forms and patient narratives for all deaths, discontinuations due to adverse events, SAEs and all responders to treatment
- Submission of radiographic images via [] a third-party reviewer
- Pooling data from the two single-arm phase II trials in MRCC for both the summaries of clinical efficacy and safety, as well as presenting the data from each separately
- Submission of available safety data from ongoing studies listing SAEs, discontinuations due to adverse events and deaths occurring during the safety data collection period.
- The NDA may be submitted without the QT study data; however, these results should be submitted as soon as possible.
- Submission of ACTH stimulation testing results from approximately 150 patients on the GIST phase III trial.

April 19, 2005

Pre-NDA/Guidance meeting regarding auditing of digitized images.

- Agreed upon the RECIST Working Group's criteria for partial response
- Sponsor verified independent reviewer procedure to include at least 2 reviewers (and a third when in disagreement).
- FDA requested financial disclosure on independent primary reviewers.
- FDA requested that the sponsor submit the same background and medical history information that the sponsor provided to independent reviewer on each patient.

August 1, 2005

Meeting held to discuss ACTH stimulation test results.

- ACTH results from most patients in the placebo-controlled GIST Phase 3 trial were missing. This trial was the only placebo controlled trial in which to isolate a drug effect on adrenal function. In the absence of this data, the effect of sunitinib on adrenal function is unclear.
- Dr. Perlstein, consultant from the Division of Metabolic and Endocrine Drug Products, recommended that labeling should clearly indicate that physicians prescribing sunitinib should maintain a high index of suspicion for the presence of adrenal insufficiency.

September 29, 2005

Pre-sNDA meeting for 1st line renal cell carcinoma indication

- The sponsor informed FDA that enrollment onto the first-line MRCC phase 3 trial is complete and that they expect to file an sNDA submission based on an interim analysis of response rate (the primary endpoint is progression-free survival)
- FDA concurred with sponsor's intended sNDA contents

- FDA reminded the sponsor that the adequacy of response rate to support accelerated approval is a review issue
- The sponsor and the FDA agreed upon allowing patients on the interferon arm of the phase 3 trial who progress to enroll in the expanded access program for cytokine-refractory MRCC

2.6 Other Relevant Background Information

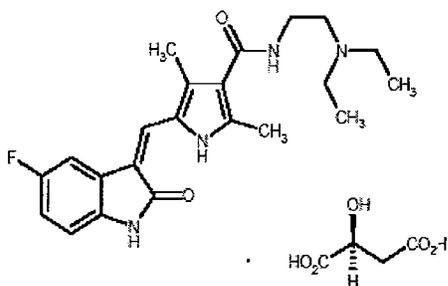
This drug has not been approved for marketing outside the U.S.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Description of the Drug Product(s) and Drug Substance(s)

SUTENT™ (sunitinib malate) is an oral, multi-targeted receptor tyrosine kinase inhibitor that targets and blocks the signaling pathways of selected receptor tyrosine kinases (RTKs). Sunitinib malate is described chemically as (Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate. The molecular formula is C₂₂H₂₇FN₄O₂ • C₄H₆O₅ and has the following structural formula:



The drug substance is a fine, yellowish crystalline powder and is soluble in water and ethanol.

Three orally administered immediate release hard gelatin capsules have been developed representing doses of 12.5 mg, 25 mg and 50 mg of SU011248 as sunitinib malate. The 12.5 mg capsule uses a blend formula containing [] w/w sunitinib malate, whereas the 25 mg and 50 mg capsules use a blend formula containing [] w/w sunitinib malate.

SUTENT (sunitinib) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

3.2 Animal Pharmacology/Toxicology

Pharmacology

Sunitinib is a receptor tyrosine kinase inhibitor with affinity for numerous receptor tyrosine kinases proposed for use in metastatic renal cell carcinoma. Sunitinib inhibited Class V and III split kinase domain receptor tyrosine kinases VEGFR1, 2, and 3, PDGFR α and β , FLT3 and CSF-1R as well as RET in biochemical, cellular and/or functional assays. *In vitro* and *in vivo* studies demonstrated decreases in cell proliferation in cell lines and tumors expressing VEGFR2, PDGFR α and β , KIT, RET, and FLT.

Safety Pharmacology

- Sunitinib and its active metabolite SU011262 blocked hERG currents with an IC₅₀ of 266 nM and 4.1 μ M, respectively.
- In monkeys, corrected QT intervals were increased by 20-50 msec.

Toxicology

- In rats and monkeys, major target organs of SU010398 toxicity are hematopoietic organs (thymus, marrow, spleen, lymph nodes), liver, gastrointestinal tract, glands (pancreas, adrenals, salivary), skeletal, and female reproductive organs (ovaries, uterus).
- GI toxicity included abnormal feces in both species and emesis in the monkey. These findings were corroborated by histological findings of inflammation, mucosal erosion, epithelial depletion, necrosis and hemorrhage in the gastrointestinal tract. These findings were reversible by the end of each recovery period.
- In both rat and monkey repeat dose studies, hematological changes included decreases in red blood cells, with concomitant decrease in red cell mass. Reductions in white blood cells were observed with histological evidence of lymphoid depletion in the spleen, thymus, and lymph nodes and atrophy in the bone marrow.
- In adrenals, toxicity was noted in studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Toxicity was routinely characterized by hemorrhage in both species, but necrosis, congestion, hypertrophy and inflammation were also noted. These findings were reversible within the recovery period.
- Increases in serum hepatic enzymes (AST, ALT and occasionally GGT and total bilirubin) were accompanied by histological changes of peribiliary inflammation, bile duct hyperplasia and degeneration of the portal hepatocytes.
- In the three and nine month oral toxicity studies in the monkey, changes in cardiovascular function were observed. Reductions in heart rate were noted in the both studies at doses of ≥ 120 mg/m². Changes in echocardiogram parameters included reductions in the ratio

of left atrial diameter to aortic diameter, the left atrial diameter, left ventricular ejection time and left ventricular area.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The following sources of clinical data were used to perform this review:

- The eCTD submission to the EDR dated August 10, 2005
- Updates and responses to queries submitted to EDR
- Literature Review
- The sponsor's slides from the presentation to FDA DDOP on September 22, 2005
- Tabulated data from the clinical adrenal function and imaging studies submitted by the sponsor to the sunitinib IND on May 31, 2005
- The reports of consultants from The Division of Hematology and Medical Imaging and The Division of Metabolic and Endocrine Drug Products

4.2 Tables of Clinical Studies

Clinical studies submitted by the sponsor are divided below into MRCC efficacy studies, GIST efficacy studies, dose finding studies and pharmacokinetic studies. Note that some studies are listed in more than one table. For example, study 013 was a phase 1/2 study in GIST patients that incorporated a dose-finding component as well as an efficacy component.

Table 1: MRCC Efficacy Studies

Study ID	Phase	# Patients	Primary Efficacy Endpoint	Status
014	2	63	ORR (CR+PR)	Completed 8/04
1006	2	106	ORR (CR+PR)	Ongoing; data cutoff 1/28/05

Table 2: GIST Efficacy Studies

Study ID	Phase	# Patients	Primary Efficacy Endpoint	Status
013	1/2	55 (at 50 mg 4/2 dose/schedule)	ORR (CR+PR)	Completed
1004	3	312 (207 sunitinib, 105 placebo)	TTP	Ongoing; data cutoff 1/1/05

Table 3: Dose Finding Studies

Study ID	Phase	Population	# Patients	Doses	Schedule
002	1	Solid tumors	28	25-150 mg QD or QOD	4 weeks on/2 weeks off
005	1	Solid tumors	42	25-75 mg QD or QOD	4 weeks on/2 weeks off or 2 weeks on/2 weeks off
013	1/2	GIST	97	25-75 mg QD	4 weeks on/2 weeks off or 2 weeks on/2 weeks off or 2 weeks on/1 week off

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Table 4: Pharmacokinetic Studies

Protocol	Design	Type	Population	Sampling	SU011248 Formulation	Dosing	N enrolled
248-ONC-0511-001	Randomized, double-blind, placebo-controlled, single-dose study	SD1	Healthy volunteers	Full PK	free base powder in bottle	50 mg Oral Single dose	9
248-ONC-0511-002 (Study 002)	Open-label, non-randomized, dose-escalation study	MD2	Solid tumor	Full PK and Trough	free base and L-malate salt capsule	25, 50, 75, or 100 mg Oral Repeat doses QD or QOD on Schedule 4/2 ³	28
248-ONC-0511-004	Randomized, open-label, 3-way crossover study of SU011248 free base and L-malate salt and the effect of food,	SD	Healthy volunteers	Full PK	free base and L-malate salt capsule	50 mg, 3 single Oral doses free base fasted, L-malate salt fed	15
RTKC-0511-005 (Study 005)	Open-label, non-randomized, dose-escalation study	MD	Solid tumor	Full PK and Trough	free base and L-malate salt capsule	50, 75 QD or QOD Oral Repeat doses on Schedule 4/2 or 2/2 ⁴	41
248-ONC-0511-006	Open-label, single-treatment, escalating-dose study	SD	AML	Full PK	free base and L-malate salt capsule	Single dose of 50-350 mg	29
RTKC-0511-009	Randomized, open label, 2-way crossover study of SU011248 with and without concomitant administration of Ketoconazole	SD	Healthy volunteers	Full PK	L-malate salt powder in bottle	10 mg + ketoconazole: 400mg po QD x 7 days	27
A6181001	Open-label, crossover study of SU011248 with and without concomitant administration of Rifampin	SD	Healthy volunteers	Full PK	L-malate salt capsule	50 mg + rifampin: 400mg po QD x 7 days	28
RTKC-0511-013 (Study 013)	Open-label, single arm, non-randomized, dose-escalating study of 3 treatment schedules	MD	GIST	Trough and Full PK (18 Full PK)	L-malate salt capsule	25, 50, or 75 mg Oral Repeat doses QD on Schedule 2/2, 4/2, or 4/15	97 (18 with full PK)
RTKC-0511-016	Open-label, non-randomized study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50 mg Oral Repeat doses QD on schedule 2/16	12
RTKC-0511-018	Open-label, dose escalation study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50-175 mg loading dose on day 1 50 mg Oral Repeat doses QD on schedule 2/1	27

1: Single Dose 2: Multiple Dose 3: 4 weeks of dosing followed by 2 weeks off drug 4: 2 weeks of dosing followed by 2 weeks off drug 5: 4 weeks of dosing followed by 1 week off drug 6: 2 weeks of dosing followed by 1 week off drug
Table adapted from clinical pharmacology review (Dr. Roshni Ramchandani)

4.3 Review Strategy

The primary source of data used in this review was the data from the two MRCC trials submitted with the NDA (see Table 1). These two studies were the primary focus of both the efficacy and safety evaluations as they represent the most relevant patient population for the advanced RCC indication. Data from the trials in Gastrointestinal Stromal Tumors (GIST), including the only

placebo-controlled randomized trial, were reviewed concurrently by Dr. Edwin Rock under NDA 21-938. Safety data from other trials were reviewed in summary form in the submitted study reports.

4.4 Data Quality and Integrity

According to the Clinical Study Reports for Studies 014 and 1006 section 5.9:

“The sponsor monitored the study through routine center visits. At these visits, study procedures were reviewed, CRF/DCT data compared to original clinical records, data queries resolved, and protocol deviations discussed with the investigator. Telephone and e-mail contact was maintained with the investigators between center visits. In addition, the overall study conduct was subject to internal quality review by the sponsor.

After resolving data issues detected at the site, all data on the CRFs were entered into a computer database. Data management was accomplished according to standard operating procedures, which included double entry of data from each CRF and a quality control check, to ensure a match between data reported on the CRF and data entered into the clinical database. Data were checked for completeness, consistency, and reasonableness by a series of computer and manual procedures based on a study-specific data clarification policies document prepared before beginning data processing for the study. Any missing or questionable items that were detected were recorded on a data query form for resolution at the study site and returned with appropriate documentation. If a change was required, it was documented on the CRF, and the database was updated to reflect the change.

After all data queries were resolved, a data quality control check was performed before the database was frozen for analysis. Key safety variables were compared between the CRFs and the database for all patients, and any problems detected were resolved. In addition, all data for a random sample consisting of 10% of the patients were compared between the CRFs and the database. If more than 0.5% of the data items were in error, an additional sample was checked. All possible data problems found in this review were also resolved before freezing the database.”

The two clinical sites with the highest accrual across both renal cell carcinoma studies were chosen by the clinical review team for inspection by the Division of Scientific Investigation (DSI). These sites were responsible for 42% of all patients enrolled across both trials (24% at Massachusetts General Hospital and 18% at Memorial Sloan Kettering Cancer Center). No FDA form 483 was issued at either site. One site had no significant findings; findings at the other site included some missing study visits or assessments and out-of-window visit dates. Missing assessments included weights, performance status, and temperature.

4.5 Compliance with Good Clinical Practices

According to the sponsor:

“The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) and/or the Institutional Ethics Committee(s) (IEC).

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki (Revised Edinburgh, 2000) and in compliance with IRB/IEC, informed consent regulations, and International Congress of Harmonization (ICH) Good Clinical Practices (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants. The clinical protocol was also conducted in accordance with FDA Regulations (Title 21 Code of Federal Regulations [21 CFR], Parts 50, 56, and 312).

Written informed consent was obtained prior to the subject entering the study (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent form.”

4.6 Financial Disclosures

The sponsor certified that they had entered into no financial arrangement with any investigator under which the value of the compensation depended on the outcome of the study.

The sponsor’s procedures for obtaining financial disclosure from the investigators were as follows:

The listed investigators were sent the Financial Disclosure Form directly. If necessary, Pfizer contacted the site by telephone and/or sent 2 separate follow-up letters to those individuals who did not return the Financial Disclosure Form. The investigators contacted were reminded to disclose financial information for Pfizer Inc and affiliated companies, including Warner-Lambert, Agouron, Pharmacia, Pharmacia & Upjohn, Searle/Monsanto and Sugem, which are wholly owned by Pfizer.

For study [REDACTED] investigators at 11 clinical sites and the core imaging laboratory reported no financial interests. The sponsor reported that one investigator, Dr. [REDACTED] received a payment of \$50,000 to his institution, [REDACTED].

For study [REDACTED] investigators at 7 clinical sites and the core imaging laboratory reported no financial interests. The sponsor reported a disclosure by Dr. [REDACTED] that [REDACTED] was a co-investigator on a study funded by an independent research grant. Dr. [REDACTED] reported that this protocol, [REDACTED] was funded by Pharmacia through [REDACTED] in the amount of \$100,000. One investigator did not respond or could not be reached.

None of the investigators at the core imaging facility reported a financial arrangement with the sponsor.

Steps taken by the sponsor to minimize bias included:

During the conduct of this trial, including the processing, analyzing and reporting of data, Pfizer applied procedures designed to minimize the potential of bias in the data.

The trials were conducted according to ICH Good Clinical Practices and Pfizer or Pharmacia SOPs in place at the time. In addition, the current FDA Debarment list and the Disqualified/Totally Restricted List for Clinical Investigators were checked:

<http://www.fda.gov/0ra/co1npliance ref/debar/default.htm> and

<http://www.fda.gov/0ra/co1npliance ref/bimo/disqlist.htm> respectively. In addition, the Public Health System Administrative Actions Listing was checked for researchers who have had administrative actions imposed against them by the Office of Research Integrity:

[http://silk.nih.gov/public/CBZ 1 B JE.@,WWW.ORIDTLS.HTML](http://silk.nih.gov/public/CBZ%201%20JE.%40WWW.ORIDTLS.HTML) - TOP.

Other processes used to minimize potential bias are as follows:

1. The facilities performing the safety and efficacy evaluations were determined to be acceptable based on appropriate certification or historical performance and/or qualifications and credentials.
2. Frequent monitoring of investigator trial sites. The validity of the data collected during the study was confirmed by standard monitoring procedures.
3. Selected individual sites were audited.
4. During the course of processing, analyzing and reporting data from clinical trials, Pfizer applied procedures (e.g., querying data through electronic edit checks) designed to ensure that errors were eliminated.
5. Efficacy and safety data are listed by site.
6. The study report was appropriately reviewed and audited by members of the project team and Quality Assurance, respectively.
7. Appropriate statistical methods were employed by use of an approved statistical analysis plan.
8. Third-party, blinded analysis was conducted by an independent core imaging vendor (for study 1006).

5 CLINICAL PHARMACOLOGY

Pharmacokinetics, pharmacodynamics and Exposure-Response Relationships were evaluated by the Clinical Pharmacology team from the Division of Clinical Pharmacology and Biopharmaceutics V, including Drs. Roshni Ramchandani, Sophia Abraham and Carol Noory. The figures in sections 5.1-5.3 were taken from the Clinical Pharmacology Review written by Dr. Roshni Ramchandani.

5.1 Pharmacokinetics

C_{max} and AUC for sunitinib and its active metabolite, SU0122662, in oncology patients are described in Table 5.

Table 5: Pharmacokinetic Parameters of Sunitinib

Analyte	Parameter	Range of values
Sunitinib	C _{max} (ng/ml)	18.6-28.9
	AUC ₀₋₂₄ (ng·hr/ml)	299-430
SU012662	C _{max} (ng/ml)	1.9-6.0
	AUC ₀₋₂₄ (ng·hr/ml)	34.0-98.4

C_{max}=maximum concentration

AUC₀₋₂₄=area under the plasma concentration time curve from 0-24 hours

Absorption of sunitinib following oral administration occurred with a median T_{max} of 4 to 12 hours post-dose following single and multiple doses. SU012662 peaked at approximately the same time as sunitinib, with median T_{max} occurring at 4 to 12 hours postdose.

Sunitinib is highly bound to human plasma proteins; 95.2±1.6% bound at *in vitro* concentrations of 0.1-4.0 µg/ml (Report PDM-060). The primary active metabolite, SU012662, is 89.8±1.1% bound to human plasma proteins at *in vitro* concentrations of 0.1-4.0 µg/ml.

SU011248, along with its de-ethylated metabolite, SU012662, were the primary species identified in plasma. Plasma SU011248 and its major N-de-ethyl metabolite, SU012662, accounted for about 66% of the total plasma radioactivity based on AUC_{inf} (42% and 24%, respectively)

Metabolism

In vitro studies with human liver microsomes indicate that sunitinib (SU011248) undergoes CYP3A4-mediated N-de-ethylation to form a major, pharmacologic-ally active N-de-ethyl metabolite, SU012662 (Study SU011248-PDM-043).

SU012662 undergoes further metabolism (N-de-ethylation), which is also primarily by CYP3A4 to form an inactive metabolite (SU014335), but at a much slower rate than the N-deethylation of sunitinib in human liver microsomes. Only trace amounts of other metabolites, including an N-oxide metabolite (SU012487), are formed *in vitro*. The formation of the N-oxide metabolite (SU012487) is catalyzed by flavin-containing monooxygenases (FMO). The percent of compound remained in incubation mixtures after 2 hours was 54.2% as parent drug, 41.6% as the N-de-ethyl metabolite, 1.12% as the N-oxide metabolite, and 3.1% as an unknown metabolite.

Excretion

Fecal excretion is the major route of elimination of sunitinib. Over a 21-day collection period, total recovery of radioactivity averaged $77\pm 8.8\%$, with $61\pm 7.2\%$ in the feces and $16\pm 2.5\%$ in urine. Sunitinib is the primary species identified in feces and urine, followed by SU012662.

The dose proportionality of sunitinib, its active metabolite SU012662, and total drug (sunitinib + SU012662) has been evaluated in oncology patients following single dosing with sunitinib doses ranging from 50 to 350 mg, and multiple (QD) dosing with doses of 25 to 100 mg (Schedule 4/2).

Comparison of dose-normalized C_{max} and dose-normalized AUCs indicated that the PK of sunitinib and its primary metabolite SU012662 were dose-proportional in the range of doses evaluated. Log-log plots of C_{max} vs. dose and AUC vs. dose had slopes close to 1 also indicating that the PK of sunitinib and SU012662 are dose-proportional.

Recommended dosing adjustments in patients receiving CYP 3A4 inducers/inhibitors:

Dosing adjustments for patients on CYP3A4 inhibitors

There was an approximately 50% increase in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with ketoconazole. To adjust for this increase, the clinical pharmacology reviewers recommend that the sunitinib dose be reduced to 66% of the recommended dose in patients who must receive strong CYP3A4 inhibitors concomitantly.

Dosing adjustments for patients on CYP3A4 inducers

There was an approximately 50% decrease in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with rifampin. To adjust for this decrease, the clinical pharmacology reviewers recommended that the sunitinib dose be increased to 175% of the recommended dose in patients who must receive CYP3A4 inducers concomitantly.

No dose adjustments are recommended based on age, race or gender in the advanced RCC population.

5.2 Pharmacodynamics

The sponsor has an ongoing QT prolongation study to definitively address the potential for QT prolongation. See section 5.3 for pharmacodynamic data.

5.3 Exposure-Response Relationships

Efficacy

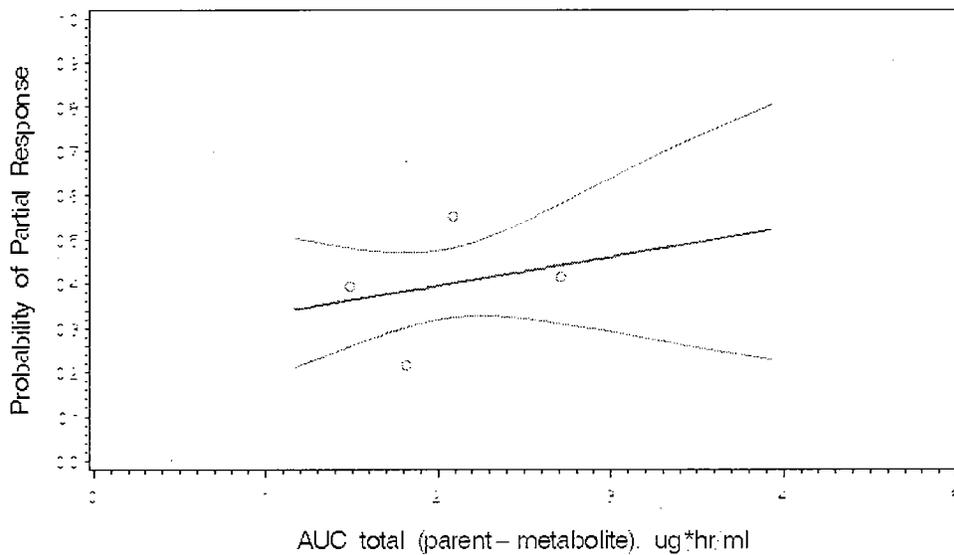
The effect of exposure on partial response rate was evaluated using logistic regression. Partial response rates were evaluated since no complete responses were seen in these studies.

In the MRCC studies, the analysis showed a high rate of partial responses across exposures, but did not show a significant effect of exposure on the probability of partial responses. Possible reasons for the lack of a significant relationship may be the large variability in response, and the relatively limited range of exposure.

The probability of partial response vs. AUC and the largest change in tumor size vs. AUC are demonstrated in Figures 1 and 2.

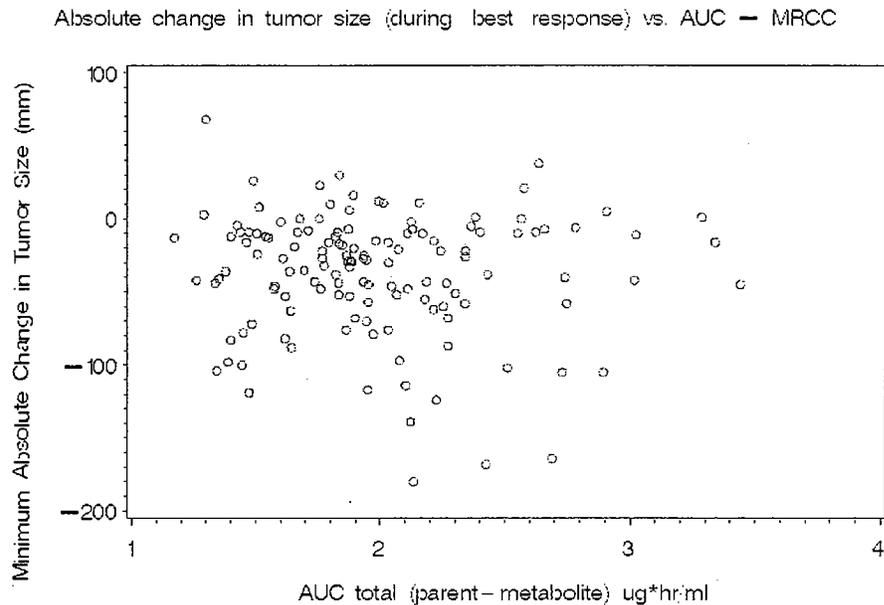
Figure 1: Probability of partial responses (based on RECIST criteria) vs. AUC total (parent + metabolite) for patients with MRCC

Probability of Partial Response vs. AUCTOT (base_all13) (parent – metabolite) – MRCC



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Figure 2: Largest absolute change in tumor size post-treatment as a function of total AUC (parent + metabolite) in MRCC patients



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As shown in Figure 2, there is no significant association between exposure and largest absolute change in tumor size seen in MRCC patients treated with sunitinib.

Safety

Major toxicities included severe fatigue, diarrhea, neutropenia, thrombocytopenia, anemia, vomiting, hypertension and left ventricular ejection fraction (LVEF) dysfunction.

The toxicity data was evaluated using logistic regression for all the above adverse events for all patients who received sunitinib throughout the clinical development program. The frequency of severe grade 3/4 toxicity for all the above measures (except nausea and vomiting where all grades were included and hypertension where grade 2/3 toxicity was used) was modeled as a function of AUC_{total} (parent + metabolite).

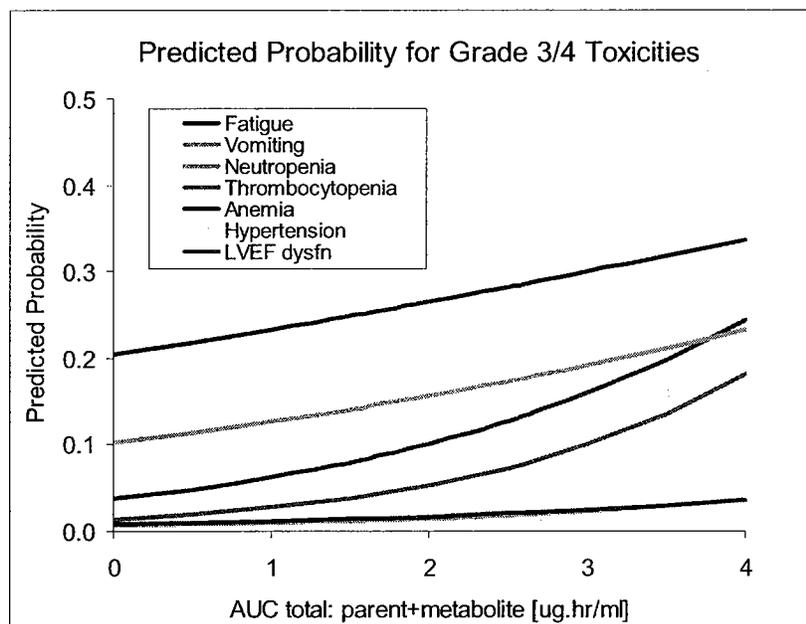
Table 6 summarizes the results of this evaluation.

Table 6: Common Toxicities as a Function of AUC

Toxicity	Frequency	Odds ratio for AUCtot (p-value)
Grade 3/4 fatigue	46/516	1.70 (p=0.0038)
Grade 3/4 vomiting	8/544	1.57 (p=0.04)
Grade 3/4 neutropenia	81/544	1.28 (p=0.02)
Grade 3/4 thrombocytopenia	29/544	1.99 (p=0.0001)
Grade 3/4 anemia	139/544	1.19 (p=0.06)
Grade 3/4 pancreatic dysfunction	58/544	NS
Grade 2/3 hypertension	113/544	1.22 (p=0.04)
Grade 2/3/4 LVEF dysfunction	9/544	1.48 (p=0.08)

Figure 3 shows a composite of the predicted probabilities for the various toxicities as a function of exposure.

Figure 3: Predicted probability of severe grade 3/4 toxicities vs. total AUC (parent + metabolite) in GIST and MRCC patients



As seen in the table and figure, increases in exposure, as measured by AUC, correspond with increases in the incidence of fatigue, vomiting, neutropenia, thrombocytopenia, and hypertension.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor's original proposed indication is as follows:

SUTENT is indicated for L

1

The proposed indication is consistent with the population studied on the two submitted renal cell carcinoma trials. The eligibility criteria for the two submitted trials were similar in that both required one prior cytokine-based therapy for MRCC. Most patients enrolled had clear-cell histology, the predominant subtype of RCC which accounts for 75-85% of all cases; 15% of patients on one of the two trials (014) had other histologic subtypes. This reviewer therefore concludes that the sponsor's proposed indication accurately reflects the population studied.

All patients enrolled on the two trials received cytokine-based therapy as mandated by the protocols. Cytokine therapy (either IFN- α , IL-2 or both) is the standard first-line therapy for MRCC. IL-2 is the only FDA-approved cytokine for this indication, but IFN- α is also commonly used in this setting. As discussed in section 2.2, both of these therapies are highly toxic, available to only the most fit patients, and have poor efficacy. As a result, restricting the indication to the second-line following cytokine failure would create an "artificial" clinical scenario (one that is inconsistent with expected clinical practice) in which a patient would be required to complete treatment with a highly toxic regimen of minimal benefit prior to receiving a significantly less toxic regimen with a higher response rate. After discussion between the review team, the DDOP and OODP leadership, and later the sponsor, we therefore propose to expand this indication to include all patients with advanced renal cell carcinoma, without a requirement for prior cytokine therapy.

An expansion of the approved indication beyond the patient population studied in this setting is based on the very limited efficacy and extreme toxicity of its treatment, leading to the conclusion that treatment-naïve patients are as likely to benefit from this therapy as cytokine-treated patients, and should not be exposed unnecessarily to a highly toxic treatment in order to be considered "cytokine failures".

It should be noted that the sponsor currently has an ongoing clinical trial in which treatment-naïve MRCC patients have been randomized to receive either sunitinib or IFN- α . This trial is intended to confirm clinical benefit in advanced RCC. The expanded indication is not expected to interfere with the conduct of this trial, which has completed enrollment at this time. Furthermore, the sponsor was intending to submit data from an interim analysis, with ORR as the endpoint, in order to support accelerated approval for the first-line indication. This submission, which was expected in the first quarter of 2006, will now be a mandatory post-marketing commitment under subpart H. The submission of the interim analysis data will not support a new indication, but will instead be a labeling supplement intended to update the clinical studies

and safety sections with comparative information for sunitinib vs. IFN- α . The PMC for the labeling supplement will be in addition to the requirement for the submission of the final analysis of that trial, with a progression-free survival endpoint, as the confirmatory trial intended to demonstrate clinical benefit for sunitinib in advanced RCC.

Based upon these considerations, the proposed indication is:

SUTENT is indicated for the treatment of advanced renal cell carcinoma.

6.1.1 Methods

The sponsor submitted two studies to support the efficacy of sunitinib in MRCC. These studies are summarized in Table 7. Efficacy results of both studies were reviewed with particular attention to the primary endpoint (response rate) and the duration of responses.

Table 7: MRCC Efficacy Studies

Study number	Number of patients	Population	Design/endpoints
1006	106	Cytokine-refractory MRCC Clear cell Histology Requirement for nephrectomy	Open-label, single arm phase 2 Primary endpoint: response rate Duration of response also evaluated
014	63	Cytokine-refractory/intolerant MRCC Any histology No requirement for nephrectomy	Open-label, single arm phase 2 Primary endpoint: response rate Duration of response also evaluated

6.1.2 General Discussion of Endpoints

The primary endpoint of the two submitted renal cell carcinoma trials was overall response rate (ORR). The larger study (1006) was the subject of a special protocol assessment in November of 2003. At that time, FDA noted that the sponsor intended this study to support accelerated approval and stated that the adequacy of this study to support accelerated approval was a review issue which would require consideration of ORR, the numbers of complete and partial responses, duration of response, toxicity profile and the adequacy of planned confirmatory trial(s).

Tumor responses in the second-line treatment of MRCC are unusual, with a historic RR of <5%. The relationship between response rate and endpoints of defined clinical benefit such as survival is unknown. Only the cytokines IFN and IL-2 have demonstrated biologic activity in the form of responses in MRCC. Response rates with cytokine treatment are low (10-15%), but in those patients who achieve complete response following high dose IL-2, prolonged remissions have been seen. Partial responses are of less certain benefit but may be considered reasonably likely to predict clinical benefit if of sufficient duration, in the setting of a drug with a favorable toxicity profile.

6.1.3 Study Design

Study 1006:

This study is an ongoing, open-label, single-arm, multi-center clinical trial evaluating the efficacy and safety of sunitinib as a single agent in patients with metastatic RCC who are refractory to one cytokine therapy (IL-2, IFN or IL-2 + IFN).

Primary objective:

- To determine the anti-tumor efficacy of single-agent sunitinib at a dose of 50 mg orally once daily for 4 consecutive weeks repeated every 6 weeks in patients with progressive MRCC who are refractory to 1 prior cytokine therapy (IL-2, IFN or IL-2 + IFN).

Secondary objectives:

- To assess measures of duration of tumor control
- To assess survival
- To evaluate the safety and tolerability of sunitinib
- To evaluate sunitinib and SU012662 (an active metabolite of sunitinib) trough plasma concentrations and to correlate these plasma concentrations with efficacy and safety parameters

Inclusion Criteria:

- Histologically proven renal cell carcinoma of clear cell histology with metastases
- Unidimensionally measurable disease
- Radiographic evidence of disease progression defined by RECIST or WHO during or within 9 months of completion of 1 cytokine therapy (IL-2, IFN or IL-2 + IFN). If IFN alone was used, the patient must have received IFN for at least 28 days.
- Prior nephrectomy
- Male or female age ≥ 18 years
- ECOG performance status 0-1
- Resolution of all acute toxic effects of prior cytokine therapy, radiotherapy, or surgical procedure to NCI CTCAE grade ≤ 1
- Adequate organ function (as defined in the protocol)
- Informed consent

Exclusion Criteria:

- RCC of papillary, collecting duct or chromophobe type
- Prior treatment with any systemic therapy other than 1 prior cytokine therapy (IL-2, IFN or IL-2 + IFN) for RCC
- Prior surgery, radiation therapy, or systemic therapy within 4 weeks of starting study
- NCI CTCAE grade 3 hemorrhage within 4 weeks of starting study
- Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell carcinoma, squamous cell skin cancer, or *in situ* cervical cancer

- History of or known brain metastases, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease on screening CT/MRI
- Ischemic heart disease, heart failure, cerebrovascular disease or pulmonary embolism in the last 12 months
- Ongoing cardiac dysrhythmias of NCI CTCAE grade ≥ 2 , QT prolongation
- Uncontrolled hypertension
- HIV (+) or AIDS related illness
- Pregnant or breast feeding female; unwilling to use adequate contraception
- Current enrollment in another treatment clinical trial
- Other condition which in the investigator's opinion renders the patient inappropriate for the study

Study Design: The planned sample size was 100 patients. This was an open-label, single-arm, multi-center trial of sunitinib as a single agent in patients who were refractory to one cytokine therapy. Sunitinib was given at a fixed dose of 50 mg once daily by mouth for 4 out of 6 weeks, with a two week rest period between cycles (the 4/2 Schedule). Patients could continue to receive sunitinib in the absence of any of the withdrawal criteria outlined in the protocol.

Efficacy Evaluations: Overall confirmed objective tumor response rate measured by the core imaging laboratory () using the RECIST criteria was the primary efficacy endpoint. Confirmed responses were those that persisted on repeat imaging study ≥ 4 weeks after initial documentation of response. Secondary efficacy endpoints included time to tumor progression (TTP), duration of response (DR), overall survival (OS) and progression-free survival (PFS). These endpoint measurements are defined below.

Time to tumor progression (TTP) was defined as the time from start of study treatment to first documentation of objective tumor progression or to death due to cancer, whichever came first. TTP data was censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and were still on study at the time of an analysis, were given anti-tumor treatment other than the study treatment, were removed from study prior to documentation of objective tumor progression, or died of non-cancer-related symptoms including deaths due to an unknown cause in the absence of documented disease progression. Patients lacking an evaluation of tumor response after their first dose had their event time censored at 1 day.

Duration of response (DR) was 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, whichever came first. DR data was censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and were still on study at the time of an analysis, were given anti-tumor treatment other than the study treatment, were removed from study prior to documentation of objective tumor progression, or died of non-cancer-related causes including death due to an unknown cause in the absence of documented disease progression. DR was only calculated for the subgroup of patients with ORR.

Overall survival (OS) was defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive. Patients lacking data beyond the day of first dose had their survival time censored at 1 day.

Progression-free survival (PFS) was defined as the time from start of study treatment to first documentation of objective tumor progression or to death due to any cause, whichever came first. PFS data was censored on the day following the date of the last tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and were still on study at the time of an analysis, were given anti-tumor treatment other than the study treatment, or were removed from study prior to documentation of objective tumor progression. Patients lacking an evaluation of tumor response after their first dose had their event time censored at 1 day.

Survival follow-up:

Follow-up survival information was collected by clinic visit or telephone contact every 2 months until death to obtain survival status and disease progression information.

Reviewer comment: Time-to- event endpoints including TTP, PFS and OS are considered exploratory when performed in a single-arm trial.

Radiographic assessments:

- CT/MRI of the chest, abdomen, and pelvis was performed at baseline (within 28 days prior to initiating treatment), day 28 ± 3 of cycles 1, 2, 3, 4 and subsequently every even cycle on day 28 ± 3 and at the end of treatment/withdrawal. Scans were also performed whenever disease progression was suspected. All patients with CR or PR required confirmation of response at least 4 weeks after initial documentation of response.
- Bone scan was performed at baseline. If negative, no further bone scans were required unless symptoms suggestive of bone metastases developed. Patients with bone metastases had follow-up bone scans at the same interval as CT/MRI.
- The same method and technique of assessment was used to follow-up documented lesions.
- All radiographic tumor assessments were reviewed by [] the independent third party reviewer. [] reviewers were blinded to the investigators report of response status. Two radiologists reviewed each case. In the event of disagreement between the two readings, a third radiologist was asked to adjudicate. The adjudicating radiologist read the reports from both primary readers and either agreed with one and rejected the other, or rejected both. In the event that this reader disagreed with both initial readers, the reading provided by the adjudicating radiologist was the reported reading.

Statistical Methods:

The sample size was calculated to have 90% power to detect an ORR of $\geq 15\%$, assuming a historical response rate of $< 5\%$.

The protocol specified primary efficacy analysis population was the modified intention-to-treat population (MITT), which included patients who received at least one dose of study therapy and were refractory to one cytokine therapy as confirmed by a third-party [] review. All patients who received at least one dose of study medication were considered in the ITT population which was defined in the protocol as the primary safety population and a secondary efficacy population.

Reviewer comment: Following a meeting with the FDA in February, 2005 regarding the GIST indication, the population for the primary efficacy analyses of both the MRCC study and the GIST study were changed to the ITT due to concern that retrospective evaluation of eligibility could introduce bias. The ITT population is therefore the primary efficacy population for both MRCC studies.

Descriptive statistics were used to summarize all patient characteristics, treatment administration/compliance, efficacy endpoints, safety parameters, and pharmacokinetic variables.

For the primary efficacy analysis, the number (%) of patients who achieve an objective response (PR or CR) was summarized along with the corresponding 95% confidence interval. Time-to-event data were summarized using the Kaplan-Meier method.

The protocol also specified that patients who did not have a baseline assessment of disease or who were inadvertently enrolled and later determined to have the incorrect histologic cancer type were to be excluded from analyses of TTP, ORR, DR and PFS.

Protocol Amendments/Study Landmarks--1006:

November 20, 2003

Original protocol

February 18, 2004

First subject began study therapy

March 5, 2004

Protocol amendment #1: The following changes were made.

- The requirement for at least 28 days of cytokine therapy was changed to apply only to patients receiving IFN, since 1 cycle of IL-2 can be less than 28 days.
- The eligibility requirement with respect to baseline amylase and lipase values was removed.
- The requirement for normal ACTH stimulation testing at entry was removed.
- The requirement of absence of deep venous thrombosis over a 12 month period was removed as patients on anti-coagulation were permitted to enroll.
- A minus one day window was added for day 1 of cycle visits to allow flexibility.
- Repeat ACTH stimulation testing was limited to those patients with normal baseline.
- Additional ECG testing was added at cycle 1 day 28 to increase tracings from 1 to 3.

- Lymphopenia was excluded from consideration as hematologic toxicity warranting dose reduction.
- Dose modifications for cardiac toxicity added.
- Rules for dose modification with respect to cardiac toxicity were changed.
- Palliative radiation and/or surgery were prohibited during the study due to the complication of efficacy assessment.
- Updated informed consent to reflect the above changes.

July 28, 2004

Protocol amendment #2: The following changes were made:

- PFS added as a secondary endpoint
- ACTH stimulation testing removed from the study
- Modification in SAE reporting requirements to be compliant with new European Directives
- MITT population added
- Modified informed consent template with updated safety information and changes in assessments

November 23, 2004

Last subject begins study therapy

January 28, 2005

Data cutoff date

Study 014:

This was an open-label, single-arm, multi-center, phase 2 clinical trial to evaluate the efficacy and safety of single-agent sunitinib as second-line therapy in patients with metastatic RCC who were intolerant of or had experienced disease progression during or following treatment with one prior cytokine-based therapy.

Primary objective:

- To determine the overall objective tumor response rate during treatment with orally administered sunitinib in patients with progressive, metastatic renal cell carcinoma (RCC) who have received 1 prior cytokine-based therapy.

Secondary objectives:

- To assess measures of duration of tumor control and overall survival
- To evaluate the safety of sunitinib; to evaluate patient-assessed, investigator-assessed, and laboratory evidence of disease and treatment-related signs and symptoms in patients with RCC receiving sunitinib
- To evaluate drug exposure levels and to correlate these plasma concentrations with efficacy and safety parameters

- To explore the correlations of potential cancer biomarkers and other specialized endocrine and cytokine parameters with cancer and treatment-related outcomes

Inclusion Criteria:

- Male or female patients age ≥ 18 years
- Histologically proven RCC with metastatic disease (unresected primary tumor is okay if metastatic disease is also present)
- Unidimensionally measurable disease
- Failure of or intolerance to 1 prior cytokine-based therapy regimen
- ECOG performance status 0-1
- Resolution of acute toxic effects of prior therapy to NCI CTC Grade ≤ 1
- Adequate organ function (as defined in the protocol)
- Informed consent

Exclusion Criteria:

- Prior treatment with any systemic therapy other than 1 prior cytokine-based treatment; prior surgery or radiotherapy ≤ 4 weeks before enrollment
- Prior surgical resection of or irradiation to the only site of measurable disease
- Known brain or leptomeningeal disease
- Ongoing NCI CTC grade 4 hematuria
- Active second malignancy except basal cell carcinoma. Patients with other malignancies must be disease free for ≥ 2 years
- Ischemic heart disease, heart failure, cerebrovascular disease or significant thromboembolic event in the last 12 months
- Significant cardiac dysrhythmias, QT prolongation
- HIV (+) or AIDS related illness
- Pregnant or breast feeding female; unwilling to use adequate contraception
- Current enrollment in another treatment clinical trial
- Extensive prior anthracyclines, prior trastuzumab
- Other condition which in the investigator's opinion renders the patient inappropriate for the study

Study Design: A total of up to 63 patients was planned to evaluate the objective tumor response rate. Thirty eight patients were to be treated in Stage 1. If ≤ 1 objective tumor response was observed in the first 38 treated patients, then the trial was to be terminated. However, if ≥ 2 objective tumor responses were observed in the first 38 treated patients, then the study was to be expanded to enroll a total of 63 treated patients (25 new patients to be treated in Stage 2). Patients treated on this study received sunitinib at a starting dose of 50 mg/day for 4 weeks followed by a 2-week rest period to form a 6-week treatment cycle. Cycles could be repeated for up to 1 year.

Study Treatment: Patients treated on this study received sunitinib at a starting dose of 50 mg/day for 4 weeks followed by a 2-week rest period to form a 6-week treatment cycle.

Sunitinib was self-administered orally, as a single-agent, once daily in the morning with a glass of water and without regard to meals. In the event of significant toxicity, one dose reduction to 37.5 mg was permitted. Additionally, the rest period could be extended by one week to allow resolution of toxicity. In the absence of treatment-related toxicities of protocol-defined severity, dose escalation was permitted on an individual basis after discussion with the study's medical monitor to 62.5 mg and, if that was well tolerated, to 75 mg. One escalation per cycle was permitted. Patients were allowed to continue protocol treatment for up to one year; a continuation protocol was available for those patients continuing to benefit from the drug after that time.

Efficacy Evaluations: Objective tumor response rate as determined using RECIST criteria was the primary efficacy endpoint.

Secondary efficacy endpoints included time to tumor response, time to treatment failure (TTF), time to tumor progression (TTP), overall survival and duration of objective tumor response. These endpoint measurements are defined below.

Objective tumor response rate was defined as the total proportion of patients with either complete response (CR) or partial response (PR) as characterized by RECIST criteria. CR requires the disappearance of all target and non-target lesions with no new lesions present. PR requires a decrease of $\geq 30\%$ in the sum of the longest diameters of all target lesions, taking the baseline evaluation as the point of reference, and no evidence of new lesions or progression of pre-existing non-target lesions. All responses must be confirmed at least 4 weeks after the initial evaluation documenting a response.

Time to objective tumor response was defined as the time from the first dose of study treatment to the first documentation of objective tumor response that is subsequently confirmed. For patients proceeding from PR to CR, the onset of PR was taken as the onset of response.

Duration of objective tumor response was defined as the time from the first documentation of objective tumor response that is subsequently confirmed to the date of tumor progression, or the date of death due to cancer or all unknown causes, or the date of initiation of other anti-tumor therapy after the first on study treatment assessment in the absence of documented disease progression, or the date of withdrawal from the trial due to unknown reasons, whichever comes first. Patients still on study treatment, or in follow-up in the absence of progressive disease (PD), or lost to follow-up in the absence of PD, or who died of non-cancer related causes were censored at the date of the last non-PD tumor assessment.

Survival Follow-up:

Information on survival status and disease progression was collected by clinic visit or telephone contact every 3 months for up to 2 years from the start of therapy and was included on the case report form.

Reviewer comment: Time-to- event endpoints including TTP, PFS and overall survival (OS) are considered exploratory when performed in a single-arm trial.

Radiographic assessments:

- CT/MRI of the chest, abdomen, and pelvis was performed at baseline (within 28 days prior to initiating treatment), day 28-36 of cycles 1, 2, 4, 6 and 8 and end of treatment/withdrawal. All patients with CR or PR require confirmation of response 4-6 weeks after initial documentation of response.
- Bone scan was performed at baseline. If negative, no further bone scans were required unless symptoms suggestive of bone metastases developed. Patients with bone metastases had follow-up bone scans at the same interval as CT/MRI.
- The same method and technique of assessment was used to follow-up documented lesions. When a lesion was assessable both clinically and radiographically, radiographic assessment was preferred. All measurements were made using calipers/ruler in metric notation.
- Verification of responders by a third party imaging core laboratory was specified in the protocol. Since only those patients assessed by investigators to be responders were sent to [] the reviewers were not blinded to the investigators assessment. Two radiologists reviewed each submitted case; in the event of a disagreement, a third radiologist was asked to adjudicate.

Statistical Methods:

The study was designed to test the null hypothesis that the true objective response rate was $\leq 5\%$ versus the alternative hypothesis that the true response rate is $\geq 15\%$. With an alpha level of 5% and 85% power, a total of 63 treated patients were required to evaluate objective response rate. A two-stage design was used to ensure enrollment of enough patients to assess the primary endpoint but to minimize patient exposure to drug if anti-tumor activity was minimal or absent. Therefore, an assessment of response rate after 38 patients was defined in the protocol. If at that time ≤ 1 patient had a response, the study was to be terminated. If ≥ 2 responses were observed, an additional 25 patients were to be enrolled for a total of 63 patients. At the end of the study, if ≥ 7 responses were observed, the null hypothesis was to be rejected and further study in this patient population was felt to be warranted.

The study population for safety and efficacy analyses was defined as all patients enrolled in the study that received at least 1 dose of study medication. All patients who had evaluable pharmacokinetic (PK) data on at least 1 study day were included in the PK population. Descriptive statistics are presented for patient population, efficacy, and safety parameters. Descriptive statistics for continuous variables include the number of observations, mean, standard deviation, minimum and maximum values, and 95% confidence interval (CI) as appropriate; descriptive statistics for continuous variables include number and percent. For time-to-event variables, observations were censored according to the Kaplan-Meier technique.

Protocol Amendments/Study Landmarks—Study 014:

September 20, 2002
Original protocol

November 13, 2002

Protocol revised as follows:

- Reduced starting dose from 75 mg to 50 mg based on updated safety data from other trials
- Modified eligibility criteria to exclude patients with left ventricular dysfunction or history of extensive anthracycline exposure or trastuzumab exposure
- Increased monitoring for LV dysfunction
- Updated safety information in protocol text
- Allowed dose escalation for patients meeting defined criteria
- Allowed dose reductions for patients with unacceptable toxicity
- Added additional PK sampling
- Added a Data Safety Monitoring Plan

January 28, 2003

First subject begins therapy

June 24 and 25, 2003

Protocol amendments 1 and 2

- Clarified baseline ACTH interpretation
- Encouraged investigators to discuss dermatologic symptoms with patients to determine need for dose reductions
- Changes to laboratory monitoring , frequency of PK and biomarkers
- Removed exclusion criteria for prior anthracycline and trastuzumab exposure
- Added -2 dose level (25 mg)

July 23, 2003

Last subject begins protocol therapy

August 23, 2004

Last subject visit

Reviewer comment on study populations and efficacy analyses:

The smaller study, 014, included patients with metastatic renal cell carcinoma regardless of histology (e.g. clear cell vs. chromophobe, papillary or collecting duct type). Approximately 85% of patients on this study had clear cell histology, which is the most common subtype of renal cell carcinoma. The population studied in the larger of the two submitted trials (1006) included patients with metastatic renal cell carcinoma with at least some component of clear cell histology (approximately 75-85% of all patients with RCC). Patients with clear cell histology have highly vascular tumors that over-express a number of pro-angiogenic growth factors including vascular endothelial growth factor (VEGF) and thus may be more likely to respond to agents which inhibit the function of VEGF receptors and other pro-angiogenic receptor tyrosine kinases.

Study 014 required that patients have failed one prior cytokine-based therapy as evidenced by either disease progression or unacceptable toxicity. No data were collected on this study to evaluate the percentage of patients qualifying due to cytokine intolerance, but an estimate by the sponsor based the number of patients with early discontinuation of prior cytokine therapy is that approximately 8% of enrolled patients were intolerant. No time point for the interval between therapy and disease progression was included in this definition of cytokine failure. In contrast, study 1006 required that patients failed one cytokine-based therapy (as demonstrated by radiographic evidence of progressive disease within 9 months of the completion of therapy). Both protocols excluded patients who had received any systemic therapy other than one cytokine-based therapy.

While the differences in eligibility are minor, the studies are considered individually in terms of efficacy because of a small, but significant, difference in the primary endpoint analysis. The primary endpoint of both trials was ORR. However, this endpoint was based on investigator assessment in 014 and on third-party review for 1006. This is likely the explanation for the approximately 10% difference in ORR between the two trials. In fact, if one looks at the ORR of both studies using the same assessor (e.g. either the investigators or the third-party reviewer), the response rates are nearly identical.

6.1.4 Efficacy Findings

All 106 patients enrolled on study 1006 and 63 patients enrolled on study 014 are included in the intent-to-treat (ITT) populations for the efficacy analysis of sunitinib for cytokine-refractory metastatic renal cell carcinoma. The demographics, tumor characteristics and prior treatment for patients enrolled in study 1006 are described for both the ITT population (all patients enrolled on study) and the modified ITT (MITT) population (all patients who had retrospective confirmation of progression while receiving or within 9 months of completing cytokine therapy).

Study 1006:

Table 8: Patient Demographics—1006

Variable	ITT N=106	MITT N=97
Age (years), median (range)	56 (32-79)	56 (32-79)
Age (years), n (%)		
<65	87 (82.1)	79 (81.4)
≥65	19 (17.9)	18 (18.6)
Sex, n (%)		
Male	67 (63.2)	64 (66.0)
Female	39 (36.8)	33 (34.0)
Race, n (%)		
White	100 (94.3)	92 (94.8)
Asian	2 (1.9)	1 (1.0)
Not listed	4 (3.8)	4 (4.1)

Table 9: Patient Tumor Characteristics—1006

Parameter	ITT N=106	MITT N=97
Tumor type, n (%)		
Renal cell carcinoma*	106 (100)	97 (100)
Histology, n (%)		
Clear cell	97 (91.5)	90 (92.8)
Clear cell/granular	4 (3.8)	3 (3.1)
Clear cell/sarcomatoid	3 (2.8)	2 (2.1)
Clear cell/chromophobe	2 (1.9)	2 (2.1)
Time from diagnosis to Study entry (weeks), median (range)	79.4 (10-918)	79.1 (10-918)
Sites of disease, n (%)		
Lung	86 (81.1)	78 (80.4)
Lymph nodes	62 (58.5)	56 (57.7)
Liver	29 (27.4)	27 (27.8)
Bone	27 (25.5)	25 (25.8)
Local recurrence	21 (19.8)	20 (20.6)
Soft tissue	20 (18.9)	18 (18.6)
Visceral**	20 (18.9)	18 (18.6)
Peritoneal	13 (12.3)	13 (13.4)
Pleural Effusion	10 (9.4)	9 (9.3)

*all patients had a diagnosis of renal cell carcinoma at study entry, however, one patient was later discovered to have seminoma; this pt. is included in both the ITT and MITT populations

** included adrenal, pancreatic, contralateral kidney and gastric

Table 10: Prior Therapy--1006

Prior Therapy	ITT N=106	MITT N=97
Surgery, n (%)		
Nephrectomy	106 (100)	97 (100)
Radiation Therapy	20 (18.9)	18 (18.6)
Systemic Therapy, n (%)		
Cytokine-based	106 (100)	97 (100)
IFN- α	47 (44.3)	42 (43.3)
IL-2	50 (47.2)	47 (48.5)
IFN + IL-2*	9 (8.5)	8 (8.2)

*one patient received both agents individually

As required by the protocol, all patients had received a prior nephrectomy. All patients had also received at least one prior cytokine therapy (one patient had both IL-2 and IFN individually). Additionally, approximately 20% had received prior radiation to one or more sites of disease.

The demographics, tumor characteristics and prior therapy are similar in the ITT and MITT populations.

The median duration of treatment was 5.5 months (range 0.8-11.2).

The primary endpoint was response rate, as determined by third-party [] review of the imaging data. Images were digitally submitted to [] and read by two independent radiologists. In the event of discordance between the two readings, a third radiologist (who was not blinded to the reading of the first 2) adjudicated. This adjudication consisted of reviewing the first two readings, and determining which reading accurately reflected the best overall response, date of response and date of progression. In the event that the adjudicator disagreed with both readers, the adjudicator's reading was considered the final reported reading.

Tumor response was determined according to RECIST. Briefly, the RECIST response categories are defined as follows:

Target Lesions

- **Complete response (CR)** was defined as the disappearance of all target lesions.
- **Partial response (PR)** was defined as a $\geq 30\%$ decrease in the sum of the longest diameters of the target lesions taking as a reference the baseline sum of the longest diameters.
- **Progressive disease (PD)** was defined as a $\geq 20\%$ increase in the sum of the longest diameters of the target lesions taking as a reference the smallest sum of the longest diameters recorded since the treatment started, or the appearance of one or more new lesions.
- **Stable disease (SD)** was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest diameters since the treatment started.

Non-Target Lesions

- **Complete response (CR)** was defined as the disappearance of all non-target lesions.
- **Incomplete response/SD** was defined as a persistence of ≥ 1 non-target lesions.
- **Progressive disease (PD)** was defined as unequivocal progression of existing non-target lesions, or the appearance of ≥ 1 new lesions. The cytological confirmation of the neoplastic origin of any effusion that appeared or worsened during treatment when the measurable tumor had met criteria for response or stable disease was mandatory to differentiate between response or stable disease and progressive disease.

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors had to be confirmed by repeat studies that were performed ≥ 4 weeks after the criteria for response were first met. In the case of SD, follow-up measurements were required to have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

All 106 patients had a baseline assessment and all had a diagnosis of MRCC with some component of clear cell histology, as required by the protocol. Therefore, all patients were eligible for consideration in the ITT population (as noted in the table above, one patient had a histologic diagnosis of MRCC at screening, but was later found to have seminoma. This patient is included in the ITT analysis.)

The RR as determined by [redacted] was 25.5% (27/106) [95% CI 17.5 to 34.9%], all were PRs. The duration of response (DR) report was preliminary, as only a small fraction of patients with responses had progressed. At the time of the NDA submission, 4 patients had progressed (15%), and the DR was reported as 27.1 weeks (95% CI 24.4-*). The sponsor reported updated duration of response data at the NDA presentation to DDOP on September 22, 2005. At that time, they presented a median DR as assessed by the investigators of 43 weeks (95% CI 34.3, upper boundary could not be estimated). No data regarding the [redacted] DR was provided, and tabulations of the data in support of the update were not provided for review.

The sponsor's analysis of the primary endpoint is described in Table 11.

Table 11: Response Data for the Primary Endpoint Analysis of ORR on Study 1006—Sponsor's Analysis

Patients with Baseline Assessment, n (%)	106 (100)
Patients with Measurable Disease at Baseline, n (%)	105 (99.1)
Best Overall Response, n (%)	
Complete Response	0 (0.0)
Partial Response	27 (25.5)
Stable Disease	65 (61.3)
Progressive Disease	14 (13.2)
Objective Response Rate (CR+PR), % (95% CI)	25.5 (17.5-34.9)

The sponsor also reported several secondary ORR endpoints, including the investigator assessment of ORR in both the ITT and MITT populations, and the core imaging laboratory assessment of ORR in the MITT population. These data are summarized in Table 12.

Table 12: Secondary ORR Endpoints—Sponsor's Analysis

ORR, Investigator assessment ITT (n=106)	35.8
MITT (n=97)	38.1
ORR, [redacted] assessment MITT	24.7

These analyses are supportive of the efficacy data for the primary endpoint analysis, with a somewhat more favorable response rate reported by the investigators in comparison to the third-party reviewers. Responses in the MITT population, those with retrospectively confirmed documentation of progressive disease following cytokine therapy, are not substantially different than those in the ITT population.

Additionally, the sponsor conducted several logistic regression analyses to determine the effect of baseline factors on ORR in both the ITT and MITT populations, as assessed by both the investigators and the core imaging laboratory. Baseline factors examined individually included age (< 65 vs. ≥ 65 years), gender (male vs. female), ECOG performance status (0 vs. 1), hemoglobin (<LLN vs. ≥ LLN), corrected calcium (>10 mg/dl or ≤ 10 mg/dl) and time since diagnosis (< 6 months vs. ≥ 6 months). The results in all populations studied were similar; only the results of the ITT population as assessed by third-party review are presented here.

Table 13: Result of Logistic Regression of Tumor Response Controlling for Individual Baseline Factors One at a Time, Core Radiology Laboratory Assessment on the ITT Population

Baseline factor	Odds Ratio	95 % CI	p-value
Age (< 65 vs. ≥ 65 years)	1.348	0.405-4.481	0.627
Gender (male vs. female)	1.945	0.737-5.136	0.179
ECOG (0 vs. 1)	1.900	0.761-4.744	0.169
Hemoglobin (<LLN vs. ≥ LLN)	0.170	0.054-0.535	0.002
Corrected Calcium (>10 mg/dl or ≤ 10 mg/dl)	1.481	0.129-17.012	0.753
Time since diagnosis (< 6 months vs. ≥ 6 months)	0.971	0.285-3.312	0.963

In this analysis, the baseline hemoglobin was found to have a significant effect on the likelihood of tumor response; age, gender, ECOG performance status, calcium and the time since diagnosis did not effect the likelihood of response.

Several time-to-event analyses were conducted by the sponsor as noted in section 6.1.3. Because there is no control arm against which to compare these data, an analysis of the drug effect (versus the natural history of the disease) on these endpoints can not be adequately performed in a single-arm trial. This problem applies especially to renal cell carcinoma, a disease with a very variable natural history which can include long periods of stable disease even in the absence of anti-tumor therapies. Such time-to-event endpoints are therefore considered exploratory when performed in single-arm trials. The data from the sponsor are reported here; these data were not confirmed by the FDA reviewer

The median TTP for the ITT population (using the core radiology assessments and based on 36 progressions) was 34.0 weeks, with a 95% CI of 24.1 to 36.0 weeks. The median PFS for the ITT population (based on 39 events) was also 34.0 weeks, with a 95% CI of 23.3 to 36.0 weeks. The median DR could not be reliably estimated because of 27 responses experienced during the study, 23 were ongoing at the time of this report.

At the time of this interim report, > 80% of the ITT population was alive, so OS could not be estimated. There were insufficient data to estimate survival at 1 or 2 years.

FDA analysis:

Analysis of the primary endpoint for the 1006 trial included verification of response based on lesion measurements in the database as well as an audit of the [] radiology review. The clinical reviewer focused on the analysis of the primary endpoint, ORR as reported by the []

core imaging laboratory, and the duration of response. Review of responses in the database addressed the following questions:

- Did the documentation of the radiographic data support response as defined by RECIST criteria? Specifically,
 - Was response confirmed based upon at least a 30% reduction in the sum of the longest diameters of all target lesions?
 - Did the evaluation of non-target lesions support a lack of progression?
 - Was there an absence of new lesions?
- Did the reported times of response and progression correlate with reported response dates and progression dates?

As “stable disease” is not considered in the determination of ORR, and is not a valid measure of anti-tumor activity in a single-arm trial, this analysis focused only on responders.

All 27 reported PRs were evaluated by this method, and response was verified in all cases except one. One patient (32) was reported as a responder, and review of the data base demonstrated that only reader 1 had documented a response based on the measurements provided. The second reader had prospectively identified 8 target lesions. The clinical reviewer noted that the 8th lesion, which did not change in size over the 3 time points in which it was evaluated, was not evaluated in subsequent cycles. An analysis of the sum of the longest diameters of the target lesions excluding the 8th lesion was consistent with a PR and with the first reader’s interpretation. The sponsor was asked to provide an explanation for why this lesion was dropped from the analysis.

Their reply is below.

“Reader 2 picked 8 target lesions at baseline. After Cycle 3, Reader 2 decided this lesion (target lesion 8) was a benign liver cyst and therefore it should not have been included as a target lesion. This lesion was dropped as a target lesion; therefore there are no measurements for lesion #8 starting at Cycle 4. Based on the fact that this lesion should not have been picked at baseline as a target lesion, the reader retrospectively calculated the sum of the longest dimension (SLD) for each time point and assessed response on the basis of the corrected SLD. This change was made according to the Use Case Scenario for Dropping a Target or a Non-Target Lesion. This scenario was the subject of past discussions between [redacted] and the Division of Medical Imaging and Radiopharmaceuticals.”

Dr. Tom Ju, the radiology consultant from the FDA Division of Medical Imaging and Hematology provided a copy of the Use Case Scenarios referenced above by the sponsor (dated February 28, 2005). The first scenario outlined in this document describes the procedure for removing a lesion from the analysis in the event that evidence arises that a designated lesion is in fact benign. An example of this scenario presented a soft tissue “mass” adjacent to the bladder which on subsequent scans is noted to fill with oral contrast, and therefore represents a previously un-opacified loop of bowel rather than a metastasis. In this case, the lesion can be excluded retrospectively from analysis of ORR. The situation for patient 32 is somewhat different in that there was no new evidence that this lesion was benign. As a result, it is unclear what evidence (other than a lack of change in size) prompted the radiologist to consider the

lesion benign. Dr. Ju was asked to provide input on the likelihood that this lesion was malignant. He agreed with the interpretation that this was a benign liver lesion. As a result, this reviewer agrees with the interpretation of the sponsor that this patient achieved a PR.

An FDA radiology audit, performed by Drs. Tom Ju and Lydia Martynec of FDA's Division of Medical Imaging and Hematology Products, included 55 of the 106 (52%) patients in the intent-to-treat population. Their review verified the measurements of all target lesions and the descriptions of non-target lesions of the independent readers for all the reviewed subjects. No significant discrepancies were noted and inter-reader variability was deemed acceptable.

The clinical review therefore confirms a response rate of 25.5% (27/106) as analyzed by the core imaging laboratory for study 1006.

Study 014:

Table 14: Patient Demographics--Study 014

Variable	N=63
Age (years), median (range)	60 (24-87)
Age (years), n (%)	
<65	43 (68.3)
≥65	20 (31.7)
Sex, n (%)	
Male	43 (68.3)
Female	20 (31.7)
Race, n (%)	
White	54 (85.7)
Asian	4 (6.3)
Black	3 (4.8)
Unknown	2 (3.2)

The mean age of patients on study was 60, with approximately one-third of patients over age 65. Two-thirds of patients were male (reflecting a higher incidence of RCC among males), and 85% were white.

Table 15: Deviations from Inclusion/Exclusion Criteria on Study 014—Sponsor's Analysis

Criteria	Number of Patients (%)
Prior treatment with systemic therapy other than one cytokine-based regimen* or surgery or radiation within 4 weeks of study therapy	3
ECOG Performance status ≥2	1
Inadequate organ function	12

*all patients received a prior cytokine-based regimen; violations to this criterion consisted of patients receiving more than one prior regimen (2) or receiving radiation less than 4 weeks prior to initiation of therapy (1).

FDA analysis of Eligibility Criteria:

Prior therapy:

All patients received at least one prior cytokine-based regimen. This included IFN in 36 patients (57%), IL-2 in 19 patients (30%) and the combination in 8 patients (13%). Other therapies received in combination with cytokines (and therefore not in violation of the eligibility criteria) included celecoxib (3), thalidomide (2), CCI-779 (2), retinoic acid (1), FUDR (1), and 5FU (1). One patient also received Megace as a single agent in addition to a cytokine therapy, this was correctly listed by the sponsor as a protocol violation.

Two patients received adjuvant therapies in addition to one regimen for metastatic disease; because these treatments were administered as adjuvant therapy and not for metastatic disease, they were not considered to be protocol violations by the sponsor.

2 patients (21 and 38) completed XRT 27 days prior to starting study drug, despite a protocol-specified minimum of 28 days. One of these patients had been given a protocol exemption by the sponsor.

Table 16: Deviations from Inclusion/Exclusion Criteria on Study 014—FDA Analysis

Criteria	Number of Patients (%)
Prior treatment with systemic therapy other than one cytokine-based regimen*	4
Surgery or radiation within 4 weeks of study therapy	2
ECOG Performance status ≥ 2	1
Known brain metastases	1
Inadequate organ function	12

Appears This Way
On Original

Table 17: Tumor Characteristics—Study 014

Parameter	N=63
Tumor type, n (%)	
Renal cell carcinoma	63 (100)
Histology, n (%)	
Clear cell*	54 (85.7)
Papillary	4 (6.3)
Sarcomatoid	2 (3.2)
Unclassified/unknown	3 (4.8)
Time from diagnosis to Study entry (weeks), median (range)	89.9 (10.6-1473.3)
Sites of disease, n (%)	
Lung	51 (81)
Lymph nodes	34 (54)
Bone	32 (51)
Local recurrence	13 (21)
Soft tissue	13 (21)
Liver	10 (16)
Visceral	10 (16)
Primary Tumor	4 (6.3)

*includes those with mixed histology
with a clear cell component (n=5)

All patients had a diagnosis of renal cell carcinoma, and the majority had some component of clear cell histology. Major sites of disease included lung, lymph nodes, and bone. Local and soft tissue disease were also present in about 20% of patients, while metastases to liver and other visceral organs were present in only about 10% of patients. Other sites of disease included pleural effusion (9), adrenal (5), kidney (3), skin (2), peritoneal (2), thyroid (1), breast (1), ileocecal (1) and pleural (1). In violation of the eligibility criteria, one patient had known brain metastases.

Table 18: Prior Therapy—Study 014

Prior Therapy	N=63
Surgery, n (%)	
Nephrectomy	58 (92)
Metastatectomy only	1 (2)
Biopsy only	4 (6)
Radiation Therapy	25 (40)
Systemic Therapy, n (%)	
Cytokine-based	63 (100)
IFN- α	36 (57)
IL-2	19 (30)
IFN + IL-2	8 (13)
Non-cytokine based	1 (2)

All patients received at least one prior cytokine-based regimen. This included IFN in 36 patients (57%), IL-2 in 19 patients (30%) and the combination in 8 patients (13%). Other therapies received in combination with cytokines included celecoxib (3), thalidomide (2), CCI-779 (2), retinoic acid (1), FUDR (1), and 5FU (1). One patient received single-agent Megace in addition to one prior cytokine therapy. This patient received a protocol exemption from the sponsor to participate in the study.

Best response to cytokine therapy included 1 CR, and 3 PR. All responses except one PR occurred with IL-2 based therapy, and one PR occurred with the combination of IFN+CCI 779. 43 patients had PD as the best response, 15 patients had SD and 2 unknown.

Response data (014):

The median duration of treatment was 7.7 months (range 0.2-16.1).

The number (%) of patients who achieved an objective response (CR or PR) was summarized along with the corresponding 95% confidence interval.

The sponsor's analysis of the primary endpoint, response rate (CR+PR) as assessed by the investigators, is reported below.

All assignments of response were based on the RECIST criteria as described on pp. 41-42. Unconfirmed partial responses (those with only one assessment documenting response) were reported as stable disease. If two assessments documenting partial response were separated by an assessment which documented stable disease or was not evaluable, this was considered a confirmed response, as long as at least 4 weeks elapsed between the initial response documentation and the confirmatory scan.

Table 19: Sponsor's Analysis of ORR—Study 014 (sponsor's study report p. 70)

Summary of Best Overall Tumor Response

Variable	Total (N = 63)
Best confirmed overall response [n (%)]	
Complete response	0 (0.0)
Partial response	23 (37)
Stable disease	24 (38)
Progressive disease	7 (11)
Not evaluable	6 (10)
Missing	3 (5)
Response rate (CR + PR) [n (%)]	23 (37)
Duration of SD [n (%)]	
≥ 3 – < 6 months	9 (14)
≥ 6 months	9 (14)

Twenty-three patients (37%; 95% CI: 24.7 – 49.6) were assessed by the investigators as achieving a partial response to study therapy. There were no complete responses reported. Best response of stable disease was reported for 24 (38%) of patients, and progressive disease as best response was seen in 7 patients (11%); the response was missing for 3 patients (5%), and 6 patients (11%) were not evaluable for response.

Eighteen patients who completed therapy on study 014 enrolled in one of two continuation studies. These patients included 14 patients who had achieved a PR, 3 patients who had stable disease, and one patient who was considered “not evaluable” by the investigator’s assessment based upon incomplete assessment of non-target lesions identified at baseline but who had achieved a PR based upon the [redacted] review.

For the 23 patients who experienced a PR, the median time to tumor response was 10.1 weeks (95% CI: 10.0 – 21.7) and the median duration of tumor response was 54.0 weeks (95% CI: 34.3-70.1).

The sponsor also calculated several “time-to-event” endpoints as secondary analyses (time to progression, progression-free survival, and overall survival.) As noted for study 1006, in the absence of a control arm against which to compare these data, time-to-event endpoints are considered exploratory. The data from the sponsor are presented here; these endpoints were not independently assessed by the reviewer.

The median time to tumor progression was 37.7 weeks (95% CI: 24.0 – 46.4) and the median progression-free survival was 37.7 weeks (95% CI: 24.0-46.4). The median overall survival was 71.1 weeks (95% CI: 46.7, upper CI could not be determined).

The images from the twenty-three patients assessed by the investigator as having achieved a PR, and those of two additional patients (see below) were submitted to a third-party reviewer [redacted] for confirmation of response. 16 patients (25.4%) had confirmation of partial response through this review process. Three patients were assessed by [redacted] as unconfirmed PR, these patients and six others (nine total) were assessed as having stable disease. Independent radiographic review was not performed for patients assessed by investigators as having SD or PD as a best response.

One patient originally assessed by the investigator as a PR was subsequently discovered to have had incomplete assessments after cycle 2. This patient had lesions on bone scan that were followed through cycle 2, at which point the patient achieved an unconfirmed PR. Subsequent assessments did not include bone scan and therefore the patient was not evaluable for response. The images were sent to [redacted] before the omission of bone scans was discovered. The reviewers at [redacted] recorded this patient as a PR on the basis of the CT scans only (the bone lesions were considered assessable by CT). One additional patient had multiple non-target lesions which were not assessed by the investigator in follow-up scans and was therefore considered not evaluable for response despite initial investigator assessment as a partial response. This patient had a complete assessment following enrollment onto a continuation study and was subsequently confirmed as a PR by [redacted] review. These two patients are not

considered in the primary endpoint, which relies solely on the investigator's assessment of response.

FDA analysis:

Analysis of response rate focused on the investigator reported responses, as this was the pre-specified primary endpoint of the trial.

As in Study 1006, review of responses in the database addressed the following questions:

- Did the documentation of the radiographic data support response as defined by RECIST criteria? Specifically,
 - Was response confirmed based upon at least a 30% reduction in the sum of the longest diameters of all target lesions?
 - Did the evaluation of non-target lesions support a lack of progression?
 - Was there an absence of new lesions?
- Did the reported times of response and progression correlate with reported response dates and progression dates?

For all 23 patients reported as investigator-assessed responders, an evaluation of the sum of the longest dimensions of the target lesions at baseline and in all follow-up scans was conducted to confirm the achievement of response as defined by RECIST. Additionally, in patients in whom one or more target lesions did not meet RECIST criteria for minimum baseline size for measurability (≥ 20 mm by conventional CT/MRI or ≥ 10 mm by spiral CT), analyses including both all reported lesions and the RECIST-qualifying target lesions was performed. Each patient achieving a response had to have at least one further assessment at least four weeks from the original response documentation confirming the response. A review of the non-target lesion assessments was then performed to document any new lesions or clear progression of previously identified non-target lesions; these findings are evidence of progressive disease and are incompatible with response.

This review confirmed all the responses reported by the sponsor as well as the timing of the responses with respect to cycle number. In cases where progression later occurred, these dates were verified as well and all agreed with the sponsor's report.

One patient was initially identified by the clinical reviewer as unevaluable due to an apparent lack of measurable lesions among 5 target lesions identified by both the investigator and the independent reviewer. All the identified lesions were less than the 20 mm required for measurability using conventional CT as the imaging modality. A query to the investigator determined that, although the imaging studies were reported in the CRF and database as conventional CT, they were in fact performed by spiral CT, and thus the reported lesions were evaluable. This was confirmed by Dr. Tom Ju, the consultant from FDA Division of Medical Imaging and Hematology Products who reviewed the films as a consultant.

Dr. Ju also conducted an audit of the [] film reviews. For study 014, only the images of patients assessed as responders were submitted for independent review. Dr. Ju reviewed the radiology core laboratory readings for 14 of the subjects whose data were submitted for review (22% of all patients on study and 60% of the responders.) His review confirmed the [] data with only minor discrepancies which did not alter the results of the efficacy analysis.

Table 20: ORR and Duration of Response on Study 014—FDA Analysis

	N=63
Partial response rate (%) [95% CI]	23 (37) [24.7-49.6]
Duration of response (weeks), median [95% CI]	54.0 [34.3-70.1]

Evaluation of responses by age, gender and race was performed by the review team.

Table 21: ORR by Age, Gender and Race

Variable	Study 1006 N=106	Study 014 N=63
Age		
≤65	23/87 (26.4)	15/43 (34.9)
>65	4/19 (21.1)	8/20 (40.0)
Gender		
Male	20/67 (29.9)	16/43 (37.2)
Female	7/39 (17.9)	7/20 (35.0)
Race		
Caucasian	26/100 (26.0)	22/54 (40.7)
Other	1/6 (16.7)	1/9 (11.1)

No conclusion can be drawn about the likelihood of response based on age: study 1006 has a higher response rate in younger patients while study 014 had more responders among patients over 65. Study 1006 demonstrates a higher response rate among males; the response rate was similar between males and females on study 014. Although the response rate among non-Caucasian patients is low, the number of patients evaluated is too small to permit any conclusions from this data.

Review of the primary efficacy analyses for both studies support the sponsor's conclusions of an ORR of 25.5-37%. Duration of response was measured as a secondary endpoint on both studies and is an important consideration when evaluating the likelihood of benefit of response rate. A summary of the major efficacy findings in the two MRCC trials is shown in Table 22.

Table 22: Summary of Major Efficacy Findings in MRCC

Study	ORR(%)* [95%CI]	DR (weeks) [95% CI]
1006	25.5 [17.5-34.9%]	27.1 [95% CI 24.4-**]
014	37 [24.7 – 49.6%]	54.0 [95% CI: 34.3-70.1]

*Reported for the primary endpoint assessment [] analysis for 1006, investigator analysis for 014)

** Upper boundary could not be calculated due to immaturity of the data

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Two single-arm, open-label phase 2 studies were submitted to support the advanced RCC indication. The two studies enrolled a total of 169 patients. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between the two studies. Approximately 86-94% of patients in the 2 studies were Caucasian. Men comprised 65% of the population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients were required to have metastatic disease, and to have failed one prior cytokine-based therapy. The 014 study enrolled patients with MRCC regardless of histology, while the 1006 study required at least some component of clear cell histology, the most common histologic subtype of renal cell carcinoma (approximately 85% of all cases). Most patients had undergone nephrectomy (92% on 014, 100% on 1006). Prior cytokine therapy included IL-2 and/or IFN- α .

Patients in both studies received sunitinib at 50 mg daily on a 4 weeks on/2 weeks off schedule, for a cycle length of 6 weeks. Median duration of treatment was 34 weeks for study 014 (including participation in the continuation studies) and 23.6 weeks in study 1006 at the time of data cutoff.

The primary efficacy endpoint was ORR using RECIST criteria, as measured by the investigator (014) or the [] core imaging laboratory (1006). ORR was measured in the intention-to-treat (ITT) population for both studies, and in a modified ITT (MITT population) consisting of patients with retrospective core imaging laboratory confirmation of prior disease progression in study 1006. Duration of response was assessed in both studies as a secondary endpoint. All responses on both studies were partial responses. The ORR was 25.5% (95% CI 17.5-34.9%) for study 1006, and 37% (95% CI 24.7-49.6%) for study 014. These results were supported by three secondary analyses of ORR in the 1006 trial: the investigator assessed ORR in both the ITT and MITT populations, and the third-party radiology core laboratory assessment of ORR in the MITT population.

Duration of response, measured from the time of first documentation of a response to the first documentation of progression, was a secondary endpoint on both studies. DR data were immature for study 1006: with 4/27 (15%) progression events occurring, the median DR was 27.1 weeks (95% CI 24.4; upper limit could not be calculated). On study 014, 13/23 (56.5%) events had occurred with a median DR of 54.0 weeks (95% CI: 34.3-70.1).

Tumor responses in the second-line treatment of MRCC are rare, with historical response rates of $\leq 5\%$ with either cytokine or cytotoxic therapies. Response rates of 25-37% have not previously been demonstrated with any agent in MRCC, in either the second-line or first-line setting. Recently, sorafenib was given regular approval for the treatment of advanced renal cell carcinoma based on an improvement in progression-free survival (PFS) demonstrated in a randomized trial. Patients receiving sorafenib had a median PFS of 167 days while patients receiving placebo had a median PFS of 84 days; the hazard ratio for progression was 0.44 (95% CI 0.35, 0.55). The response rate in both arms was negligible (2% for sorafenib-treated patients vs. 0% for placebo-treated patients). The substantial response rate of sunitinib may provide a benefit over sorafenib in some advanced renal cell carcinoma patients, particularly those with bulky disease in whom cytoreduction may be an important goal of treatment.

The demonstration of an impressive response rate with sunitinib in MRCC is supported by a significant duration of response. While an effect on an endpoint of known clinical benefit such as survival or symptom benefit has not been demonstrated for sunitinib in MRCC, the combination of response rate and response duration demonstrated in this application is reasonably likely to predict a clinical benefit in patients with advanced renal cell carcinoma.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review focused on the two sunitinib MRCC trials 1006 and 014 as the most relevant studies to evaluate safety for the proposed indication. Data from other studies included in the NDA submission, in particular the phase 3 trial in GIST which contains the only placebo-controlled data, were reviewed when the reviewer felt that they were pertinent to this indication and where they might provide additional information not available in the two single-arm studies. These studies were reviewed separately by Dr. Edwin Rock under NDA 21-938.

Safety was evaluated in the two MRCC studies in the "intent-to-treat" population, which in this case includes all patients enrolled in either study, a total of 169 patients. Demographics were very similar across the two study populations.

In addition to the standard analyses of adverse events, several potential safety issues identified in preclinical studies were examined. These included cardiac toxicity, as manifested by changes in left ventricular ejection fraction, congestive heart failure, cardiac enzyme changes, ischemic events and QT prolongation; adrenal toxicity as manifested by changes in ACTH stimulation

testing, adverse event reports of adrenal insufficiency, and clinical symptoms and laboratory evidence of adrenal insufficiency; and pancreatic toxicity as manifested by amylase and lipase elevations and reports of pancreatitis.

7.1.1 Deaths

On-study deaths were defined as those occurring within 30 days (014) or 28 days (1006) of discontinuation of the study drug.

The CRFs and patient narratives for all patients who died on study were reviewed.

Study 1006:

Eight patients died within 28 days of discontinuing study therapy on 1006. One of these deaths was attributed to study drug. This was a 60 year old female patient who went to the emergency room on day 30 of cycle 1 complaining of shortness of breath and cold hands. ECG and cardiac enzymes were consistent with a diagnosis of myocardial infarction. The patient subsequently was intubated for respiratory failure and died from cardio-respiratory arrest. Her prior history included emphysema and hypertension but no history of coronary artery disease.

Four patient's deaths were attributed to disease progression; in the remaining three cases, the cause of death was listed as renal failure (1), pleural effusion (1), and arrhythmia (1). All were considered related to malignant disease progression by the investigator.

In the first case, the patient was a 42 year old woman who developed symptomatic ascites, nausea and vomiting, and renal failure. She underwent abdominal paracentesis twice and total parenteral nutrition, but died of renal failure about two weeks later. In the second case, the patient was a 47 year old man who was noted to have progressive disease following one cycle of study therapy. Approximately three weeks later, he developed worsening of a pleural effusion secondary to progression of pulmonary metastases leading to his death.

Finally, a 62 year old woman on the last day of treatment of the first cycle of study therapy developed petechiae, purpura and stomatitis. She was admitted to the hospital, and the next day developed fever; E. coli bacteremia was documented by blood culture. The infection, fever, stomatitis and cytopenias including thrombocytopenia, anemia and leucopenia were all considered related to study drug. The patient also developed acute renal failure (the time course in relation to hospitalization is unclear), and subsequent arrhythmia which resulted in her death; these events were considered related to underlying disease.

Study 014:

One subject death occurred on-study on 014. Following six cycles of therapy, this 58 year old male patient was found to have progressive disease on imaging performed per protocol. The patient discontinued study therapy at that time and died two weeks later. The death was attributed to metastatic renal cell carcinoma.

7.1.2 Other Serious Adverse Events

A serious adverse event was defined as any adverse event at any dose that:

- Resulted in death (described in section 7.1.1);
- Was life-threatening;
- Required in-patient hospitalization or prolongation of existing hospitalization;
- Resulted in a persistent or significant disability/incapacity; or
- Resulted in congenital anomaly/birth defect.
- Other important medical events were considered serious adverse events if they jeopardized the subject or required medical or surgical intervention to prevent one of the outcomes listed in this definition.

Study 1006:

All serious adverse events were summarized by MedDRA SOC and preferred term. Twenty-nine patients (27%) experienced 72 SAEs (including deaths).

SAEs reported in more than one patient included: vomiting (2), disease progression (4), abdominal pain (2), pneumonia (2), dehydration (5), failure to thrive (2), convulsions NOS (2), dyspnea (2), pleural effusion (3), renal failure (4—2 acute, 2 NOS).

The most common system organ classes (SOC) with reported SAEs were gastrointestinal (7), general disorders (6), infections and infestations (5), investigations (5), metabolism and nutrition disorders (8), and respiratory, thoracic and mediastinal disorders (5).

There was one SAE report of acute adrenal insufficiency which is described in section 7.1.4.

Cardiac SAEs included (one each): myocardial ischemia, myocardial infarction (reported above as a death), and arrhythmia.

Other SAEs reported in a single patient included:

Blood: thrombocytopenia

GI: diarrhea, nausea, pancreatitis, perirectal abscess, rectal hemorrhage, stomatitis

General: chest pain, peripheral edema, systemic inflammatory response syndrome

Infections: Infection NOS, sepsis, staphylococcal infection, urinary tract infection

Investigations: ejection fraction decreased, INR increased, oxygen saturation decreased, platelet count decreased, troponin I increased

Metabolism/Nutrition: hypercalcemia

Musculoskeletal/Connective Tissue: arthralgia, buttock pain, chest wall pain

Neoplasms: myelodysplastic syndrome

Nervous System: hypoglycemic coma, syncope

Psychiatric: depressed mood, mental status changes

Respiratory: cough, lung disorder, pulmonary embolism, respiratory arrest

Skin: purpura

Surgical/Medical Procedures: operation
Vascular Disorders: petechiae

Study 014:

All serious adverse events were summarized by MedDRA SOC and preferred term. In this protocol, all relevant cardiovascular adverse events were required to be reported as serious, even if there were no clinical symptoms. Twenty-nine patients (46%) experienced a total of 60 SAEs.

The following events were reported as SAEs in more than one patient: pain NOS (3), sepsis NOS (2), ejection fraction abnormal (3), speech disorder (2), dyspnea NOS (5), pleural effusion (2). One additional patient experienced an adverse event of ejection fraction abnormal; the investigator did not report the event as an SAE because he did not consider the grade 2 event to be a "relevant cardiovascular event."

Other SAEs occurring in a single patient included myocardial ischemia and coronary artery disease (in the same patient), blurred vision, abdominal pain, small intestinal obstruction, fatigue, pyrexia, weakness, acute cholecystitis, infection NOS, sinusitis NOS, lung collapse, hip fracture, arthralgia aggravated, hepatic neoplasm, confusion, acute glomerulonephritis, renal failure NOS, pneumothorax NOS, skin lesion NOS, failure to thrive, hypertension NOS, pulmonary embolism and thrombosis NOS.

Eight neurologic events occurred in 4 patients and included drooling, facial palsy, neurologic disorder NOS, peripheral motor neuropathy, peripheral sensory neuropathy, spinal cord compression as well as the two instances of speech disorder listed above.

Laboratory abnormalities reported as SAEs included (one each): prolonged prothrombin time, prolonged partial thromboplastin time, alanine aminotransferase increased, blood CK-MB increased, blood TSH increased, cardiac troponin I increased, and hyponatremia.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Thirteen patients (12%) on study 1006 and eleven patients (18%) on study 014 withdrew due to adverse events. Patients who discontinued the study with the termination reason 'lack of efficacy' (disease progression) were not counted as having discontinued because of adverse events, even if they have adverse events with an action taken of 'drug discontinued permanently,' because the adverse events leading to study drug discontinuation are considered to be secondary to the disease progression.

7.1.3.2 Adverse events associated with dropouts

Study 1006:

Thirteen patients (12%) had a total of 17 adverse events for which the “action taken” was discontinuation of study drug. Four of these patients had grade 5 events and are listed under deaths (1 cardiorespiratory arrest, 2 disease progression, and 1 renal failure). There were no discrepancies between patients listed by the sponsor as withdrawals due to AEs and those identified by the clinical reviewer.

Events leading to discontinuation for the other nine patients are shown in Table 23.

Table 23: Adverse Events Leading to Drug Discontinuation on Study 1006

Pt. number	Adverse Event 1	Grade	Adverse Event 2	Grade
8	Fatigue	3		
13	MDS	4	Thrombocytopenia	4
23	Nausea	2	Vomiting	2
25	Dehydration	3	Nausea	1
26	Tumor resection	4		
47	Epistaxis	1		
53	Wound complication	3		
75	Increased lipase	3		
82	Dyspnea	3		

Study 014:

The sponsor reported 11 patient withdrawals due to adverse events. Three discrepancies were identified between the sponsor’s report of patients withdrawn due to adverse events and the adverse event database report where “action taken” was discontinuation of the drug. In the case of patient 4, the sponsor reported this as a withdrawal from treatment but this was not verified in the database. Review of the CRF supported the sponsor’s conclusion that the patient was withdrawn due to an AE. Patients 11 and 58 were not reported by the sponsor as withdrawals due to AEs, but were listed as withdrawals due to AEs in the AE database. Review of the CRF for patient 58 supports treatment withdrawal due to motor and sensory neuropathy. The investigator who treated patient 11 reported ‘lack of efficacy’ as the reason for treatment withdrawal, rather than an AE. The AE listed in the database as the reason for withdrawal was ‘small bowel obstruction’, which the CRF confirms was due to metastases. Thus, this patient was not included in the reviewer’s table. The reasons for withdrawal for the 12 patients are listed in table 24.

Table 24: Adverse Events Leading to Drug Discontinuation on Study 014

Pt. number	Adverse Event 1	Grade	Adverse Event 2	Grade
4	Dyspnea	3		
7	Vomiting	3	Headache	3
13	Infection	3		
31	Abnormal LVEF	2		
32	Abnormal LVEF	2		
35	Confusion	3	Costal pain	2
37	Renal failure	3		
38	Spinal cord compression	4		
39	Proteinuria	3		
41	Pathologic Hip fracture	3		
43	Abnormal LVEF	2		
58	Motor neuropathy	3	Sensory neuropathy	3

Three patients withdrew from study treatment due to decreases in left ventricular ejection fraction; the protocol for study 014 mandated patient withdrawal for decreases in LVEF as outlined in section 7.1.3.3.

7.1.3.3 Other significant adverse events

Dose interruptions and dose reductions:

Dose interruptions and dose reductions were common on both studies. On study 1006, 48 (45%) of patients experienced at least one dose interruption and 23 (22%) patients experienced at least one dose reduction. Of the 23 patients whose dose was reduced once (to 37.5 mg), 6 (6% of total) required an additional dose reduction to 25 mg. On study 014, 45 (71%) of patients experienced at least one dose interruption and 22 (35%) patients experienced at least one dose reduction. The higher incidence of dose interruptions and reductions on study 014 reflects protocol-mandated dose interruptions and reductions for certain laboratory abnormalities.

Changes in left ventricular ejection fraction (LVEF):

Several patients enrolled in a phase 1 study of sunitinib in AML developed signs and symptoms of cardiac failure. These patients received sunitinib at doses of 75 mg -100 mg and had received prior cardiotoxic anthracyclines chemotherapy. As a result of this toxicity, the sponsor began monitoring ejection fraction routinely in clinical studies, including the MRCC phase 2 trials.

Procedures for collecting LVEF data on the two MRCC studies were as follows:

1006

A normal LVEF as assessed by MUGA scan was required for study entry. During the conduct of the study, LVEF was assessed by MUGA on the last treatment day of cycles 2, 4, and all

subsequent even cycles, at end of treatment or withdrawal, and 30 days after discontinuation if the end of treatment study was abnormal.

014

A normal LVEF as assessed by either echocardiogram or multigated acquisition (MUGA) scan was required for study entry. Subsequent LVEF monitoring included echocardiogram or MUGA scan on the last treatment day (day 28) of each cycle and at end of treatment/withdrawal from study.

Tables 25 and 26 describe population median LVEF over the course of treatment with sunitinib on study 1006 and 014, respectively.

Table 25: LVEF during treatment with sunitinib (1006)

	Baseline N=85	Cycle #2 N=80	Cycle #4 N=51	Cycle #6 N=19
LVEF, median (range)	62 (50-79)	60 (37-80)	60 (37-77)	61 (29-76)
Absolute change from baseline, median (range)	--	-2.0 (-20-24.7)	-2.0 (-28-8)	-3.0 (-22-8)
% changes from baseline, median (range)	--	-3.1 (-35.1-44.9)	-3.2 (-43.1-13.7)	-4.8 (-43.1-14)

Table 26: LVEF during treatment with sunitinib (014)

	Baseline N=61	Cycle #1 N=51	Cycle #2 N=48	Cycle #3 N=41	Cycle #4 N=36
LVEF, median (range)	65 (45-82)	64 (41-83)	64 (23-82)	60 (41-79)	62 (48-74)
Absolute change from baseline, median (range)	--	-1.0 (-34-13.4)	-1.0 (-31-20)	-4.0 (-21.6-16)	-0.70 (-27-10)
% changes from baseline, median (range)	--	-1.4 (-45.3-23.5)	-1.5 (-57.4-44.4)	-6.7 (-34.5-25.4)	-1.1 (-32.9-22.2)

Although the median LVEF does not change significantly over the course of treatment, several patients experienced decreases of LVEF over the course of therapy as evidenced by the low end of the range.

As reported by the sponsor, 7/169 (4.1%) patients treated on these two studies had declines in LVEF of $\geq 20\%$ AND to values below the lower limit of normal. (these criteria, considered *independently*, constitute grade 2 toxicity by CTC v2 version 3—LVEF 40-50%). However, a total of 25 patients (14.8%) had LVEF drops below normal at some point during the study. LVEF data for all these patients are described below.

Twelve patients (11.3%) on study 1006 with normal baseline LVEF experienced declines to below the lower limit of normal, as reported in Table 27.

Table 27: LVEF (%) in Patients with Declines to Below Normal During Treatment with Sunitinib--1006

PT #	Baseline	Cycle 2	Cycle 4	Cycle 6	Term	30 d f/u
7	54	57	45			
16	51	38	58	29		
19	59	54	43		65	
28	64	55	48		49	54
46	57	37	39			
58	50	57	49			
62	56	49				
63	51.4	48.9	40.4	57*		
65	67	48				
79	55	45	46			
81	65	53	37			
97	59	47				

*cycle #5

An additional 5 patients had absolute decreases in LVEF of 10% but did not drop below normal.

Patients 7, 58, 62, 79 and 97 had relatively small decreases in LVEF that are likely to be clinically insignificant. Recovery after a drop in LVEF is seen in patients 19 and 63, and partial recovery of LVEF is seen in patient 28. Patients 16, 46 and 81 remain on study and no further LVEF data are available at this time. These three patients are of particular concern, and follow-up LVEF data will be requested from the sponsor after study completion.

Thirteen patients on study 014 with normal baseline LVEF experienced declines to below the lower limit of normal. Changes in LVEF in these patients are described in Table 28.

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Table 28: LVEF (%) by Cycle in Patients with Declines to Below Normal During Treatment with Sunitinib on Study 014

Pt. #	Baseline	1	2	3	4	5	6	7	8	9
8	65	59	56	64	50	63				
11	55	49	55	57	48					
24	52	54	48	48						
25	63	64	64	65	53	60	61			
31	54	45	23	57*	37**	46***				
32	75	41	41*	30**						
34	82	67	58	72	55	46	48*			
43	63	55	51	41						
44	60	60	50	48	50	55	50	55	55	
49	55	51	65	56	55	60	63	68	65	64
51	59	67	58	65	59	58	46	61	54	
60	52	50	46	60	49	54	56	58	60	58
62	58	53	51	46	51	55	54	51	60	

* study termination

**30 day follow-up

***subsequent follow-up

Transient and/or minor decreases in LVEF are seen in patients 8, 11, 24, 25, 44, 49, 51, 60 and 62.

For those patients with significant declines in LVEF and for whom no follow-up cardiac imaging data were available in the database, CRFs and SAE narratives were examined for additional information regarding cardiac evaluations and treatments for CHF.

The 014 protocol mandated patient withdrawal from the study in the event of:

- Congestive heart failure (new cardiomegaly by X-ray, S3 gallop, paroxysmal nocturnal dyspnea, and/or orthopnea); onset of such signs or symptoms should prompt objective evaluation of LVEF by echocardiogram or MUGA scan.
- Decline from baseline in LVEF by $\geq 20\%$ and to $< \text{LLN}$ for the institution (e.g., if the LLN is 50% and baseline value is 59%, a decline to 39% would require patient withdrawal from study).
- An LVEF of $\geq 10\%$ below the LLN for the institution (e.g., if the LLN is 50%, a LVEF $\leq 40\%$ would require patient withdrawal from the study).

Patients 31, 32 and 43 were withdrawn from the study due to changes in ejection fraction meeting these criteria.

Patient 31 was a 56 year old male with a history of coronary artery disease, hypertension and diabetes. On day 28 of cycle 2, the subject was found to have an LVEF of 23% on MUGA scan versus 54% at screening (lower limit of normal: 50%). This was assessed as cardiovascular toxicity Grade 2. No therapeutic measures were instituted for treatment of CHF. The subject was taken off the treatment protocol on that date because of this event. An echocardiogram was repeated approximately 11 days later and demonstrated an LVEF of 57%. At study termination,

and 11 days after the preceding echocardiogram, a MUGA scan showed an LVEF of 37%. A final follow-up echocardiogram was performed two and a half months later and at that time LVEF was 46%.

Patient 32 was a 72 year old woman with a history of hypertension who completed 27 days of study treatment for MRCC. On day 28, a scheduled echocardiogram demonstrated a decline in ejection fraction from 75% to 41%. The patient was withdrawn from the study, hospitalized and a cardiac catheterization was performed. No results from the catheterization were provided. At study termination, EF remained 41%. A 30-day follow-up echo demonstrated an EF of 30%. No CHF symptoms were reported and the patient was not treated for heart failure. The patient was subsequently lost to follow-up; a family member later reported the patient's death due to renal cell carcinoma.

Patient 43 was a 62 year old female with no prior history of cardiac disease. Her LVEF gradually declined over the course of nearly 5 months on study from a baseline of 62.6% to 41% at the time of her withdrawal from the study. There was no treatment administered for congestive heart failure. No subsequent LVEF data are available.

Although patient 34 also met the withdrawal criteria, she was not withdrawn from the study for that reason. This 57 year old female patient initially had a response to therapy. At her clinic visit on day 28 of cycle 5 she complained of fatigue and weakness and had a Grade 3 decreased left ventricular ejection fraction of 46% (LLN: 55%) versus LVEF at baseline of 82%, and elevated blood pressure of 146/102 (118/70 baseline). As a result, she was hospitalized for two days and cardiac enzymes and blood pressure were monitored. She was subsequently discharged on a diuretic and ACE inhibitor for hypertension. Treatment with sunitinib was terminated following documentation of progressive disease; LVEF at the time of study termination was 48%. The patient died of progressive renal cell carcinoma two months after the last cardiac study.

Conclusions:

Approximately 15% of patients across the two MRCC studies had changes in LVEF to below the limit of normal at some time during treatment with sunitinib. While many of these changes were mild and/or transient, seven patients across the two studies had more significant changes for which reversibility is undetermined or incompletely demonstrated. At least one of these patients was treated with a diuretic and ACE inhibitor (although reportedly for hypertension, not heart failure). The three patients on study 1006 with significant LVEF changes who remain on study should continue to receive LVEF monitoring while on study, and after treatment discontinuation if the results remain abnormal at termination. Submission of these data and corresponding clinical narratives including any relevant diagnostic tests and treatments should be considered as a post-marketing commitment.

7.1.4 Other Search Strategies

Based on preclinical evidence of adrenal toxicity (adrenal hemorrhage, congestion and necrosis) in rat and monkey multiple-dose toxicology studies (13 week studies), FDA requested that the sponsor conduct ACTH stimulation testing as well as adrenal gland imaging at baseline and during treatment to determine whether the drug had adrenal toxicity in human subjects. This testing was performed in multiple single-arm trials throughout early drug development. This testing was discontinued by the sponsor during later phases of drug development. As a result, placebo-controlled data are very limited with data available from the phase 3 GIST trial for only 35 patients receiving sunitinib and 8 placebo patients. The ACTH stimulation and adrenal radiographic data collected on these trials were submitted to the IND in summary format for FDA review. The Division of Drug Oncology Products consulted Dr. Richard Perlstein in the Division of Metabolic and Endocrine Drug Products (DMEDP) for interpretation of the results. Additionally, the sponsor consulted with [redacted]

[redacted] to review and interpret the results. The findings of both consultants, as well as the DDOP clinical reviewer's findings based on the NDA submission, are presented here.

Dr. [redacted] (the sponsor's consultant) concluded the following:

- The criteria used by the sponsor to screen for adrenal insufficiency in the human trials were too stringent and likely led to false positive findings. The assessments included pre-stimulation cortisol (which must be greater than 5 mcg/ml to be considered normal) and post-stimulation (60 minute) cortisol levels. To be declared normal requires an absolute increase from the pre-stimulation value of at least 7 mcg/dl in addition to achieving an absolute level of 18 mcg/dl. Dr. [redacted] asserted that most endocrinologists use a single test measuring whether the patient achieves an absolute value of 18 mcg/dl to screen for adrenal insufficiency.
- Dr. [redacted] concluded that most of the abnormalities seen reflected the overly stringent criteria used for screening or random occurrence (such as a periodic low pre-stimulation cortisol level which reflected the pulsatility of ACTH and cortisol secretion). He further concluded that there did not appear to be any human counterpart to what was seen in the animal studies, and noted that the radiographic data in human subjects did not provide evidence of adrenal hemorrhage in humans.

The observations of Dr. Perlstein (FDA DMEDP) are as follows.

- Lack of new radiographic changes in adrenals of patients treated with sunitinib is reassuring.
- Adverse event data from phase 1 and phase 2 sunitinib trials as of May 2005 yielded 6 patients with adrenal insufficiency coded as an AE out of 1400 patients. None of these events appeared to be drug-related (the 3 MRCC patients are reviewed below).
- 1 patient from the GIST Phase 3 trial and 3 patients from other sunitinib trials appeared to develop subclinical adrenal insufficiency with unequivocally low baseline (< 1 mcg/dL) and/or peak post-stimulation cortisol (6-11 mcg/dL).

- Such patients may be susceptible to adrenal crisis in the setting of a superimposed physiologic stress such as infection, trauma, or surgery.
- Additional data, including substantial placebo-controlled ACTH stimulation testing, would be of value to delineate more precisely the incidence of drug-related adrenal insufficiency following use of sunitinib.

MRCC NDA submission:

Adverse events reported as adrenal insufficiency on the two MRCC trials were uncommon. One patient on study 014 (patient #1) had adrenal insufficiency reported on cycles 2, 3, and 4; all were grade 2. Two patients on study 1006 had reports of adrenal insufficiency, one grade 3 and the other grade 2, both during the first cycle.

The case report forms for these patients were reviewed. The CRF for patient 1, study 014, revealed that the patient had normal baseline ACTH stimulation results (post-stimulation cortisol of 30). Subsequently, the patient had abnormal pre- and post-stimulation cortisol (<10) on day 28 of cycle 2. This occurred after the initiation of megestrol acetate (Megace) for appetite stimulation, and most likely represents secondary adrenal insufficiency secondary to the glucocorticoid effects of that drug. ACTH stimulation testing returned to normal following discontinuation of Megace, and the patient completed 9 cycles of sunitinib without further evidence of adrenal insufficiency. Dr. Perlstein had reviewed the data available for this patient prior to NDA submission, and also felt the abnormal results were most likely caused by the initiation of Megace therapy. The event occurred following initiation of a drug known to cause adrenal suppression, and resolved following discontinuation of the drug (while the patient was still receiving sunitinib). Thus, this event is thus unlikely to be related to sunitinib.

The narrative for patient 48 (study 1006) was also reviewed by Dr. Perlstein. Review of the CRF confirms that the patient had an abnormal baseline cortisol (pre-stimulation value of 11, no post-stimulation increase). After receiving one dose of sunitinib, the patient was hospitalized with sepsis, and subsequently developed adrenal crisis. This event is unlikely to be related to the single dose of sunitinib and is likely related to pre-existing adrenal insufficiency with adrenal crisis precipitated by sepsis.

Patient 106 (study 1006) had undergone bilateral adrenalectomy prior to study entry and was on chronic replacement. This event is clearly unrelated to sunitinib administration. Dr. Perlstein concurred with this conclusion in his report.

Of the 4 patients ACTH stimulation test results were the most concerning to Dr. Perlstein, 2 were treated on an MRCC protocol (study 014 patients 10 and 58). The CRFs for all four patients were reviewed for additional information.

Patient 10 had normal ACTH stimulation testing at screening and in the first 2 cycles. At the end of cycle 2, on May 13, the pre-stimulation cortisol was 11.7 and the post-stimulation cortisol was 32.4. The patient subsequently developed brain metastases and was begun on dexamethasone on June 29 for "blurred vision". At termination on August 5, the pre-stimulation cortisol was 0.9

and the post-stimulation cortisol was 6.9. The abnormal result obtained at termination occurred while the patient was receiving dexamethasone.

Patient 58 received 3 cycles of sunitinib and developed progressive disease. This patient had normal baseline and post-stimulation cortisol at screening, and cycles 1 and 2. A pre-stimulation cortisol of 21.8 and post-stimulation cortisol of 34.7 were obtained at the end of cycle 2 on September 10th. However, at termination on October 23, the pre-stimulation cortisol was 0.9 and the post-stimulation cortisol was 11. Review of the CRF found that his patient had initiated dexamethasone on October 15 due to neurologic compromise resulting from vertebral metastases.

An additional patient, study 0018 patient 7 (a phase 1 solid tumor study patient) had normal ACTH stimulation testing results at screening and cycle 1 (cycle 1 pre- and post-stimulation cortisol 17.2 and 29.3, respectively). The patient began treatment with dexamethasone on June 19 prior to a stereotactic surgical procedure for brain metastases. The final ACTH stimulation test was performed on June 23, 4 days after the initiation of dexamethasone, and the values were 0.50 prior to stimulation and 10.6 post-stimulation.

Finally, patient 36 on study 1004 (GIST phase 3) was randomized to sunitinib and had a normal screening ACTH stimulation test result (pre-stimulation cortisol 13.3, post-stimulation cortisol 22.7). The patient subsequently had 3 abnormal ACTH stimulation test results at the end of cycles 2, 4 and 6 with peak, post-stimulation cortisol levels of 9.8, 16.1, and 12.5, respectively). Review of the CRF was unrevealing with respect to the cause of this abnormality. Apparently, ACTH levels were not performed as the test results were marked 'normal' by the investigator. The investigator also reported no symptoms or signs of adrenal insufficiency.

Attempts to uncover symptom complexes associated with adrenal insufficiency (hyponatremia, hyperkalemia, hypotension) found one case with both hypotension and hyponatremia during cycle 1. The clinical reviewer believes that this was unlikely to be due to unrecognized adrenal insufficiency because: 1) The patient's ACTH stimulation testing as well as adrenal imaging were normal at both baseline and the end of cycle 1; and (2) The hyponatremia was reported over a 9-day period which ended approximately one week prior to the onset of hypotension, which was transient (<24 hours). No other evidence of unreported adrenal insufficiency was found in the laboratory data for the two MRCC studies.

Adrenal imaging data from the MRCC trials was reviewed. Of the 10 patients on study 014 with abnormalities reported, 9 had abnormalities prior to receiving sunitinib (pt 46). An additional patient not reported as abnormal was reported as having evidence of adrenal hemorrhage in cycle 1 (patient 52). This entry was apparently incorrect and was subsequently corrected on a data clarification form. The patient had normal ACTH stimulation testing throughout the study.

Conclusions:

Clinical evidence of adrenal insufficiency was evaluated using adrenal imaging (CT/MRI), ACTH stimulation testing, adverse event reports and laboratory data. Review of the adrenal imaging data in 336 patients across all solid tumor studies and reported adverse events pertaining

to adrenal function did not provide evidence supporting sunitinib-induced adrenal toxicity. Interpretation of the ACTH stimulation testing data was limited by the lack of adequate placebo controlled data. Additionally, the criteria used by the sponsor to interpret ACTH stimulation testing results were too stringent, which led to many “false positive” results. As a result, the review of the data by both Dr. Perlstein of DMEDP and this clinical reviewer defined abnormalities on the basis of the single criterion of a post-stimulation cortisol level of less than 18. Dr. Perlstein focused his review on those patients in whom the peak was either consistently less than 18, or in whom the final available post-stimulation value was less than 18. As described above, review of the CRFs for these patients found that for three of the four patients of concern, the initiation of dexamethasone is the likely explanation for the subsequently abnormal test results. The fourth patient, a patient with GIST randomized to sunitinib, had persistently abnormal test results following the initiation of the drug with no apparent alternative explanation for the development of adrenal insufficiency.

In summary, while there is no clinical evidence of radiographically detectable adrenal hemorrhage or necrosis, there may be a rare incidence of adrenal toxicity as demonstrated by the abnormal ACTH stimulation test results of the GIST patient. Several etiologies may be responsible for the development of functional adrenal suppression in patients with advanced cancer, including adrenal metastases, adrenalectomy and the introduction of certain drugs (e.g. corticosteroids). In the absence of adequate placebo controlled data, it is impossible to rule out a sunitinib-induced adrenal toxicity which may be clinically silent until the introduction of a stressor such as surgery or severe infection. The recommendation of the clinical reviewer is to add a section to the product labeling under “precautions” summarizing the available data and advising prescribing physicians to maintain a high index of suspicion for adrenal insufficiency in patients receiving sunitinib, especially in situations of significant physiologic stress. Routine ACTH stimulation testing in the clinical practice setting does not appear to be warranted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Patients were queried about adverse events during all clinic visits. On study 014, these visits occurred on days 1, 14, 28 and 35 of cycle 1, and on days 1, 14 and 28 of all subsequent cycles; for study 1006 clinic visits occurred on day 1, 14 and 28 of cycle 1 and days 1 and 28 of subsequent cycles. The investigator obtained and recorded on the CRF/DCT all observed or volunteered adverse events, the severity (NCI CTC grade version 2.0 for study 014 and version 3.0 for study 1006) of the events, and the investigator’s opinion of the relationship to the study treatment. Adverse events included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator recorded as adverse events any clinically significant changes in physical examination findings and abnormal objective test findings (e.g., ECG, x-ray, laboratory).

For all adverse events, the investigator pursued and obtained information adequate to determine both the outcome of the adverse event and whether or not it met the criteria for classification as a serious adverse event. If the adverse event or its sequelae persisted, follow-up was required until resolution or stabilization occurred at a level acceptable to the investigator and sponsor.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse events were reported according to the investigator's verbatim term as well as the Medical Dictionary for Regulatory Activities (MedDRA) Version 7.1 system organ class (SOC), preferred term, and maximum severity grade. In general, the classification by preferred term matched well to the verbatim terms chosen by the investigators. Events were graded using the NCI Common Terminology Criteria for Adverse Events version 3.0 (1006) or 2.0 (014).

7.1.5.3 Incidence of common adverse events

This review will focus on the adverse events most common in the MRCC patient population and therefore contains a review of data from two single arm trials. Adverse event data from these trials represent the most relevant population for the MRCC indication. Furthermore, a review of the phase 3 placebo-controlled data in patients with gastrointestinal stromal tumors will be performed under NDA 21-938 by Dr. Edwin Rock. Data from this trial was also reviewed in summary format by this reviewer as indicated during the course of the review. For most common adverse events, the incidence is similar in the MRCC and GIST (sunitinib arm) trials. However, fatigue, the most common event overall, appears to be more common in MRCC patients receiving sunitinib than in GIST patients receiving sunitinib.

7.1.5.4 Common adverse event tables

Analysis of the most common adverse events on study 1006 as analyzed by the sponsor and the clinical reviewer is shown in the tables below.

**Appears This Way
On Original**

Table 29: Number and Percent of Patients who Experienced the Most Common (≥20%) Treatment-Emergent Adverse Events by Maximum CTCAE v.3 Grade (ITT population) on Study 1006—Sponsor’s Analysis

Preferred Term	Maximum NCI CTCAE v3.0 Grade					Total
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Fatigue	37 (35)	23 (22)	11 (10)	0 (0)	0 (0)	71 (67)
Diarrhea NOS	34 (32)	15 (14)	4 (4)	0 (0)	0 (0)	53 (50)
Nausea	33 (31)	17 (16)	2 (2)	0 (0)	0 (0)	52 (49)
Dysgeusia	40 (38)	10 (9)	0 (0)	0 (0)	0 (0)	50 (47)
Dyspepsia	29 (27)	16 (15)	1 (1)	0 (0)	0 (0)	46 (43)
Stomatitis	26 (25)	10 (9)	5 (5)	0 (0)	0 (0)	41 (39)
Anorexia	22 (21)	13 (12)	1 (1)	0 (0)	0 (0)	36 (34)
Vomiting NOS	19 (18)	14 (13)	3 (3)	0 (0)	0 (0)	36 (34)
Skin discoloration	31 (29)	1 (1)	0 (0)	0 (0)	0 (0)	32 (30)
Hypertension NOS	12 (11)	12 (11)	7 (7)	0 (0)	0 (0)	31 (29)
Constipation	21 (20)	10 (9)	0 (0)	0 (0)	0 (0)	31 (29)
Rash NOS	24 (23)	6 (6)	0 (0)	0 (0)	0 (0)	30 (28)
Headache	19 (18)	6 (6)	0 (0)	0 (0)	0 (0)	25 (24)
Mucosal inflammation NOS	12 (11)	10 (9)	1 (1)	0 (0)	0 (0)	23 (22)

Table 30: Number and Percent of Patients who Experienced the Most Common (≥ 20%) Treatment-Emergent Adverse Events by Maximum CTCAE v.3 Grade (ITT population) on Study 1006—FDA Analysis

Adverse Event, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total*
Fatigue	37 (35)	24 (23)	12 (11)	0 (0)	73 (69)
Mucositis/Stomatitis	33 (31)	19 (18)	6 (6)	0 (0)	58 (55)
Diarrhea	34 (32)	15 (14)	4 (4)	0 (0)	53 (50)
Nausea	33 (31)	17 (16)	2 (2)	0 (0)	52 (49)
Taste disturbance	41 (39)	10 (9)	0 (0)	0 (0)	51 (48)
Dyspepsia	29 (27)	16 (15)	1 (1)	0 (0)	46 (43)
Rash	33 (31)	8 (8)	0 (0)	0 (0)	41 (39)
Anorexia	22 (21)	13 (12)	1 (1)	0 (0)	36 (34)
Vomiting	19 (18)	14 (13)	3 (3)	0 (0)	36 (34)
Skin Discoloration	31 (29)	1 (1)	0 (0)	0 (0)	32 (30)
Hypertension	12 (11)	13 (12)	7 (7)	0 (0)	32 (30)
Constipation	21 (20)	10 (9)	0 (0)	0 (0)	31 (29)
Bleeding**	21 (20)	5 (5)	1 (1)	0 (0)	27 (25)
Dyspnea	15 (14)	7 (7)	4 (4)	0 (0)	26 (25)
Headache	19 (18)	6 (6)	0 (0)	0 (0)	25 (24)

* There were no grade 5 events (deaths) attributed to any of these events

**bleeding events included epistaxis (13), gingival bleeding (3), hemorrhoidal bleeding (3), rectal (2), vaginal (1), abdominal wound (1), non-infectious wound of L foot (1), ear (1), scrotum (1), penile (1)

(note: the sum of the individual events is greater than the total number of reported events in the table as an individual patient may have had more than one event)

Differences in the FDA reviewer's analysis from that of the sponsor are in bold and explained below. Two additional reports of fatigue were reported as "fatigue aggravated" by the investigators and were added to the 71 events reported by the sponsor. Taste disturbance was reported as "dysgeusia" by the sponsor and therefore omitted one report of loss of taste (ageusia). Stomatitis and mucositis were reported separately as "stomatitis" and "mucosal inflammation". Since stomatitis is mucositis occurring in the mouth, and is also commonly called mucositis, these events should be considered together. As expected, there was considerable overlap between reports of both terms in the same patients, accounting for the difference between the combined total and the total for each term as reported by the sponsor. The FDA reviewer's analysis of hypertension contains one additional reported event of "labile hypertension"; while the term "rash" considers all reported rashes, rather than only those categorized as "rash NOS", and therefore also includes events reported by the sponsor under several terms including: "rash, generalized", "rash, maculo-papular", "rash, follicular" and "rash, genital". Dyspnea was not reported in the sponsor's table. Neither "dyspnea NOS" nor "exertional dyspnea", the two terms under which these events were reported, meet the 20% cutoff for inclusion in that table. However, when these events are pooled, 26% of patients in the study experienced dyspnea as an adverse event. Finally, as bleeding events are a known complication of VEGF-inhibiting therapies, bleeding events were reported in aggregate bringing the total incidence to 25%.

As demonstrated in the table, among the most common adverse events, there were no reported grade 4 events and no deaths attributable to these events. A few of the most common adverse events had significant numbers of grade 3 events including fatigue, mucositis, diarrhea, vomiting, hypertension and dyspnea.

Analysis of the most common adverse events on study 014 as analyzed by the sponsor and the clinical reviewer is shown in the tables below.

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Table 31: Summary of the Most Common Treatment-Emergent Adverse Events (>20%) on Study 014 by CTC Grade (v. 2)—Sponsor’s Analysis

Preferred Term	CTC Grade				Total
	Grade 1	Grade 2	Grade 3	Grade 4	
Any Adverse Events	2 (3)	11 (18)	36 (57)	14 (22)	63 (100)
Fatigue	23 (37)	20 (32)	7 (11)	0 (0)	50 (79)
Diarrhea NOS	20 (31)	16 (25)	4 (6)	0 (0)	40 (64)
Nausea	25 (40)	13 (21)	2 (3)	0 (0)	40 (64)
Dyspepsia	21 (33)	10 (16)	0 (0)	0 (0)	31 (49)
Stomatitis	21 (33)	7 (11)	1 (2)	0 (0)	29 (46)
Arthralgia	21 (33)	7 (11)	0 (0)	0 (0)	28 (44)
Vomiting NOS	15 (24)	8 (13)	4 (6)	0 (0)	27 (43)
Constipation	14 (22)	11 (18)	1 (2)	0 (0)	26 (41)
Taste disturbance	21 (33)	1 (2)	0 (0)	0 (0)	22 (35)
Skin discoloration	22 (35)	1 (2)	0 (0)	0 (0)	23 (37)
Dyspnoea NOS	10 (16)	4 (6)	5 (8)	0 (0)	19 (30)
Headache NOS	14 (22)	2 (3)	2 (3)	0 (0)	18 (29)
Dermatitis NOS	10 (16)	6 (10)	1 (2)	0 (0)	17 (27)
Pain in Limb	14 (22)	3 (5)	0 (0)	0 (0)	17 (27)
Anorexia	12 (19)	5 (8)	0 (0)	0 (0)	17 (27)
Abdominal Pain	12 (19)	3 (5)	2 (3)	0 (0)	17 (27)
Hypertension NOS	10 (16)	3 (5)	3 (5)	0 (0)	16 (25)
Ejection fraction abnormal	4 (6)	11 (18)	1 (2)	0 (0)	16 (25)
Glossodynia	14 (22)	1 (2)	0 (0)	0 (0)	15 (24)
Dizziness (exc vertigo)	10 (16)	4 (6)	0 (0)	0 (0)	14 (22)
Dry Skin	13 (21)	1 (2)	0 (0)	0 (0)	14 (22)
Flatulence	10 (16)	4 (6)	0 (0)	0 (0)	14 (22)
Back Pain	10 (16)	3 (5)	0 (0)	0 (0)	13 (21)
Pyrexia	9 (14)	2 (3)	2 (3)	0 (0)	13 (21)
Cough	13 (21)	0 (0)	0 (0)	0 (0)	13 (21)
Myalgia	8 (13)	4 (6)	1 (2)	0 (0)	13 (21)

The FDA clinical reviewer’s analysis is summarized in Table 31. Differences with the sponsor’s analysis are in bold.

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On Original

Table 32: Summary of the Most Common Treatment-Emergent Adverse Events (>20%) on Study 014 by CTC Grade (v. 2)—FDA Analysis

Adverse Event, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Fatigue	24 (38)	21 (33)	7 (11)	0 (0)	52 (83)
Diarrhea	20 (31)	16 (25)	4 (6)	0 (0)	40 (64)
Nausea	25 (40)	13 (21)	2 (3)	0 (0)	40 (64)
Stomatitis/Mucositis	22 (35)	9 (14)	1 (2)	0 (0)	32 (51)
Dyspepsia	21 (33)	10 (16)	0 (0)	0 (0)	31 (49)
Ejection fraction decreased*	16 (25)	13 (21)	1 (2)	0 (0)	30 (48)
Arthralgia	21 (33)	7 (11)	1 (2)	0 (0)	29 (46)
Vomiting	15 (24)	8 (13)	4 (6)	0 (0)	27 (43)
Constipation	14 (22)	11 (18)	1 (2)	0 (0)	26 (41)
Skin Discoloration	22 (35)	1 (2)	0 (0)	0 (0)	23 (37)
Rash	14 (22)	8 (13)	1 (2)	0 (0)	23 (37)
Taste disturbance	21 (33)	1 (2)	0 (0)	0 (0)	22 (35)
Dyspnea	11 (18)	6 (10)	4 (6)	0 (0)	21 (33)
Headache	14 (22)	2 (3)	2 (3)	0 (0)	18 (29)
Pain in limb	15 (24)	3 (5)	0 (0)	0 (0)	18 (29)
Anorexia	12 (19)	5 (8)	0 (0)	0 (0)	17 (27)
Abdominal Pain	12 (19)	3 (5)	2 (3)	0 (0)	17 (27)
Bleeding**	15 (24)	2 (3)	0 (0)	0 (0)	17 (27)
Hypertension NOS	10 (16)	3 (5)	3 (5)	0 (0)	16 (25)
Glossodynia	14 (22)	1 (2)	0 (0)	0 (0)	15 (24)
Dizziness	10 (16)	4 (6)	0 (0)	0 (0)	14 (22)
Cough	14 (22)	0 (0)	0 (0)	0 (0)	14 (22)
Dry Skin	13 (21)	1 (2)	0 (0)	0 (0)	14 (22)
Flatulence	10 (16)	4 (6)	0 (0)	0 (0)	14 (22)
Back Pain	10 (16)	3 (5)	0 (0)	0 (0)	13 (21)
Pyrexia	9 (14)	2 (3)	2 (3)	0 (0)	13 (21)
Myalgia	8 (13)	4 (6)	1 (2)	0 (0)	13 (21)

* as reported in either the AE table or the LVEF table using CTCAE version 2

** bleeding events included epistaxis (11), gingival (2), rectal (4), hemorrhoidal (1) and scrotal (1).

(note: the sum of the individual events is greater than the total number of reported events in the table as an individual patient may have had more than one event)

Most discrepancies with the sponsor's analysis involved one or two additional reports of an adverse event not identified by the sponsor. Dermatitis NOS has been reclassified as "rash" to be more inclusive and more specific (all cases reported by the term "dermatitis NOS" were reported by the investigator as "rash", but not all cases reported by the investigator as rashes were termed "dermatitis NOS").

Decreased ejection fraction was included in this table as the sponsor required reporting of this laboratory abnormality as an adverse event. Cases identified here were those reported as adverse events as well as cases where there were ejection fraction changes noted on routine echocardiogram which met the NCI CTC criteria for grade 1-2 toxicity (grade 3 and 4 toxicity are defined by symptomatic CHF).

The most common events seen in this study are similar to those seen in 1006; however, more event categories reached the 20% cutoff for inclusion in the table for this study compared to 1006. Again, there were no grade 4 events among the most commonly reported events overall. Grade 3 events that were relatively common are also similar to study 1006 and include fatigue, diarrhea, nausea, vomiting, dyspnea, headache, abdominal pain, hypertension, and pyrexia. Adverse events that met the 20% incidence cutoff for study 014 but not 1006 were evaluated for study 1006 as well and are reported in the following table.

Table 33: Number and Percent of Patients on Study 1006 who Experienced Adverse Events Which Met 20% Incidence on Study 014 Only—FDA Analysis

Adverse Event, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Arthralgia	13 (12)	5 (5)	1 (1)	0 (0)	19 (18)
Abdominal pain	8 (8)	6 (6)	3 (3)	0 (0)	17 (16)
Back pain	10 (9)	5 (5)	1 (1)	0 (0)	16 (15)
Myalgia	16 (15)	0 (0)	0 (0)	0 (0)	16 (15)
Cough	14 (13)	0 (0)	1 (1)	0 (0)	15 (14)
Dry skin	14 (13)	1 (1)	0 (0)	0 (0)	15 (14)
Pyrexia	12 (11)	1 (1)	0 (0)	0 (0)	13 (12)
Dizziness	7 (7)	3 (3)	3 (3)	0 (0)	13 (12)
Pain in Limb	9 (8)	3 (3)	1 (1)	0 (0)	13 (12)
Glossodynia	8 (8)	2 (2)	0 (0)	0 (0)	10 (9)
Flatulence	7 (7)	3 (3)	0 (0)	0 (0)	10 (9)

While not meeting the 20% cutoff for inclusion in the sponsor's table, these events were also relatively common on study 1006, with most having an incidence over 10%.

7.1.5.5 Identifying common and drug-related adverse events

While it is difficult to identify which adverse events are drug related in a single arm trial, some common adverse events identified here are likely to be drug related either based on mechanism of action or overall incidence higher than one might expect in this patient population. Additional evidence supporting drug relatedness was evaluated in the placebo controlled GIST data and from considering the adverse event profiles of related drugs.

Adverse events identified as likely to be drug related include:

Constitutional: fatigue

Cardiac: decreases in LVEF

Gastrointestinal: diarrhea, nausea, vomiting, stomatitis/mucositis, anorexia, dyspepsia, glossodynia, appetite disturbance

Dermatology: yellowing of the skin (skin discoloration), hair color changes, rash, palmar-plantar erythrodysesthesia, alopecia, blistering of the skin

Neurology: taste disturbance, peripheral neuropathy

Vascular: hypertension, bleeding events

Ophthalmology: periorbital edema, increased lacrimation

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations for common adverse events were performed.

7.1.6 Less Common Adverse Events

The events listed below did not meet the 20 % incidence for either study, but had a $\geq 10\%$ incidence on one or both studies.

Table 34: Treatment Emergent Adverse Events Occurring in at Least 10% and less than 20% of Patients on Either 014 or 1006—FDA Analysis

Adverse Event	Study 1006		Study 014	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Palmar-plantar erythrodysesthesia*	20 (19)	5 (5)	1 (2)	0 (0)
Hair color changes	20 (19)	0 (0)	9 (14)	0 (0)
Peripheral edema	16 (15)	1 (1)	12 (19)	0 (0)
Appetite disturbance	4 (4)	0 (0)	11 (17)	0 (0)
Blisters (predominantly hands/feet)	2 (2)	2 (2)	9 (14)	2 (3)
Alopecia	11 (10)	0 (0)	9 (14)	0 (0)
Dehydration	12 (11)	5 (5)	7 (11)	0 (0)
Peripheral neuropathy**	8 (8)	0 (0)	8 (13)	2 (3)
CK-MB increase	0 (0)	0 (0)	8 (13)	1 (2)
Upper Respiratory Infection	12 (11)	0 (0)	4 (6)	0 (0)
Nocturia	2 (2)	0 (0)	6 (10)	0 (0)
Lacrimation increased	2 (2)	0 (0)	8 (13)	0 (0)
Periorbital edema	5 (5)	0 (0)	6 (10)	0 (0)

* hand-foot syndrome

** includes sensory and motor neuropathy

Urinary symptoms other than nocturia (which met the 10% incidence for study 014 and is also reported above) were also noted relatively frequently, as might be expected in this patient population. The incidence of these events is summarized below.

Table 35: Incidence of Genitourinary Adverse Events on MRCC Studies 1006 and 014—FDA Analysis

Adverse Event	Study 1006		Study 014	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Nocturia	2 (2)	0 (0)	6 (10)	0 (0)
Dysuria	9 (8)	0 (0)	5 (8)	0 (0)
Urinary Tract Infection	7 (7)	1 (1)	3 (5)	0 (0)
Urinary Frequency	2 (2)	0 (0)	2 (3)	0 (0)

Additionally, there was one report of urinary urgency (grade 1) on study 1006, one report of oliguria (grade 1) on study 014 and one report of proteinuria (grade 3) also on study 014.

Hypothyroidism

The thyroid was identified as a target organ of toxicity in preclinical studies. Adverse events of either hypothyroidism or increased TSH were examined in the databases of both MRCC studies. All events were NCI CTCAE version 2 grade 1 or 2.

Table 36: Treatment-Emergent Hypothyroidism and TSH Elevations in MRCC Studies 1006 and 014

Adverse Event	Study 1006	Study 014	Total
Total hypothyroid events	6 (5.7)	5 (7.9)	11 (6.5)
Hypothyroidism, n (%)	5 (4.7)	2 (3.2)	7 (4.1)
TSH increased, n (%)	1 (1.0)	3 (4.8)	4 (2.4)

Note that none of the patients reported to have hypothyroidism were also reported to have increased TSH, so these two populations are not overlapping. Therefore, overall, 6.5% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism.

Other significant events included 2 patients (1.2%) with congestive heart failure and one patient with pancreatitis. These events are notable because there is laboratory evidence of changes in left ventricular ejection fraction and in pancreatic enzymes (lipase and amylase) associated with use of sunitinib (see 7.1.3.1 and 7.1.7).

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

For study 1006, clinical laboratory tests for chemistries and hematology were performed before dosing on day 1, 14 and 28 of cycles 1-4, and then day 1 and 28 for all subsequent cycles and included the following:

- Serum Chemistry: sodium, potassium, calcium, chloride, phosphorus, carbon dioxide, creatinine, creatine kinase, globulin, total bilirubin, indirect bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT, glucose, blood urea nitrogen (BUN), uric acid, amylase, lipase, and lactic dehydrogenase (LDH);
- Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, platelets, hematocrit, mean corpuscular volume (MCV), and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils);

Laboratories performed at screening and as clinically indicated included:

- Urinalysis: specific gravity, pH, protein, glucose, ketones, blood, leukocyte esterase, and nitrite;
- Coagulation: partial thromboplastin time (PTT) and prothrombin time (PT) or PT expressed as the International Normalized Ratio (INR);
- Pregnancy: serum or urine pregnancy tests for women of childbearing potential were performed before administration of the first dose of sunitinib (results must have been available for eligibility determination).

For study 014, clinical laboratory tests were performed before dosing and included the following:

- Serum Chemistry: sodium, potassium, calcium, chloride, phosphorus, carbon dioxide, creatinine, creatine kinase (CK), globulin, total bilirubin, indirect bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT, glucose, blood urea nitrogen (BUN), uric acid, amylase and lipase
- Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, platelets, hematocrit, mean corpuscular volume (MCV), and WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils);
- Cardiac enzymes: cTnI, total CK, and CK-myocardial band (CK-MB);
- Fatigue markers: serum cortisol, lactate dehydrogenase (LDH), prealbumin, C-reactive protein (CRP), thyroid-stimulating hormone (TSH); in addition, antibody titers (IgG and IgM) for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were to be performed if patients experienced grade 3 or 4 fatigue;
- ACTH-stimulation testing: pre- and post-stimulation cortisol levels;

The following labs were performed at screening only:

- Urinalysis: specific gravity, pH, protein, glucose, ketones, WBC, RBC, casts, and bacteria;
- Coagulation: partial thromboplastin time (PTT) or prothrombin time (PT) expressed as the International Normalized Ratio (INR);
- Pregnancy: for females of child-bearing potential

All clinically important abnormal laboratory tests occurring during the study were repeated at appropriate intervals until laboratory values returned to baseline, returned to a level deemed acceptable by the investigator and the sponsor or the designated representative, or were explained by a diagnosis.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The two single-arm trials in MRCC form the basis of this laboratory safety review, as this is the most relevant population in which to assess safety for the MRCC indication.

A single placebo-controlled randomized trial was performed in imatinib-resistant GIST; this study is reviewed under NDA 21-938.

7.1.7.3 Standard analyses and explorations of laboratory data

This review focuses on the most severe (grade 3 and 4) laboratory abnormalities, as well as those of any grade in the cardiac enzymes troponin I and CK-MB. The hematology data are pooled across the two studies. The chemistry data are pooled for all but the cardiac enzyme evaluations, which were collected for study 014 only.

7.1.7.3.1 Analyses focused on measures of central tendency

Analyses of central tendency for laboratory data was performed for creatinine based upon changes reported in the GIST trial, where creatinine elevations were noted more frequently in the sunitinib arm compared to the placebo arm. An evaluation of creatinine in the MRCC population included changes in the mean over time.

Table 37: Mean Serum Creatinine by Cycle in MRCC Study 1006

Cycle	N*	Mean (mg/dl)
Baseline	114	1.18
1	290	1.24
2	184	1.26
3	146	1.30
4	117	1.36
5	47	1.28
6	34	1.35

*number of measurements:
multiple measurements
per patient per cycle

Table 38: Mean Serum Creatinine by Cycle in MRCC Study 014

Cycle	N*	Mean (mg/dl)
Baseline	72	1.21
1	325	1.29
2	162	1.27
3	139	1.27
4	121	1.30
5	49	1.31
6	40	1.27

*number of measurements:
multiple measurements
per patient per cycle

Small changes in mean creatinine were seen in study 1006, while in study 014 no significant changes in mean creatinine were seen over time. These changes are not likely to be clinically significant, and the relationship to study drug is unclear.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Hematology

Grade 3-4 hematology abnormalities for patients with normal baseline or a baseline abnormality of Grade 2 or less were reported by the sponsor in the tables below.

Table 39: Treatment-Emergent Hematology Laboratory Abnormalities on Study 1006—Sponsor’s Analysis (source: study report p. 89)

Number and Percent of Patients with Shifts from Grade \leq 2 to Grade \geq 3 for Hematology Variables

Variable	SU011248	
	All Cycles Combined	Cycle 1 Only
	(N = 106)	(N = 106)
ANC	14 (13)	3 (3)
Hemoglobin	6 (6)	1 (1)
Lymphocytes	10 (9)	5 (5)
Platelets	5 (5)	0 (0)
WBC	7 (7)	1 (1)

Table 40: Treatment-Emergent Hematology Laboratory Abnormalities on Study 014—Sponsor’s Analysis (source: study report p. 84)

Number and Percent of Patients with Shifts from Grade \leq 2 to Grade \geq 3 for Hematology and Coagulation Variables in Cycle 1

Variable	Total n(%) (N = 63)
ANC	4 (6)
WBC	2 (3)
Hemoglobin	4 (6)
Lymphocytes	14 (22)
Platelets	0 (0)
PTT	1 (2)
PT	0 (0)

Note that these tables do not include all treatment-emergent grade 3 and 4 hematology abnormalities because a patient with a baseline grade 3 abnormality which worsened to grade 4 on treatment would not be included. Treatment-emergent grade 3 and 4 laboratory abnormalities for studies 014 and 1006 are summarized in Table 41.

Table 41: Treatment-Emergent Grade 3/4 Hematology Laboratory Abnormalities—Pooled Data from Studies 014 and 1006—FDA Analysis

MRCC n=169				
Laboratory Test	Unit	Grade 3	Grade 4	Total (Grade 3 + 4)
Hematology, n (%)		54 (32.0)	4 (2.4)	58 (34.3)
Neutropenia	10 ⁹ /L	21(12.4)	1 0.6	22 (13.0)
Anemia	g/L	9 (5.3)	3 (1.8)	12 (7.1)
Lymphopenia	10 ⁹ /L	33 (19.5)	2 (1.2)	35 (20.7)
Thrombocytopenia	10 ⁹ /L	5 (3.0)	0 (0)	5 (3.0)
Leukopenia	10 ⁹ /L	12 (7.1)	0 (0)	12 (7.1)

Hematology abnormalities grade ≥ 3 were observed in 32% of the combined MRCC population. Four patients had six grade 4 events including anemia (3), lymphopenia (2) and neutropenia (1).

Chemistry

Study 1006:

All grade 3 and grade 4 laboratory abnormalities that were “treatment-emergent” (not present at baseline or worsened from baseline) were reviewed. The most common Grade 3 and 4 laboratory abnormalities included hematology (multiple cytopenias), amylase and lipase elevations, hypophosphatemia and uric acid elevations.

A table of all Grade 3 and 4 laboratory abnormalities in patients with normal to Grade ≤ 2 baseline values is shown below.

Appears This Way
On Original

**Table 42: Treatment-Emergent Chemistry Laboratory Abnormalities on Study 1006—
Sponsor’s Analysis** (source: 1006 study report p. 90)

**Number and Percent of Patients with Shifts from Grade \leq 2 to Grade \geq 3 fo
Serum Chemistry Variables**

Variable	SU011248	
	All Cycles Combined (N = 106)	Cycle 1 Only (N = 106)
ALT	1 (1)	0 (0)
AST	2 (2)	1 (1)
Albumin	0 (0)	0 (0)
Alkaline phosphatase	2 (2)	2 (2)
Amylase	2 (2)	2 (2)
Hypercalcemia	1 (1)	0 (0)
Hypocalcemia	0 (0)	0 (0)
CK	0 (0)	0 (0)
Creatinine	2 (2)	0 (0)
Hyperglycemia	3 (3)	1 (1)
Hypoglycemia	0 (0)	0 (0)
Lipase	13 (12)	8 (8)
Hypophosphatemia	7 (7)	1 (1)
Hyperkalemia	3 (3)	1 (1)
Hypokalemia	0 (0)	0 (0)
Hypermnatremia	1 (1)	0 (0)
Hyponatremia	2 (2)	1 (1)
Total bilirubin	1 (1)	0 (0)
Uric acid	10 (9)	4 (4)

Appears This Way
On Original

Table 43: Treatment-Emergent Chemistry Laboratory Abnormalities on Study 014—Sponsor’s Analysis (source 014 Study Report p. 85)

Number and Percent of Patients with Shifts from Grade ≤ 2 to Grade ≥ 3 for Serum Chemistry Variables Across All Cycles

Variable	Total n(%) (N = 63)
ALT	2 (3)
AST	1 (2)
Albumin	0 (0)
Alkaline phosphatase	0 (0)
Amylase	5 (8)
Bilirubin, indirect	0 (0)
Hypercalcemia	0 (0)
Hypocalcemia	0 (0)
Creatine kinase	2 (3)
Creatinine	0 (0)
Hyperglycemia	2 (3)
Hypoglycemia	0 (0)
Lipase	12 (19)
Hypophosphatemia	8 (13)
Hyperkalemia	4 (6)
Hypokalemia	0 (0)
Hypernatremia	0 (0)
Hyponatremia	4 (6)
Total bilirubin	0 (0)
Hyperuricemia	8 (13)

Note that this table does not include a complete listing of “treatment emergent” grade 3 and 4 events, because an event that was grade 3 at baseline, which worsened to grade 4 on study, would not be counted.

Table 44: Number and Percent of the Most Common (≥ 5%) Treatment-Emergent, Grade 3 and 4 Chemistry Laboratory Abnormalities for Studies 014 and 1006—FDA Analysis

Laboratory Test	Grade 3	Grade 4	Total (Grade 3+Grade 4) N=169
Lipase	23 (13.6)	4 (2.4)	27 (16.0)
Amylase	8 (4.7)	1 (0.6)	9 (5.3)
Hypophosphatemia	16 (9.5)	1 (0.6)	17 (10.1)
Uric acid (UA)	2 (1.2)*	15 (8.9)	17 (10.1)*

* Grade 3 UA elevation requires a UA >ULN and ≤ 10 with physiologic consequences. The two events listed as grade 3 here were designated as such by the sponsor in the chemistry dataset for study 1006. The chemistry dataset did not designate grade 3-4 UA abnormalities. In the absence of this designation, the number of Grade 3 UA abnormalities can not be assessed.

Creatinine

Grade 3/4 creatinine elevations were uncommon on the two MRCC trials. However, elevations in creatinine were more common in GIST patients receiving sunitinib than in placebo patients. For this reason, creatinine changes in the MRCC trial were investigated further. Twenty-two patients on study 1006 with normal baseline creatinine developed an abnormal creatinine at one or more time points on study. These elevations were mild (≤ 2.1 mg/dl) and many were transient. Twenty-two patients on study 014 with normal baseline creatinine developed an abnormal value at one or more time points on study. None of these patients experienced a creatinine > 2 mg/dl.

The two cases of grade 3/4 creatinine elevations were identified and reviewed. Both of these occurred on study 1006. In one case, creatinine was abnormal at baseline (2.0 mg/dl) and increased to grade 3 (4.1mg/dl) during treatment. A subsequent test result demonstrates a return to near baseline (2.3 mg/dl). The other patient had a normal creatinine at baseline and in the first cycle (0.7-0.8 mg/dl) and developed a grade 4 abnormality (creatinine 7.3 mg/dl) in cycle 2. This patient developed obstructive uropathy as a result of tumor progression and was treated with nephrostomy. It is unclear whether a creatinine of 2.9 mg/dl reported the same day as the grade 4 value is a post-nephrostomy specimen; otherwise, there is no reported follow-up data. One additional patient had a creatinine of 2 mg/dl at baseline which gradually increased to 3.6 mg/dl by cycle 7. In the renal cell carcinoma population, many of whom have abnormal creatinine at baseline due to prior nephrectomy or active malignancy in the affecting the urinary tract, a definitive assessment of causality can not be made in a single-arm trial.

Cardiac Enzymes

Troponin I and CK-MB were monitored routinely on study 014 only. Troponin elevations were observed in 13/63 (20.6%) patients and CK-MB elevations were observed in 8/63 (12.7%) patients. Most of these enzyme abnormalities were not reported as clinical AEs (there was only one report of acute coronary syndrome/myocardial ischemia on study 014) although 4 of the troponin increases and 7 of the CK-MB increases were reported under “investigations”. The clinical significance of these findings is unclear.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Dropouts reportedly associated with laboratory abnormalities included one patient with grade 4 thrombocytopenia (related to myelodysplastic syndrome), one patient with a grade 3 lipase elevation, and one patient with grade 3 proteinuria. NOTE: The grade 4 thrombocytopenia is not listed in the table above because it was not captured in the laboratory data set.

7.1.7.4 Additional analyses and explorations

None performed.

7.1.7.5 Special assessments

None performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Study 014:

Clinical safety measures included vital signs measures (heart rate, systolic BP, diastolic BP, temperature, and respiration rate). A clinically significant vital sign was defined as any measure recorded at any time during the study that met the following criteria:

- Heart Rate > 120 bpm or < 50 bpm increase of ≥ 30 bpm or decrease of ≥ 30 bpm
- BP Systolic BP > 150 mmHg and/or diastolic BP > 100 mmHg
- Systolic BP > 200 mmHg and/or diastolic BP > 110 mmHg
- Temperature > 38.3°C (101°F) increase of ≥ 1.1 °C (≥ 2 °F). Note: If the baseline temperature was below 36.8°C, then only the upper limit (38.3°C) was used for the determination of clinical significance.
- Respiration rate > 40 /minute or < 8 /minute
- Weight change of 5% or more from baseline

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This review focused on the two single-arm MRCC trials for evaluation of vital signs data. Particular attention was paid to blood pressure data as hypertension is a commonly reported adverse event in patients receiving sunitinib.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

No significant changes in pulse, respiratory rate or temperature were noted on either MRCC study.

Changes in mean blood pressure (systolic and diastolic) from baseline to cycle 5 for study 1006 are summarized in the table below.

Table 45: Changes in Mean Blood Pressure from Baseline—Study 1006

Study Period**	sbp*	dbp*
Screening (n=106, o=106)	128.7	75.5
Cycle 1 (n=106, o=205)	132.5	80.8
Cycle 2 (n=84, o=165)	134.9	80.7
Cycle 3 (n=72, o=137)	133.1	79.7
Cycle 4 (n=56, o=107)	135.4	80.7
Cycle 5 (n=43, o=76)	134.0	80.5

*sbp=systolic blood pressure
 dbp=diastolic blood pressure
 ** n=number of patients, o=# of observations

Changes in mean blood pressure (systolic and diastolic) from baseline to cycle 6 for study 014 are summarized in Table 46.

Table 46: Changes in Mean Blood Pressure from Baseline—Study 014

Study Period**	sbp*	dbp*
Screening (n=63, o=63)	127.2	73.0
Cycle 1 (n=62, o=119)	132.0	77.3
Cycle 2 (n=53, o=101)	132.2	77.3
Cycle 3 (n=45, o=89)	135.9	80.0
Cycle 4 (n=40, o=78)	136.3	80.6
Cycle 5 (n=36, o=70)	136.6	79.7
Cycle 6 (n=34, o=66)	133.3	78.5
Cycle 7 (n=28, o=54)	128.5	75.7
Cycle 8 (n=26, o=52)	133.1	78.2
Cycle 9 (n=24, o=43)	132.9	79.1

*sbp=systolic blood pressure
 dbp=diastolic blood pressure
 ** n=number of patients, o=# of observations

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Study 1006

Overall, 51 patients (48.1%) experienced hypertension, defined as systolic BP > 150 and/or diastolic BP > 100 mmHg, at least once during the study. Six patients (5.7%) on study 1006 developed severe hypertension (defined as systolic bp >200 and/or diastolic bp > 110) at some time during the study. Five of the six had histories of hypertension and were on anti-hypertensive medications prior to study entry; all 6 received additional concomitant medications for hypertension after the onset of the event.

One of these patients, patient 34, met both the systolic and diastolic definitions of severe hypertension during cycle 1 of treatment (bp 207/119). This patient had hypertension at baseline (bp 171/97). The patient continued on study without treatment interruption or dose reduction. She was started on Lopressor and Norvasc in addition to the hydrochlorothiazide she had previously been taking for hypertension and had persistent hypertension throughout the study period but no other episodes of severe hypertension.

Five additional patients met the diastolic bp criteria for hypertension during the study period. In 3 of the cases, the elevated dbp occurred on only 1 occasion, with normal bp or mild-moderate hypertension throughout the remainder of the study. In two cases, the elevated dbp occurred on more than one occasion. One of these patients, who had borderline hypertension at baseline and a history of hypertension had a persistently elevated dbp (at or above 100) for cycles 1-3, with normal or near normal bp by cycle 5. The patient was taking Avapro and Norvasc for previously diagnosed hypertension and no action was taken with the study drug as a result of hypertension.

Study 014

Overall, 36 patients (57%) experienced hypertension, defined as systolic BP > 150 and/or diastolic BP > 100 mmHg, at least once during the study including 4 patients (6%) who experienced systolic BP > 200 and/or diastolic BP > 110 mmHg. Three of these four patients had hypertension at baseline. In general, the mean systolic BP and diastolic BP were at increased levels on Day 28 of each cycle and then decreased after the 2-week rest period.

According to the sponsor (014 study report), twelve patients (19%) experienced a $\geq 5\%$ increase from baseline in weight, and 30 patients (48%) experienced a $\geq 5\%$ decrease in weight from baseline. No data concerning changes in weight were reported for 1006.

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

There were no dropouts on either MRCC study due to vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Pre-clinical safety pharmacology studies, *in vivo* and *in vitro*, identified potential cardiac conduction system effects. The *in vitro* studies indicated that sunitinib and its active metabolite SU012662 blocked the hERG potassium ion channel with an IC₅₀ of 266 nM and 4100 nM, respectively. *In vivo*, corrected QT was increased by 20-50 msec in monkeys.

To further characterize the effect of SU011248 on QTc in patients, triplicate ECGs were taken at baseline and after steady state levels of drug had been achieved (cycle 1, day 28) during the MRCC trials. Attempts were made to perform all ECGs in the morning and to time-match the two sets plus/minus one hour.

Additionally, a thorough QT study is currently ongoing. Study A6181005 was designed to assess the effects of high peak plasma concentrations of sunitinib + SU012662 on the QTc interval in subjects with advanced solid tumors. The positive control is moxifloxacin, used as an internal standard to verify technical approaches. Sunitinib and SU012662 concentrations have been shown to be increased by CYP3A4 inhibition (1.8x with ketoconazole). Thus, sunitinib + SU012662 C_{max} concentrations greater than 200 ng/mL may be observed in clinical treatment settings due to drug-drug interactions.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

This review focuses on the ECGs performed in patients with metastatic renal cell carcinoma, the 169 patients evaluated on studies 014 and 1006. Placebo-controlled data are available for the phase 3 trial in patients with gastrointestinal stromal tumor, and are reviewed under NDA 21-938.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Study 1006:

No significant differences were found between baseline QTc and cycle 1 QTc as summarized in Table 47.

Table 47: QTc Median and Range (msec) at Baseline and Cycle 1—Study 1006

	Median	Range
Baseline (n=106)	411	365-486
Cycle 1 (n=100)	412	360-485

Study 014:

No significant differences were found between baseline QTc and cycle 1 or cycle 2 QTc as summarized in Table 48.

Table 48: QTc Median and Range (msec) at Baseline and Follow-up—Study 014

	Median	Range
Baseline (n=63)	424	360-469
Cycle 1 (n=57)	412	360-596*
Cycle 2 (n=38)	410	366-458

* see explanation below (7.1.9.3.2 and 7.1.9.3.3)

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Study 1006:

Seven patients had one or more abnormal QTc assessments at baseline. All were Grade 1 (>450 and ≤ 470 msec) except for a single Grade 2 evaluation (>470 msec to <500 msec). Six patients had one or more abnormal assessments at cycle 1. Two of these abnormalities were Grade 2. Three patients with cycle 1 abnormalities had abnormal baseline QTc, the other three had normal baseline QTc.

Two patients had ECG abnormalities considered clinically significant during the cycle 1 assessment. Patient 1 had a myocardial infarction on day 28 of cycle 1 (reported under “deaths”), and patient 16 had sinus tachycardia. Two patients experienced adverse events of ECG QTc interval prolonged, and both events were considered treatment related. One event was grade 1 and resolved the same day; the other event was grade 2, and the outcome was unknown.

Study 014:

Three patients had abnormal QTc at baseline; all the abnormalities were Grade 1. Five patients had one or more abnormal QTc assessments during cycle 1. Three of these patients also had abnormal baseline assessments; and all were grade 1 with one exception. One patient had a single tracing with a QTc 596 msec, which was inconsistent with the other two (normal) assessments performed on the same day.

7.1.9.3.3 *Marked outliers and dropouts for ECG abnormalities*

Study 1006:

There were no marked outliers (Grade ≥ 3) or dropouts for ECG abnormalities.

Study 014:

One patient on study had a single QTc measurement of 596 msec in cycle 1, as noted above. All baseline assessments, and the other 2 ECG tracings during cycle 1, were normal with respect to QTc. No data are available for other cycles.

7.1.9.4 Additional analyses and explorations

No additional analyses were performed.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Carcinogenicity studies were not conducted and are not necessary to support the safety of the drug for the proposed advanced renal cell carcinoma indication.

7.1.12 Special Safety Studies

Not applicable.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Although a systematic study has not been conducted to investigate withdrawal, sunitinib has not been observed to produce physical or psychological dependence in subjects with cancer.

Sunitinib has not been studied (in animals or humans) for its potential for abuse, tolerance, or physical dependence. Given the nature of a malignant disease, it is unlikely that sunitinib can be associated with drug abuse.

7.1.14 Human Reproduction and Pregnancy Data

As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of sunitinib may result in adverse effects on pregnancy. Sunitinib was evaluated in pregnant rats and rabbits for effects on embryo-fetal development when administered during organogenesis. Embryoletality and developmental abnormalities

were observed in rats at the dose of 5 mg/kg/day. In rabbits, embryoletality was also observed at 5 mg/kg/day, while developmental effects were observed at a dose of 1 mg/kg/day or higher. Developmental effects in rats consisted of increased incidence of fetal skeletal malformations and in rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate was observed at 5 mg/kg/day.

No clinical studies with sunitinib have been conducted in pregnant women, and intrauterine exposure was not reported during clinical studies of sunitinib. (Information on pregnancies occurring during clinical trials is tracked by Pfizer regulatory safety surveillance and is stored in the sponsor's regulatory safety databases.) Based on nonclinical data, sunitinib should not be taken during pregnancy or by any woman who is not using adequate contraception, unless the potential benefit justifies the potential risk to the fetus. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with sunitinib.

Sunitinib and its metabolite, SU012662, are excreted in rat milk. However, it is not known whether sunitinib or SU012662 are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for SAEs in nursing infants, women should be advised against breastfeeding while taking sunitinib.

7.1.15 Assessment of Effect on Growth

No clinical studies of sunitinib were carried out in a pediatric population. (preclinical growth effects)

7.1.16 Overdose Experience

No overdose of sunitinib was reported in completed clinical studies. Treatment of sunitinib overdose should consist of general supportive measures (no specific antidote is known for treating the effects of sunitinib overdose). If indicated, elimination of unabsorbed drug can be achieved by forcing emesis or by gastric lavage.

7.1.17 Postmarketing Experience

Not applicable as the drug is not marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Two phase 2 trials enrolling 169 patients with metastatic renal cell carcinoma were the primary clinical data sources used to evaluate safety. The clinical study reports, case report tabulations, and, as appropriate, case report forms and clinical narratives were examined during the review process. Both these studies enrolled patients with MRCC who had received one prior cytokine-based therapy. Patients received sunitinib at a starting dose of 50 mg per day on the 4/2 schedule in both studies. Studies performed in other patient populations were evaluated only in circumstances under which the reviewer felt that significant additional safety information could be obtained. Safety data from the only submitted randomized, placebo-controlled trial of approximately 300 patients with gastrointestinal stromal tumor were reviewed separately under NDA 21-938 by Dr. Edwin Rock.

7.2.1.2 Demographics

Median age across the two MRCC trials was 57 years (range 24-87 years). 65% of the pooled MRCC population was male and 91% were Caucasian.

7.2.1.3 Extent of exposure (dose/duration)

The median duration of treatment was 5.5 months for study 1006 and 7.7 months for study 014. Dose reductions occurred in 23 (22%) of patients on study 1006 and in 22 (35%) of patients on study 014.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary data sources were used in the conduct of this review.

7.2.2.1 Other studies

Not applicable; all relevant studies are considered under primary data sources.

7.2.2.2 Postmarketing experience

Not applicable, the drug is not marketed in any country.

7.2.2.3 Literature

There were no publications relevant to the safety of sunitinib which referenced studies not performed under an IND.

7.2.3 Adequacy of Overall Clinical Experience

The database for the MRCC indication contains 169 patients enrolled on two single-arm trials. Additionally, there is supporting safety data from the placebo-controlled GIST study (reviewed as NDA 21,938) in 312 patients. The overall clinical experience is therefore adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was performed.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of safety parameters was adequate and appropriate for the stage of development.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction workup was adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adrenal gland was a target organ for toxicity in two animal species. Evaluation during the clinical program included adrenal imaging (CT/MRI) and ACTH stimulation testing to evaluate for adrenal insufficiency. This testing occurred across the early clinical development plan, with results for 300-400 patients. Placebo controlled data are very limited. The available data demonstrate no imaging evidence of the necrosis and hemorrhage seen in animals, and an unexplained abnormality in ACTH stimulation testing in one of 400 patients tested. There was no evidence of clinically significant adrenal insufficiency. Although this testing is not considered optimal due to the absence of adequate placebo controlled data; the current database of 400 patients demonstrates that laboratory evidence of drug-related adrenal suppression is scant and has not been associated with clinical evidence of adrenal insufficiency in patients with advanced cancers. Continued routine testing for adrenal insufficiency is therefore not warranted in patients receiving sunitinib.

The evaluation of potential cardiac toxicity in the two MRCC studies included QTc monitoring on both studies, routine monitoring of CK-MB and cardiac troponin-I on study 014 and left ventricular ejection fraction monitoring on both studies. The evaluations of LVEF, however, did

not include adequate follow-up data for several patients in whom LVEF had decreased substantially at the time of the last evaluation. In some cases, these patients died due to progressive disease shortly thereafter. In others, patients remained on study (1006) and further data should be available in the future. These data will be requested under post-marketing commitments. Additionally, a phase 3 placebo-controlled trial in patients with earlier stage RCC is planned. The sponsor will be asked to propose a plan to evaluate LVEF changes in this population as well.

7.2.8 Assessment of Quality and Completeness of Data

The databases evaluated in the safety review were complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The 3-month safety update was reviewed following its submission on November 11, 2005. This update provided additional safety data for the ongoing MRCC study 1006, extending the date of data cutoff for safety from January 28, 2005 to June 1, 2005. Significant findings from this update are described below.

Deaths:

Two additional on-study deaths were reported for 1006.

Patient 34, a 54 year old woman, died during cycle 7 of treatment. She had a malignant pleural effusion, and prior to her death was treated with intravenous antibiotics and chest tube placement after developing an empyema. The cause of death was reported as disease progression. Patient 65, a 47 year old woman, died during cycle 2 of treatment. At baseline, she had a renal bed mass, abdominal mass, and hematuria related to malignant disease. Disease progression was confirmed on CT in cycle 2. The cause of death was reported as progressive disease.

Other Serious Adverse Events (SAEs):

At the time of the safety update, a total of 35 (33%) patients on study 1006 had experienced an SAE. The most common SAEs reported were disease progression and dehydration (5 patients each, 4.7%). Other events reported more than once included abdominal pain, vomiting, pneumonia, dyspnea, pleural effusion, thrombocytopenia (one reported as "platelet count decreased) renal failure, renal failure acute, convulsion, failure to thrive, mental status changes and tumor excision (2 each, 1.9%). [NOTE: there were a total of 4 SAE reports of renal failure, 2 acute and 2 unspecified, total % of subjects is 3.7%]. Events reported once included anemia, nausea, pulmonary embolism, diarrhea, rectal hemorrhage, cardiorespiratory arrest, chest pain, peripheral edema, infection, intestinal obstruction, syncope urinary tract infection, decreased ejection fraction, hypercalcemia, myocardial infarction, pneumothorax and sepsis.

Drop-outs due to AEs:

No new events leading to treatment discontinuation were reported for Study 1006.

No significant changes to the safety profile of sunitinib were demonstrated in the safety update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most common adverse events likely to be drug related occurring with sunitinib use include mucositis, diarrhea, nausea, taste disturbance, dyspepsia, rash, anorexia, vomiting, skin discoloration, hypertension, constipation, bleeding, glossodynia, dry skin, hand-foot syndrome, blistering of the skin, alopecia and peripheral neuropathy.

Laboratory abnormalities associated with use of the drug include cytpoenias including neutropenia, anemia and thrombocytopenia, elevations in lipase, amylase and uric acid and hypophosphatemia. Additionally, decreases in left ventricular ejection fraction have been demonstrated with sunitinib use.

All data in the MRCC population are from single-arm trials, making an assessment of causality difficult. However, many of the events described above, in particular the dermatologic side effects, are very uncommon in the absence of drug exposure; while others are seen at frequencies higher than expected. Additionally, data from the placebo-controlled trial in gastrointestinal stromal tumors support the labeling of these events as drug related.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Although the study populations in the two MRCC trials were very similar, the adverse event data were considered separately. The primary reason for this was that the monitoring and reporting requirements for certain events differed on the two studies. Safety data which was pooled included evaluation of laboratory events which were monitored in a similar fashion across both studies and a relatively small number of events had occurred. In some instances (e.g. LVEF), data from the two studies were evaluated separately but considered together in the conclusions.

7.4.1.2 Combining data

When data across the two studies were pooled, the numerator events and denominators for the two studies were summed.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Not evaluated; all patients on the MRCC trials received the same starting dose, with dose reductions for toxicity only.

7.4.2.2 Explorations for time dependency for adverse findings

Not performed.

7.4.2.3 Explorations for drug-demographic interactions

Of 22 patients requiring dose reductions on study 014, 11 were men and 11 were women; representing 26% of men and 55% of women on study. On study 1006, 7.5% of men and 23% of women required dose reductions for toxicity. The possibility of a gender-related difference in toxicity was explored by the clinical pharmacology team. Their review noted that women had higher drug exposure (AUC) than men. After accounting for AUC, there was no difference in toxicity between men and women in patients receiving sunitinib.

7.4.2.4 Explorations for drug-disease interactions

Not performed; only patients with MRCC were evaluated in this review.

7.4.2.5 Explorations for drug-drug interactions

This drug is expected to interact with drugs which inhibit or induce CYP3A4. No other drug-drug interactions were examined.

7.4.3 Causality Determination

Causality determination was limited by the study design of the MRCC trials, both of which were single arm. A determination of the likely causality was made by considering the following

- Did the event occur more frequently than might be expected in the population?
- Could the toxicity be explained based on the mechanism of action?
- Were similar toxicities described in other drugs in the class?
- Were similar toxicities seen in animal studies?

The incidence of events in sunitinib-treated vs. placebo-treated patients in the GIST trial was also used to support causality.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended starting dose and schedule for sunitinib in MRCC is 50 mg orally once daily for four consecutive weeks, followed by a two week rest period (the 4/2 schedule). Dose reductions to 37.5 mg or 25 mg daily on the 4/2 schedule are appropriate in the setting of intolerable toxicity.

8.2 Drug-Drug Interactions

The primary pathway of elimination of sunitinib is via CYP3A4. Drug-drug interaction studies have shown a 51% increase in exposure when co-administered with ketoconazole and a 46% reduction in exposure when co-administered with rifampin.

Dosing adjustments for patients on CYP3A4 inhibitors

There was an approximately 50% increase in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with ketoconazole. To adjust for this increase, the clinical pharmacology reviewers recommend that the sunitinib dose be reduced to 66% of the recommended dose in patients who must receive strong CYP3A4 inhibitors concomitantly.

Dosing adjustments for patients on CYP3A4 inducers

There was an approximately 50% decrease in combined AUC (sunitinib + active metabolite) when sunitinib was concomitantly given with rifampin. To adjust for this decrease, the clinical pharmacology reviewers recommend that the sunitinib dose be increased to 200% of the recommended dose in patients who must receive strong CYP3A4 inducers concomitantly.

8.3 Special Populations

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for age, body weight, creatinine clearance, race, gender or ECOG score. The pharmacokinetics of sunitinib have not been evaluated in pediatric patients.

No differences in safety or effectiveness were observed, regardless of age.

Hepatic Insufficiency

No clinical studies were conducted in patients with impaired hepatic function. Studies that were conducted excluded patients with ALT or AST > 2.5 x ULN or, if due to underlying disease, > 5.0 x ULN.

Renal Insufficiency

No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42 –347 mL/min.

8.4 Pediatrics

To date, sunitinib has not been studied in pediatric patients. c
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Finally, in nonclinical animal studies relatively high levels of sunitinib were found in brain tissue indicating that it was able to penetrate the blood-brain barrier

8.5 Advisory Committee Meeting

This application was not discussed at an advisory committee meeting.

8.6 Literature Review

At the time of NDA submission, there were no published data (nonclinical or clinical) of sunitinib use. During the course of this review, a report of a phase 1 trial in multiple solid tumors was published in the Journal of Clinical Oncology¹¹. This report was reviewed for additional safety data. This report confirmed the safety profile presented in the NDA submission and did not raise any additional safety concerns.

8.7 Postmarketing Risk Management Plan

The sponsor proposed a risk management plan based on their assessment of risk. Over the course of the safety data review from the GIST and MRCC clinical studies, the following issues were identified, assessed, and determined to be in 1 of 3 categories by the sponsor:

- Real risk: hypertension, hemorrhage (including tumor bleeding), and cytopenias.
- Potential risk: thromboembolic events, hypothyroidism, gastrointestinal perforations, and QTc prolongation.
- No evidence of risk: alterations in adrenal gland dysfunction, left ventricular dysfunction, and pancreatic dysfunction.

The Pharmacovigilance Plan describes the activities that will be carried out in order to progressively increase the knowledge of sunitinib exposure and its safety profile in subjects with GIST who have failed or are intolerant to prior imatinib mesylate therapy and cytokine-resistant MRCC.

After assessing real and potential safety issues identified in the GIST and MRCC clinical programs, the Pfizer risk-management committee (RMC) for sunitinib determined that routine pharmacovigilance and package label information will be sufficient to minimize the risks and maximize the benefits in the indicated patient populations.

Safety issues that have been identified in the RMP that require vigilance by the clinician are addressed in the proposed sunitinib US package insert for the treatment of GIST after failure of imatinib mesylate treatment due to resistance or intolerance, and for the treatment of MRCC after failure of cytokine-based therapy.

Clinicians should be aware of certain aspects of sunitinib's safety profile, such as the potential for gastrointestinal, hematologic and blood pressure effects. These are included in the proposed label and are likely to be managed effectively through recourse to specific therapies or, when required, a reduction or temporary delay in dosing. As none of these effects would be considered as unusual or unfamiliar, physicians would be expected to be able to recognize and manage them.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Two single-arm, open-label phase 2 studies were submitted to support the MRCC indication. The two studies enrolled a total of 169 patients with similar baseline demographics; all patients

had received prior cytokine-based therapies for metastatic disease. Patients in both studies received sunitinib at 50 mg daily on a 4 weeks on/2 weeks off schedule, for a cycle length of 6 weeks. Median duration of treatment was 34 weeks for study 014 (including participation in the continuation studies) and 23.6 weeks in study 1006 at the time of data cutoff.

The primary efficacy endpoint was ORR using RECIST criteria, as measured by the investigator (014) or the [] core imaging laboratory (1006). Duration of response was assessed in both studies as a secondary endpoint.

All responses on both studies were partial responses. The ORR was 25.5% (95% CI 17.5-34.9%) for study 1006, and 37% (95% CI 24.7-49.6%) for study 014. These results were supported by three secondary analyses of ORR in the 1006 trial: the investigator assessed ORR in both the ITT and MITT populations, and the third-party radiology core laboratory assessment of ORR in the MITT population.

Duration of response, measured from the time of first documentation of a response to the first documentation of progression, was a secondary endpoint on both studies. DR data were immature for study 1006: with 4/27 (15%) progression events occurring, the median DR was 27.1 weeks (95% CI 24.4; upper limit could not be calculated). On study 014, 13/23 (56.5%) events had occurred with a median DR of 54.0 weeks (95% CI: 34.3-70.1).

Tumor responses in the second-line treatment of MRCC are rare, with historical response rates of $\leq 5\%$ with either cytokine or cytotoxic therapies. Response rates of 25-37% have not previously been demonstrated with any agent in MRCC, in either the second-line or first-line setting. While this NDA was under review, sorafenib was given regular approval for the treatment of advanced renal cell carcinoma based on an improvement in progression-free survival (PFS) demonstrated in a randomized trial. Patients receiving sorafenib had a median PFS of 167 days while patients receiving placebo had a median PFS of 84 days; the hazard ratio for progression was 0.44 (95% CI 0.35, 0.55). The response rate in both arms was negligible (2% for sorafenib-treated patients vs. 0% for placebo-treated patients). The substantial response rate of sunitinib may provide a benefit over sorafenib in advanced renal cell carcinoma patients, particularly those with bulky disease in whom cytoreduction may be an important goal of treatment.

The demonstration of an impressive response rate with sunitinib in MRCC is supported by a significant duration of response. While an effect on an endpoint of known clinical benefit such as survival or symptom benefit has not been demonstrated for sunitinib in MRCC, the combination of response rate and response duration demonstrated in this application is reasonably likely to predict a clinical benefit in patients with advanced renal cell carcinoma.

The safety population for MRCC includes the 169 patients treated in the 2 single-arm trials. All patients received sunitinib on the 50 mg daily 4 weeks on/2 weeks off schedule. Median duration of exposure was 5.5 months on study 1006 and 7.7 months on study 014. The most common adverse events in the pooled MRCC population included fatigue (74%), diarrhea (55%), nausea (54%), mucositis/stomatitis (53%), dyspepsia (46%), taste alterations (43%), rash (38%), vomiting (37%), constipation (34%), skin discoloration (yellow skin) (33%), anorexia (31%),

hypertension (28%), dyspnea (28%), arthralgia (28%), bleeding (all sites) (26%), headache (25%), and abdominal pain (20%). Other significant events that are likely to be drug-related included peripheral edema (17%), glossodynia (15%), hand-foot syndrome (12%), peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), and periorbital edema (7%).

The most common grade 3/4 events included fatigue (11%), hypertension (6%), diarrhea (5%), dyspnea (5%), mucositis/stomatitis (4%), vomiting (4%), hand-foot syndrome (3%), dehydration (3%) and abdominal pain (3%). All of these events were grade 3.

Common grade 3/4 laboratory abnormalities included lymphopenia (21%), increased lipase (16%), neutropenia (13%), hypophosphatemia (10%), uric acid elevation (10%), leucopenia (7%), anemia (7%), thrombocytopenia (7%), and increased amylase (5%).

Twenty-five patients (15%) experienced declines in left ventricular ejection fraction (LVEF) to below normal during the study. Three patients were discontinued from study 014 due to LVEF changes. Four patients with MRCC had declines to below 40% as the last measured LVEF on study.

The sponsor has demonstrated a significant ORR and adequate duration of response, with a comparatively favorable safety profile, for use of sunitinib in metastatic renal cell carcinoma. Declines in LVEF are an ongoing safety concern which will be addressed in the sponsor's post-marketing commitments.

9.2 Recommendation on Regulatory Action

The Division of Drug Oncology Products, Office of Oncology Products, Center for Drug Evaluation and Research, Food and Drug Administration recommends *accelerated approval* of this application for sunitinib for the treatment of advanced renal cell carcinoma (RCC). This approval is based upon the evaluation of response rate, a surrogate endpoint reasonably likely to predict clinical benefit in this setting. Sunitinib has not demonstrated an effect on an endpoint of known clinical benefit, such as survival or symptom benefit, in MRCC.

Two single-arm, phase 2 studies relevant to the advanced RCC indication were submitted with this application. One hundred and sixty nine patients with metastatic renal cell carcinoma (MRCC) who had received prior cytokine therapy (interferon- α [IFN- α] and/or interleukin-2 [IL-2]) were enrolled in the two trials. The studied population differs from the proposed indicated population in two ways. First, all studied patients had metastatic disease; patients with advanced unresectable disease were excluded. In practice, these patients are treated similarly to patients with metastatic disease. Second, all studied patients had received prior cytokine therapy, which is the standard of care in MRCC. Cytokine therapies used to treat RCC are highly toxic and have limited efficacy. As a result, restricting the indication to the second-line following cytokine failure would create an "artificial" clinical scenario (one that is inconsistent with expected clinical practice) in which a patient would be required to complete treatment with a highly toxic regimen of minimal benefit prior to receiving a significantly less toxic regimen with a higher

response rate. After discussion between the review team, the DDOP and OODP leadership, and later the sponsor, we therefore propose to expand this indication to include all patients with advanced renal cell carcinoma, without a requirement for prior cytokine therapy.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. Unusual toxicities that are seen with sunitinib, including hypertension, bleeding, changes in left ventricular ejection fraction and dermatologic effects, will be described in the labeling. LVEF will continue to be monitored in the clinical trial setting and submission of this data will be the subject of a post-marketing commitment. No further risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

This application was reviewed under subpart H (accelerated approval) regulations. The sponsor will therefore be required to provide confirmation of clinical benefit. The sponsor currently has an ongoing study (A6181034) evaluating sunitinib vs. IFN- in the first-line treatment of MRCC; this is intended to be the study in which clinical benefit (as measured by disease-free survival) will be confirmed. The sponsor will be asked to submit the following:

- The response rate data from the interim efficacy analysis of study A6181034. The sponsor will also submit the comparative safety data that are available at the time of data cutoff for the interim analysis. This will include an interim study report as well as raw and derived datasets.
- Efficacy data obtained at the final analysis, including progression-free survival, overall survival, response rate and duration of response; as well as updated safety data for study A6181034. This submission will include the final study report as well as raw and derived data sets.

The duration of response data for study 1006 provided in this submission were immature, with only 15% of events occurring prior to data cutoff. At that time the median duration of response (DR) was 27.1 weeks. In a slide presentation shortly after NDA submission, the sponsor claimed a median DR of 43.1 weeks. The data tables supporting this result were not provided. They have since updated the response rate as well based on data obtained since the NDA submission. These data will be requested as a post-marketing commitment so that mature response rate and duration of response can be added to the drug labeling.

- The sponsor will submit updated raw and derived datasets containing the core imaging facility data used to derive the updated response rate and duration of response from study 1006.

Changes in left ventricular ejection fraction occurring in patients receiving sunitinib are an ongoing safety issue which may become an important clinical issue as the development of the drug moves from treatment of advanced cancers to earlier stages of disease. Several patients on both MRCC studies have a markedly abnormal LVEF as the last available measurement. On study 1006, three such patients remained on study at the time of data cutoff; these patients should have had additional assessments of LVEF throughout the study. The sponsor will therefore be asked to submit additional LVEF data for those patients, as well as clinical narratives detailing additional cardiac evaluations performed, and treatments administered for congestive heart failure. In addition, the sponsor will be asked to submit LVEF data and clinical narratives for any patient who, after the data cutoff for this submission, had a documented LVEF of $\leq 40\%$ and/or signs and symptoms of cardiac failure.

- The sponsor will submit follow-up LVEF data for patients 16, 46, and 81 on study 1006. Case narratives should be submitted and should include additional cardiac evaluations that were performed and treatments that were administered for congestive heart failure. Additionally, the sponsor will submit LVEF data and clinical narratives for any patient who, after the data cutoff for the initial NDA submission, had a documented LVEF of $\leq 40\%$ and/or signs and symptoms of cardiac failure.
- The sponsor will submit comparative LVEF data for all patients enrolled on the adjuvant RCC trial, E2805.

9.3.3 Other Phase 4 Requests

The sponsor will be asked to provide an analysis of the relationship between exposure and efficacy outcomes from the randomized trial of sunitinib versus interferon in the first-line treatment of metastatic MRCC.

9.4 Labeling Review

Summary of Major Recommended Changes to the Clinical Sections of the Labeling:

Indication:

The sponsor's proposed indication was **L**

J. This indication has been expanded to include patients who have unresectable disease as well as those with metastatic disease who have not received prior cytokine therapy for reasons discussed in section 6.1. Therefore, the revised indication is "for the treatment of advanced renal cell carcinoma."

Clinical Studies (MRCC):

- Efficacy table includes only ORR data and duration of response data.
- Efficacy data for study 1006 includes core imaging laboratory assessment (the primary efficacy endpoint), rather than the investigator assessed data.

Warnings

- A section on left ventricular function was added.

Precautions:

- All hemorrhagic events were summarized, with subheading for intratumoral hemorrhage, pulmonary hemorrhage and other events.
- Sections describing treatment-emergent hypothyroidism and pancreatitis were added.
- Data were described for MRCC and GIST patients, rather than cumulative “solid tumor” patients.

Adverse Events:

- Table was changed from treatment-related events to treatment-emergent events.
- Events were categorized by system organ class.
- All events occurring in $\geq 10\%$ of patients were included in the table; other significant events were described in the text.
- Hematologic events of grade 3 and 4 severity in the MRCC population were described in table format.
- Additional text describing cardiac enzyme elevations and hypothyroidism were added.

9.5 Comments to Applicant

None.

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10 APPENDICES

10.1 Review of Individual Study Reports

The study reports for the MRCC studies were reviewed and the data was integrated into the review where appropriate.

10.2 Line-by-Line Labeling Review

A summary of major labeling issues is included in section 9.4

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